THE JOURNAL OF Organic Chemistry®

VOLUME 33, NUMBER 7
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JULY 12, 1968

Oxymercuration of Strained Olefins. The Effect of Neighboring Groups[1]

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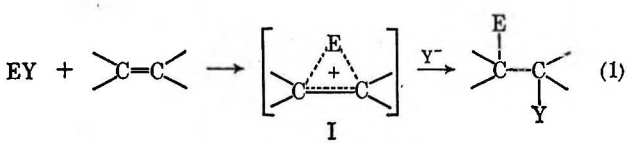
Received July 11, 1967

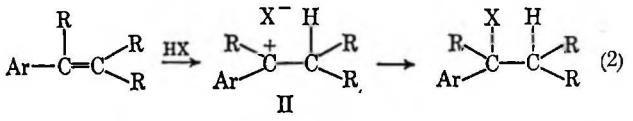
Additions of acids or mercury salts to norbornenes usually give *cis-exo* products. We have studied the effect of neighboring groups such as *endo*-5-methylol, *endo*-5-carboxylate, *endo*-5-carbomethoxy, *endo*-5-cyano, and *syn*-7-methylol upon the stereochemistry of oxymercuration of norbornene. Neighboring groups such as –COOH or $-CH_2OH$ bring about *trans* addition. The *endo*-5-CN or *endo*-5-COOMe groups participate in the addition only in the presence of water. Treatment of *endo*-5-carboxynorbornene with aqueous deuteriosulfuric acid brings about *trans* addition to give the 3-*exo*-deuteriolactone (VIID) in agreement with the oxymercuration reaction. These results do not reveal the cause of the highly stereospecific *cis-exo* additions of mercuric salts and acids to norbornene, but suggest that the demand for *cis* addition is too small to compete with neighboring-group participation in such additions. The results are consistent with either two-step oxymercuration or concerted addition.

Most electrophilic additions to olefins are considered to proceed through an intermediate three-membered ring (π complex) which opens with inversion to give *trans* addition of EY.[3]

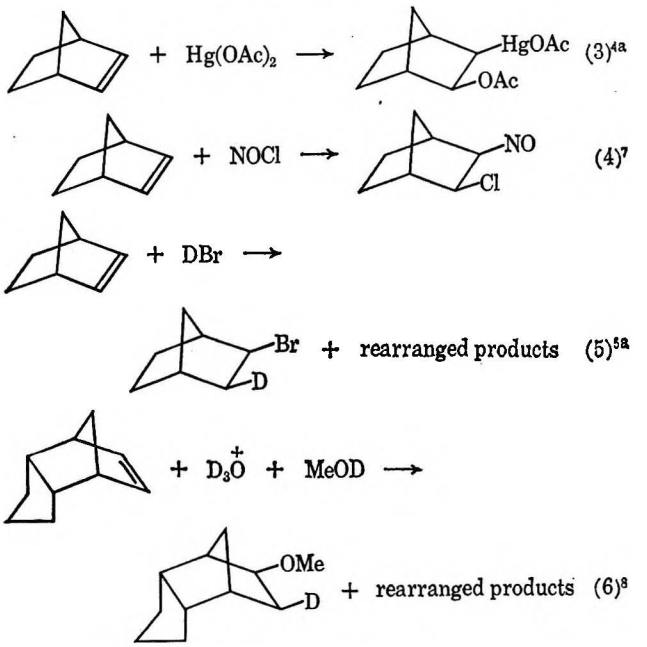


I (1)

Several instances of *cis* addition of such reagents have also been reported recently.[4-9] These *cis* additions fall into two substrate categories. (1) Addition of electrophilic reagents to aryl-substituted olefins sometimes gives *cis* addition. Evidence has been presented for the occurrence of carbonium ion pairs (II) in such systems.[9] (2) Although strained olefins such as bicycloheptene or bicyclooctene usually add electrophiles with rearrangement,[5b] or with *trans* stereochemistry,[5b] several reagents add in a *cis* fashion as indicated in eq 3–6 below.



II (2)



The stereochemistry of oxymercuration has been investigated in a wide variety of cyclic and bicyclic olefins. *cis* addition has been observed only when the olefin is strained and bicyclic.[4b] Thus oxymercuration

(1) Presented at the 147th National Meeting of The American Chemical Society, Philadelphia, Pa., April 1964. Although the abstract contains errors in configurations, the data and interpretations presented at that meeting were those recorded here.

(2) National Institutes of Health Postdoctoral Fellow, 1963–1964.

(3) (a) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1962, p 214; (b) J. Chatt, *Chem. Rev.*, **48**, 7 (1951).

(4) (a) T. G. Traylor and A. W. Baker, *Tetrahedron Lett.*, No. 19, 15 (1959); (b) *J. Amer. Chem. Soc.*, **85**, 2746 (1963); (c) T. G. Traylor, *ibid.*, **86**, 244 (1964); (d) A. Factor, unpublished results.

(5) (a) H. Kwart and J. L. Nyce, *J. Amer. Chem. Soc.*, **86**, 2601 (1964); (b) H. Kwart and R. K. Miller, *ibid.*, **78**, 5678 (1956).

(6) K. C. Pande and S. Winstein, *Tetrahedron Lett.*, No. 46, 3393 (1964).

(7) J. Meinwald, Y. C. Meinwald, and T. N. Baker, III, *J. Amer. Chem. Soc.*, **86**, 4074 (1964).

(8) (a) S. J. Cristol, W. K. Leifert, D. W. Johnson, and J. B. Jurale, *ibid.*, **84**, 3918 (1962); (b) S. J. Cristol, L. K. Gaston, and D. W. Johnson, *Tetrahedron Lett.*, No. 4, 185 (1963); (c) S. J. Cristol, N. L. Hause, and J. S. Meek, *J. Amer. Chem. Soc.*, **73**, 674 (1951).

(9) M. J. Dewar and R. C. Fahey, *ibid.*, **84**, 2012 (1962).

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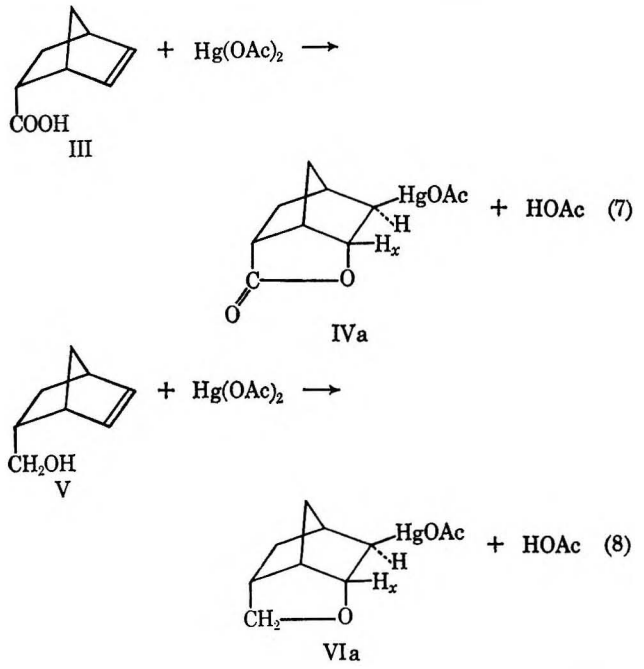
occurs in a *cis* manner with norbornenes,[4b,6,10-12] both *cis* and *trans* with bicyclo[2.2.2]octene,[4c] and *trans* with cyclohexene[4b,12] or other simple cyclic olefins.[4d] The limited data available indicate similar behavior for acid additions.[5a,7,8a,b]

We have previously suggested[4b,c] that these *cis* additions to strained olefins probably occur by a two-step path similar to that in eq 1. They are proposed to differ from the *trans* additions only in the second step in which frontside SN2 opening of the π complex becomes favorable for reasons of strain or steric hindrance.

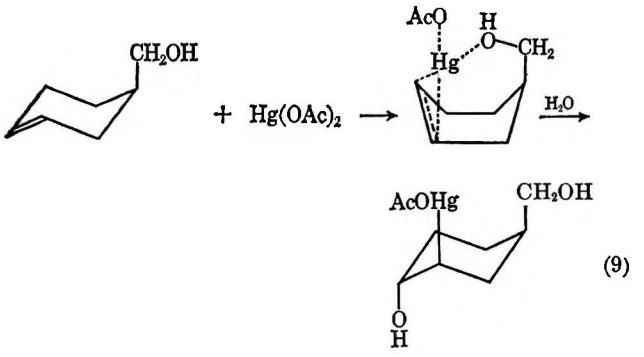
This paper reports the effects of neighboring groups on rates and stereochemistry of products from additions of acids or mercuric salts to norbornenes.

Results

Two of the oxymercurations were reported previously.[13,14] The configuration of the acetomercuri



group was not proved. Furthermore, the usual assumption that electrophiles attack norbornene from the *exo* side is not justified in these cases. There is evidence[13]

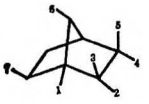


that hydroxy or carboxy groups complex with mercuric ions to lead the mercury into the olefins from the same side as the polar group. Therefore an unequivocal structure proof is needed.

We have used the nmr spectroscopy technique developed by Anderson and Henry[12] and others to indicate the stereochemistry of the reactions studied.

I. Stereochemistry of Ring Closure in 5-*endo*-Substituted Norbornenes.—To determine the stereochemistry of IV and VI, the products of oxymercuration of bicyclo[2.2.1]hept-2-ene-5-*endo*-carboxylic acid (III) and bicyclo[2.2.1]hept-2-en-5-*endo*-ylmethanol (V) were isolated[13,14a] and their nmr spectra obtained. In both IV and VI proton 2 appeared as a simple doublet centered at τ 4.71 and 4.88, respectively, with a splitting constant (J) of 5.0 Hz. The J values in the norbornyl system are well established and are tabulated in Table I.[15-17]

TABLE I



H positions	J_{HH}, Hz	Ref
1, 2	0	15
1, 3	3–4	15
1, 3	5	16
2, 4	7.7	15
2, 5	2.2–2.3	15, 17a,b
2, 6	0	12, 17a
	3–4	7
3, 5	7–8	17a
	8–9	15
3, 7	0–1.4	15

Note that J between *cis* protons is quite large (8 or 9 Hz) compared with the ~2 Hz found for the *trans* protons. Also, although the bridgehead proton (1) couples with the *exo* proton (3) with a J of 3–4 Hz, it fails to couple with the *endo* proton (2). The coupling constants between vicinal protons in the norbornyl system have been found to agree quite well with those calculated using the Karplus–Conroy relationship[18a,b] between dihedral angle, ϕ, of vicinal protons and their coupling constant. Equation 10 is as implified version of this relationship[18c] (neglecting electronegativity and C–C–H bond angle and assuming sp^3 hybridization and a C–C bond length of 1.543 Å).

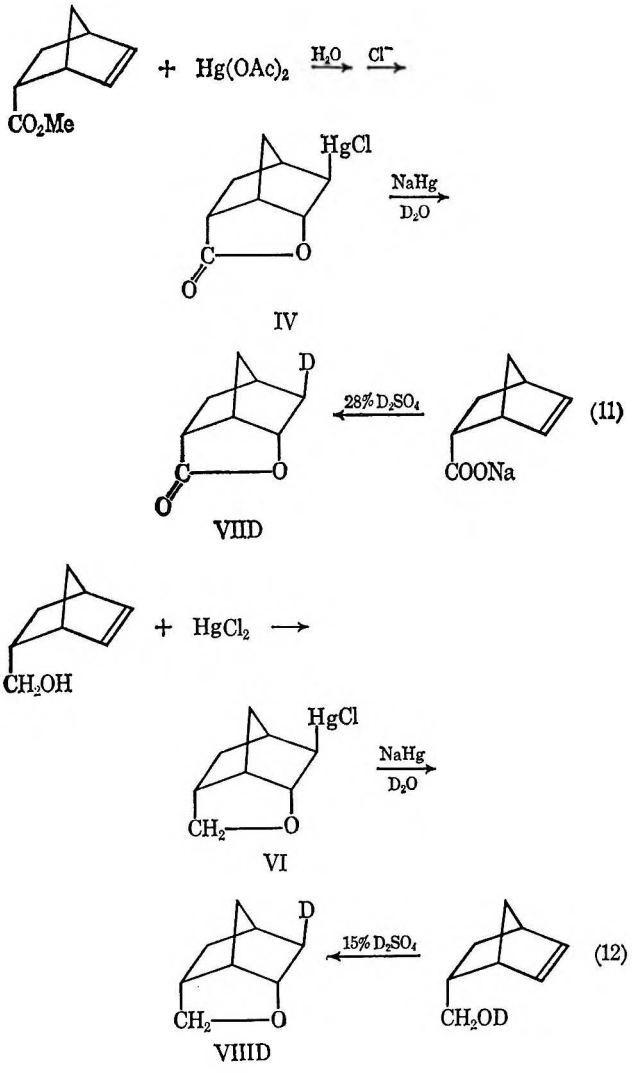
$$J = 4.22 + 4.5 \cos 2\phi - 0.5 \cos \phi \qquad (10)$$

Since the coupling constant found in IV and VI, 5.0 Hz, was intermediate between that for *cis* and *trans* protons, we suspected that some anomalous effect of the chloromercuri group might be operating. However, reduction with sodium–amalgam in D_2O, which has been shown[4b] to go with complete retention of configuration, gave compounds containing one deuterium in whose nmr spectra proton 2 again appeared as a doublet with a splitting constant of ~5.0 Hz.

Synthesis of these deuterated compounds by deuteriosulfuric acid treatment of the appropriate 5-*endo*-

(10) J. K. Stille and S. C. Stinson, *Tetrahedron*, **20**, 1387 (1964).
(11) (a) N. S. Zefirov, L. P. Prikazchikova, and Yu. K. Yurev, *Dokl. Akad. Nauk. SSSR*, **152**, 869 (1963); (b) *ibid.*, *Zh. Obsch. Khim.*, **35**, 822 (1965); (c) *ibid.*, **32**, 2744 (1962).
(12) M. M. Anderson and P. M. Henry, *Chem. Ind.* (London), 2053 (1961).
(13) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 227 (1959).
(14) (a) M. Malaiyandi and G. F Wright, *Can. J. Chem.*, **41**, 1493 (1963); (b) A. M. Bircks and G. F Wright, *J. Amer. Chem. Soc.*, **62**, 2412 (1940).
(15) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).
(16) W. D. Kumer, J. N. Schoolery, and F. V. Brutcher, Jr., *J. Amer. Chem. Soc.*, **80**, 2533 (1958).
(17) (a) P. Laszlo and P. R. Schleyer, *ibid.*, **85**, 2709 (1963); (b) *ibid.*, **86**, 1171 (1964).
(18) (a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (b) H. Conroy, "Advances in Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960, p 265; (c) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

substituted 2-norbornenes gave products identical with those from the reduction of the mercurials. This indicates that the oxymercuration and the proton addition reactions proceeded with the same stereochemistry.



The recent investigations of Cristol[8] and Kwart[5a] have shown that protons, like all other electrophiles,[5b] add to norbornene from the *exo* side. Thus, on this basis, it would appear that, in the above deuteriosulfuric acid cases, the proton added *exo* and that the overall stereochemistry of addition to the double bond was *trans*.

This same conclusion was reached by a study of the nmr spectra of undeuterated compounds (Figure 1). In the spectra of both the lactone and cyclic ether, proton X appeared as a quartet. The exact same quartet was found in the spectra of these compounds run at 100 Mc on a Varian HR-100 spectrometer,[19] showing that the quartet was due to spin–spin splitting. Interpreting this as the X part of an AMX system, it can be concluded that the separation of the outer lines is equal to the sum of J_{AX} and J_{MX}. Since this was 12 Hz and it was found that replacing a proton with mercury or deuterium left a doublet of 5 Hz, it was concluded that the other coupling involved was 7 Hz. From a study of Dreiding models of these cyclized norbornanes, it is possible to estimate the dihedral angles between protons A, M, C, and X and to calculate[18] the expected coupling constants. As shown in Figure 1, these calculations indicate that the observed coupling of 5.0 Hz in the mercurials and deuterated compounds is due to coupling between the bridgehead and *exo* protons. This interpretation was substantiated by decoupling the bridgehead proton. Upon irradiation of proton H_M the original quartet collapsed to a doublet whose splitting constant was 7 Hz. These results indicate that both the chloromercuri and deuterium groups occupied the *exo* position and that both protonation and oxymercuration proceeded by an electrophilic attack on the *exo* side of these norbornenes.[20,21] The vicinial Hg^{199}–H coupling constants in these compounds agree with this assignment.[22]

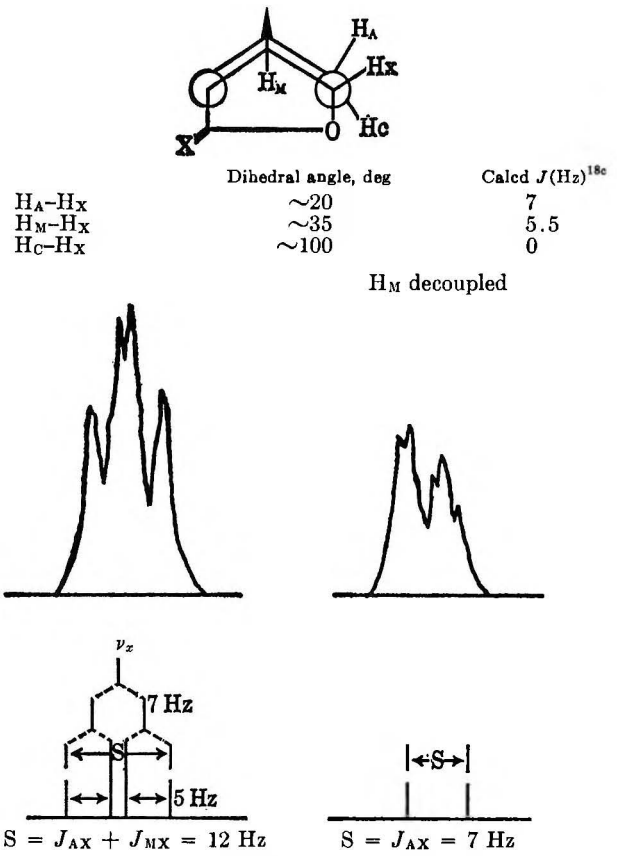


Figure 1.—Nuclear magnetic resonance spectra of cyclized norbornanes VII and VIII.

II. The Stereochemistry of Ring Closure with *syn*-7-Hydroxymethyl-2-norbornene.—Recently, Bly and Bly[23a] have shown that the oxymercuration of *syn*-7-hydroxymethyl-2-norbornene occurs with ring closure. Professor Bly very kindly sent us a sample of the mercurial for nmr analysis.

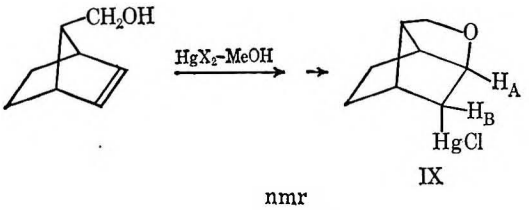
(19) We are indebted to Mr. Leroy Johnson, Varian Associates, Palo Alto, Calif., for this spectrum.

(20) K. C. Ramey, D. C. Lini, R. M. Moriarty, H. Gopal, and H. G. Walsh [*J. Amer. Chem. Soc.*, **89**, 2401 (1967)] have studied the nmr of VII in greater detail and have also assigned the 5-Hz coupling to H_1H_2.

(21) F. R. Jensen and J. J. Miller [*Tetrahedron Lett.*, No. 40, 4861 (1966)] have recently assigned the same structure to IV on the basis of a comparison of the nmr spectra of IV and its C-3 epimer. However, see ref 20 for proton assignments.

(22) M. M. Kreevoy and J. F. Schaefer, *J. Organometal. Chem.*, **6**, 589 (1966).

(23) (a) R. K. Bly and R. S. Bly, *J. Org. Chem.*, **28**, 3165 (1963); (b) R. S. Bly, R. K. Bly, A. O. Bedenbaugh, and O. R. Vail [*J. Amer. Chem. Soc.*, **89**, 881 (1967)] have more recently documented this *endo* mercury attack by obtaining both *cis-exo* and *trans* cyclic mercurials from the oxymercuration of *syn*-7-(2-hydroxyethyl)norbornene.



(13)

IX

nmr
H_A, τ 5.25
(doublet, J = 2.3 Hz)
H_B, τ 7.0
(multiplet, J = 2 Hz)

The signal from proton A appears as a doublet with J = 2.3 Hz. If proton B were in the *cis-endo* position, we would expect an AB coupling of 6 or 7 Hz (Table I). The splitting found, 2.3 Hz, indicates that proton B is in the *exo* position and that protons A and B are in a *trans* orientation. The *exo* assignment for proton B is further substantiated by the complexity of its nmr signal, due to bridgehead *exo* proton coupling. Another interpretation of the nmr spectrum of IX is that H_A and the 7-*anti* proton are coupled (J = 2.3 Hz) and that J_{AB} = 0 Hz. This would not be unreasonable because the dihedral angle between protons A and B would again be ~100° (see Figure 1). Nevertheless, this interpretation again indicates protons A and B to be in a *trans* orientation. Thus, we believe that the chloromercuri group must be *endo* in this mercurial and that the initial mercuric ion attack was in an unprecedented manner from the *endo* side.[23b]

III. The Effect of Neighboring Groups on the Oxymercuration of Norbornenes Not Leading Entirely to Ring Closure.—To see if neighboring groups, which did not lead to ring closure, affected the oxymercuration of norbornene, a study was made of the oxymercuration of *endo*-5-cyano- and *endo*-5-carbomethoxy-2-norbornenes.

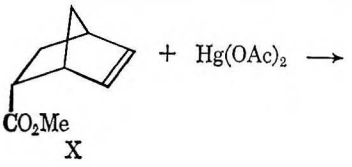
In Scheme I are summarized the results for the oxymercuration of *endo*-5-carbomethoxy-2-norbornene (X). Henbest[13] has reported that the oxymercuration of this ester in methanol gave exclusively lactone IV; so it was not surprising to find the lactone as the exclusive product when 25% acetone–water was used. However, when carefully dried methanol was used, no lactone was found. The nmr spectrum of the product, a clear liquid, indicated that the signal from proton 3 overlapped with that from an O–Me group. A careful examination indicated that the downfield Hg^{199}–H side band consisted of a doublet with $J \simeq 7$ Hz. Thus it is reasonable that the main peak was a doublet with $J \simeq 7$ Hz and that the major product is likely the *cis-exo*-3-methyl ether (XII). Henbest and Nichols[13] possibly used wet methanol.

Using acetic acid as solvent, oxymercuration of X also afforded no lactone but gave an 80% yield of sharp melting solid the elemental analysis and ir spectrum of which agreed with the 3-acetoxy structure XI (R = Ac). In the nmr spectrum of this compound proton 3 appeared as a doublet with J = 6.9 Hz indicating that the product had a *cis-exo* configuration. Thus it is seen that in the oxymercuration of this ester either *cis* or *trans* addition can be obtained by making small changes in the solvent.

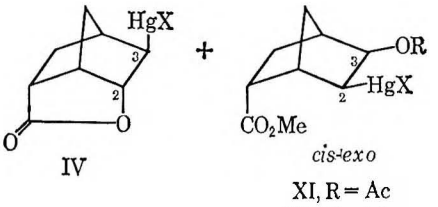
In the mercuric acetate treatment of *endo*-5-cyanonorbornene (XIII), three separate products could be isolated: two sharp-melting crystalline solids and a liquid residue. The properties of these products are summarized in Scheme II. Based on their nmr spectra the solids were assigned the *cis-exo* configurations shown. Also, acetylation of the alcohol (XV) gave the acetate (XIV). The oil showed a strong absorbtion at 5.85 μ in the infrared and showed a doublet at τ 5.87 ($J_{2,3}$ = 5.0 Hz) in its nmr spectrum. This constituent was thought to be the *trans* lactam shown. That it was not an acetate was obvious from the fact that this product was also obtained with $Hg(NO_3)_2$. However, efforts to purify this component by inducing crystallization or by chromatography on deactivated

SCHEME I

EFFECT OF REACTION CONDITIONS ON THE OXYMERCURATION OF *endo*-5-CARBOMETHOXY-2-NORBORNENE[a] (X)



X



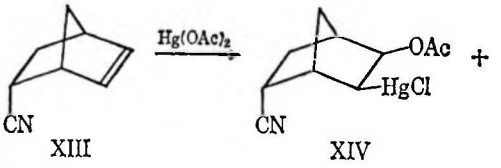
IV XI, R = Ac
XII, R = Me

		IV	XI, XII
X	25% acetone–H_2O, HOAc	90%	0%
X		0%	80% white solid, Mp 150.5–151.0°, Nmr $J_{2,3}$ = 6.9 Hz
X	anhydrous MeOH	0%	100% oil, Nmr (Hg^{199}–H side band) $J_{2,3} \cong 7$ Hz

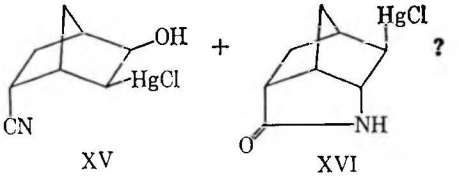
[a] X = Cl. In all cases the product was treated with sodium chloride to obtain the more stable RHgCl.

SCHEME II

OXYMERCURATION OF *endo*-5-CYANO-2-NORBORNENE

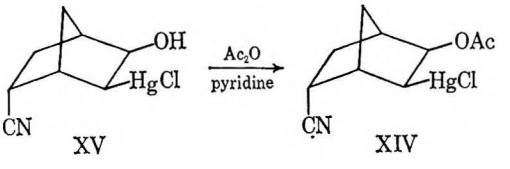


XIII XIV



XV XVI

	XIV	XV	XVI
Mp, °C	171.5	154–155	Liquid?
Ir spectrum, μ	5.78	2.75	5.85
Nmr spectrum, ppm, doublet	5.07 ($J_{2,3}$ = 7.0 Hz)	3.94 ($J_{2,3}$ = 6.9 Hz)	4.13 ($J_{1,2}$ = 5.0 Hz)

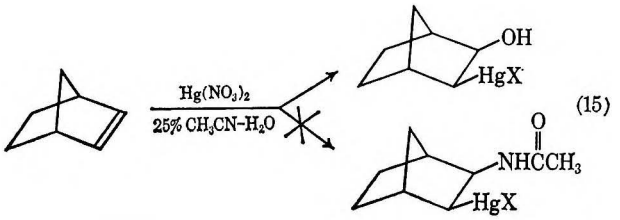


(14)

XV XIV

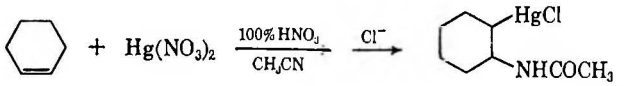
alumina (2% water) have failed, and no sample has been prepared pure enough for elemental analysis.

Experiments have shown that $Hg(NO_3)_2$ fails to react with aqueous acetonitrile at room temperature. Also, the oxymercuration of norbornene in 25% acetonitrile yielded only the *exo-cis*-2-chloromercuri-3-norborneol, and no (<1%) amide could be detected by infrared spectroscopy.



(15)

Wright[24a] has recently reported the formation of such amides when anhydrous nitric acid was present in acetonitrile solvent. These conditions are similar

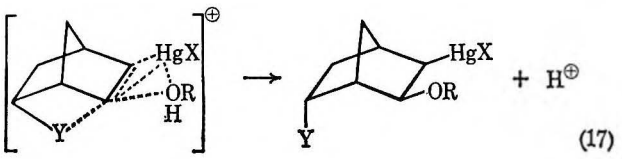


(16)

to those used for the Ritter reaction.[24b] The fact that the cyclic lactam (XVI) is formed rapidly at room temperature under very mild conditions indicates that it is important that the nitrile group be in close proximity to the double bond.

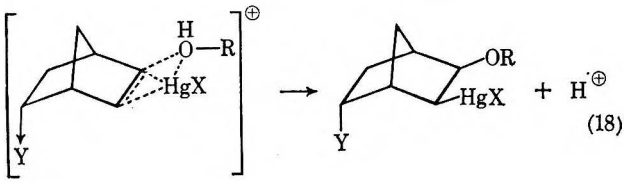
Since each of these products shown in Scheme II gave rise to an nmr doublet in a different position, an nmr spectrum of a mixture could be used as a simple means of analysis. Utilizing this, the effect of reaction conditions on product yields was studied, and the results are summarized in Scheme III. Since the acetate and the alcohol had a tendency to crystallize during the nmr analysis, the yields of these compounds represent a minimum figure, while that of the lactam is a maximum. Based on reproducibility and comparison with the values obtained by direct isolation, it is estimated that the maximum error is on the order of 5%. The product ratios shifted drastically with changing reaction conditions. Thus it was found that the addition of an equimolar amount of sodium acetate changed the yield of acetate and alcohol from 9 and 79% to 60 and 28%. Such changes in product composition were observed with norbornene[4a,b,24c] and bicyclo[2.2.2]octene.[4c]

Since XI, XIV, and XV are sharp melting, have sharp nmr doublets for proton 3, and are obtained in high yield, it is felt that only one of the two possible isomers is formed. Because there seems to be no evidence for rate acceleration from a neighboring group in the formation of these *cis* products (see Experimental Section), we can probably rule out a transition state in which the mercury is unsymmetrically displaced toward position 3. It is more likely that the inductive or field



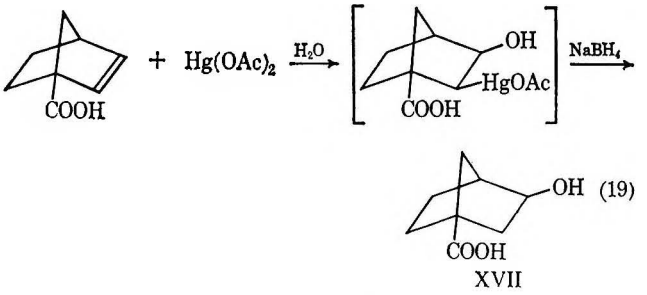
(17)

effect exerted by the cyano and ester groups makes the unsymmetric transition state having less positive charge near the substituted position the one of lowest energy,[25a]



(18)

The oxymercuration of 1-carboxynorbornene[25b] gives the product which is predicted by this hypothesis.



(19)

XVII

The hydroxy acid (XVII) differs from the known 2-*exo*-hydroxynorbornane-1-carboxylic acid.[26] Therefore, it is felt that these products have the chloromercuri group in position 2, although our evidence is equivocal on this point.

SCHEME III

EFFECT OF REACTION CONDITIONS ON THE OXYMERCURATION OF *endo*-5-CYANO-2-NORBORNENE

		XIV	XV	XVI
1.	XIII + $Hg(OAc)_2$ —HOAc→	100%	...	...
2.	XIII + $Hg(OAc)_2$ —25% acetone–H_2O→	9.4%	78.6%	12.0%
3.	XIII + $Hg(OAc)_2$ (0.1 *M*) —25% acetone–H_2O, 0.1 *M* NaOAc→	59.7%	27.5%	12.8%
4.	XIII + $Hg(NO_3)_2$ —25% acetone–H_2O→	...	86%	14%
5.	XIII + $HgCl_2$ —25% acetone–H_2O→	...	97%	3%

Discussion

It is now clear that *cis* additions to norbornenes and other strained olefins can be changed to *trans* additions by changes in either the rigidity of the olefin or in the availability of nucleophilic groups for *trans* attack. Whereas either acids or mercuric salts add to norbornenes *cis-exo* in the absence of neighboring groups (eq 3 and 5), the presence of neighboring groups causes both reactions to occur *trans* (eq 11 and 12). Indeed, eq 13 indicates that neighboring-group participation causes *trans* oxymercuration which places the mercury

(24) (a) D. Chow, J. H. Robson, and G. F Wright, *Can. J. Chem.*, **37**, 1328 (1965); (b) J. J. Ritter, *J. Amer. Chem. Soc.*, **70**, 4045, 4048 (1948); (c) M. J. Abercrombie, A. Rodgman, K. R. Bharucha, and G. F Wright, *Can. J. Chem.*, **37**, 1328 (1959).

(25) (a) We have recently observed that mercuric acetate in methanol reacts with norbornene 300 times faster than with 5-cyanonorbornene. (b) We are grateful to Dr. Richard Alden who prepared and oxymercurated this olefin for another project.

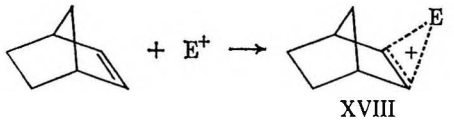
(26) W. R. Vaughan, R. Caple, J. Csapilla, and P. Scheiner, *J. Amer. Chem. Soc.*, **87**, 2204 (1965).

in the very unfavorable *endo* position.[23b] These results make it clear that those features which bring about either *cis* addition or rearrangements during electrophilic addition to norbornenes are not so strongly directing as is a neighboring hydroxyl or carboxyl function.[27] Since hydroxyl and carboxyl are not very good neighboring groups,[28] these findings set a rather low limit on the size of the much discussed steric and electronic effects in the norbornyl system.[29]

Oxymercuration is generally described as a two-step process.[30] Our finding (Scheme III, reactions 3 and 4) that approximately the same ratio of lactam to *cis-exo* product is formed under widely differing conditions agrees with this postulate. Alternatively, one-step concerted *trans* addition accompanied by one-step molecular *cis* addition would account for these results, but this would require that these two processes respond to changes in the electrophile [*e.g.*, $Hg(OAc)_2$ *vs.* Hg(OAc)(OH)] in the same way.

In the absence of definitive evidence for concerted addition we will consider this addition as a two-step process and ask the following questions. 1. What determines the direction of the electrophilic attack on norbornene? 2. What determines the position of the nucleophilic attack on the intermediate? Evidence will be presented concerning the first question in the following paper.

It is well known that there is a great preference for *exo* electrophilic attack on norbornenes. The attack of

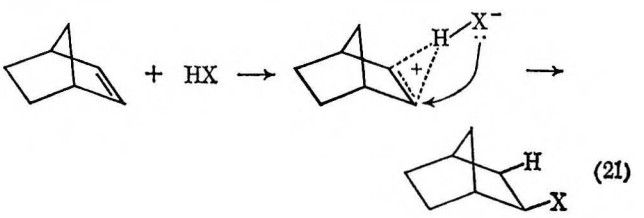


(20)

XVIII

a nucleophile on XVIII may be influenced by several things: steric hindrance by the *endo* C-6 hydrogen, carbon bridging (considered important in solvolyses[28,31]), torsional effects around C-1–C-2,[29] and torsional effects around C-2–C-3.[4] Unfortunately none of these effects can presently be shown to be dominant to the exclusion of the others. Our results in this and previous papers[4] are consistent with a mechanism in which the mercuric salt forms an *exo* complex (XVIII). *endo* attack on this complex by solvent or acetate ion can be retarded by steric hindrance by the *endo* C-6 hydrogen as well as by some nonclassical bridging[31] of C-6. In addition to these, the requirement that the norbornane skeleton be twisted in the transition state for *trans* opening of the complex must also retard *endo* attack.[4b,c] It is not possible to evaluate the relative importance of these effects from the data available.

cis additions, even to norbornene, are not general. Neither halogens nor sulfenyl halides add *cis*. The three effects just mentioned, which are common to all electrophilic additions to norbornene, should lead to some *cis* additions in all cases. We have suggested[4b] that frontside opening of complex XVIII is especially favorable to HX and $Hg(OAc)_2$ additions because the nucleophile is attached to the electrophile.



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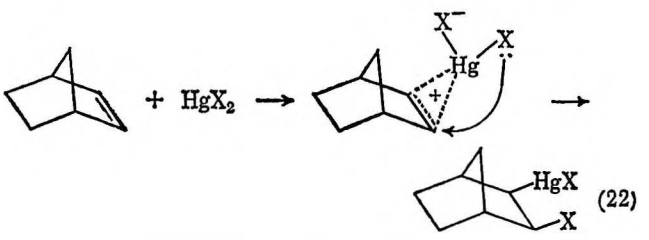
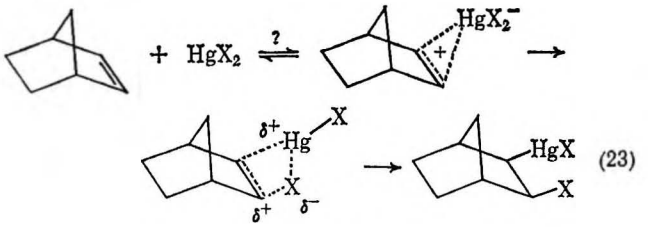


(22)

If the second step is rate limiting, as it probably is in many cases (eq 8), then the mechanisms 21 and 22 could also be described as somewhat polarized molecular or four-centered additions. In spite of many attempts



(23)

to demonstrate the existence of the mercurinium ion,[33,34] it is not possible at present to say whether it exists or, if it does exist, whether it lies so near the starting state as to be stereochemically unimportant.

We conclude that *cis-exo* additions to norbornenes result from a combination of the steric and electronic effects in the norbornene skeleton and the ability of the attacking electrophile to bind both the olefin and a nucleophile which can migrate to carbon. The combination of all these effects does not constitute a driving force sufficient to compete with the *trans* addition of a properly placed internal nucleophile.

Experimental Section

General Remarks.—Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Infracord 137B. Nmr spectra were measured with Varian Associates nuclear magnetic resonance spectrometers (Models HR-60, HR-100, and A-60). Chemical shifts are given in parts per million downfield from tetramethylsilane (δ) or as $\tau = 10 - \delta$. Vapor phase chromatograms were made with an Aereograph Autoprep gas chromatograph model A-700. Deuterium analyses were carried out by Josef Nemeth, Urkana, Ill.

Materials.—All solvents and reagents were commercial reagent grade. In many cases solvents were further purified by use

(27) S. Winstein and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 828 (1948).

(28) P. D. Bartlett, "Nonclassical Ions," Benjamin Publishing Co., New York, N. Y., 1965.

(29) P. R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 701 (1967).

(30) M. M. Kreevoy and M. A. Turner, *J. Org. Chem.*, **30**, 373 (1965).

(31) The failure of 1-methyl group to influence direction of addition in the oxymercuration of norbornene suggests that nonclassical bridging is unimportant in oxymercuration.[32]

(32) H. C. Brown, J. W. Kawakami, and S. Ikegami, *J. Amer. Chem. Soc.*, **89**, 1525 (1967).

(33) J. Halpern and H. B. Tinker, *ibid.*, **89**, 6427 (1967).

(34) S. Wolfe, P. G. G. Campbell, and G. E. Palmer [*Tetrahedron Lett.*, 4203 (1966)] have reported evidence for mercurinium ion. Thus the compound shown is reported to exchange carbon-bound acetate more rapidly than it exchanges mercury-bound acetate in tetradeuterioacetic acid. However, we observe that mercuric acetate exchanges acetates much faster than it adds to norbornene in this solvent.

$$\mathrm{PhCH_2CH(OAc)CH_2HgOAc}$$

of a suitable desiccant followed by distillation.[35] Norbornene, Aldrich Chemical Co., was used without further purification. *endo*-(III) and *exo*-bicyclo[2.2.1]hept-2-ene-5-carboxylic acid, Aldrich Chemical Co., found to be 60% *endo* and 40% *exo*, were used without further purification. *endo*- (V) and *exo*-5-hydroxymethyl-2-norbornene, cyclol, kindly donated by the Interchemical Corp., were reported to be a 80:20 mixture of *endo* and *exo* isomers which was used without further purification. *endo*-5-Cyano-2-norbornene (XIII) was separated from a mixture of the *endo* and *exo* isomers (Aldrich Chemical Co.) by preparative vpc on a 20 ft × 0.375 in. aluminum column packed with 30% phenyldiethanolamine succinate (PDEAS) on Chromosorb P. Reinjection of the *endo* sample gave only one peak. The nmr spectrum (neat) corresponded exactly with that reported.[17a] The *exo* isomer was also isolated and shown to be pure by its vpc. *endo*-5-Carbomethoxy-2-norbornene (X) was obtained by the diazomethane treatment of *endo*-2-norbornene-5-carboxylic acid prepared by the method of Wright[14a] from the *endo-exo* mixture. Vapor phase chromatography with PDEAS column produced only one peak while that of an *endo-exo* mixture gave two. The nmr (neat) spectrum corresponded exactly with that reported.[17a]

Addition to *endo*-2-Norbornene-5-carboxylic Acid (III).—The reaction solution from 40:60 *exo*- and *endo*-2-norbornene-5-carboxylic acid (28.0 g, 0.2 mol), mercuric acetate (64.0 g, 0.2 mol), and 600 ml of 20% acetone–water solution was neutralized with 29.3 g of sodium chloride and 42 g of sodium bicarbonate in 600 ml of water. The resulting precipitate was separated by filtration and slurried with a solution of 15 g of sodium chloride and 15 g of sodium bicarbonate in 300 ml of water and again filtered to yield 68.2 g of a white solid (IV), mp 195–200°. This was recrystallized from 1500 ml of dioxane to yield 21.58 g of a white microcrystalline solid (IV), mp 222–223° (lit. mp 222–224°[13,14a]). The ir spectrum of this solid in a mineral oil mull had a double carbonyl band at 5.61 and 5.67 μ. The nmr spectrum (DMSO-d_6) contained a doublet at 5.29 ppm (J = 5.0 Hz).

This mercurial IV (1.2117 g, 3.24 mmol) was reduced by shaking it with mercury amalgam [4 ml of Hg and 1.03 g of sodium (0.045 g-atom)] in 3 ml of deuterium oxide for 34 hr. This product was neutralized with 2 M hydrochloric acid and extracted with ether to yield 0.3738 g of a white solid (VIID), mp 140–148°. Recrystallization from pentane raised the melting point to 154–155° (lit.[20] mp 154.2–155.2°) for *endo*-5-hydroxybicyclo-[2.2.1]heptane-*endo*-2-carboxylic lactone). The ir spectrum had a carbonyl band at 5.59 μ (CCl_4). The nmr spectrum (CCl_4) contained a doublet at 4.65 ppm (J = 5.5 Hz) (*Anal.* Calcd % excess deuterium: 10.00 atom %. Found: 9.9 atom %).

This deuterated lactone (same melting point, ir and nmr spectrum) was also prepared by treating the sodium salt of acid III with 28% D_2SO_4 (*Anal.* Calcd % excess deuterium: 10.00 atom %. Found: 8.89 atom %). It was found that, if this reaction was carried out at reflux overnight, complete proton scrambling occurs. In a reaction solution in which deuterium (D_2SO_4 + norbornenyl acid) comprised 75.4% of the hydrogen, deuterium analysis indicated 65–75% deuterium in the lactone produced.

The sulfuric acid treatment of the bicyclic acid (III) or 5-cyano-2-norbornene (XIII) produced the nondeuterated lactone (VII) (78% yield), mp 154–155°. Its nmr spectrum (CCl_4) had a quartet at 4.69 ppm (see Figure 1).

Addition to *endo*-5-Hydroxymethyl-2-norbornene, Cyclol (V).—The reaction solution from cyclol (12.4 g, 0.1 mol) and mercuric chloride (19.0 g, 0.07 mol) in 300 ml of 50% acetone–water was filtered and the filtrate washed with 300 ml of hot water and dried at 65° to yield 24.9 g (0.07 mol)[36] of a white solid (VI), mp 227–228° (lit.[12] 228–229°). The nmr spectrum (DMSO-d_6) had a doublet at 5.12 ppm (J = 5.0 Hz).

This mercurial (6.76 g, 18.8 mmol) was reduced by shaking it with mercury amalgum [24 ml of Hg and 5.4 g of sodium (0.220 g-atom)] in 20 ml of deuterium oxide overnight to yield 2.150 g of a light yellow oil. Its nmr spectrum indicates that it was mainly (80+%) cyclol and ~10% the desired cyclic ether (VIIID). Also the presence of a tricyclic compound was indicated by the presence of two quartets (J = 2 Hz) at 0.37 and 0.54 ppm. This product was treated with mercuric chloride (4.95 g, 18 mmol) in 25 ml of methanol and made basic (pH 9) with 2 M sodium hydroxide. The resulting mixture was steam distilled and the distillate extracted with methylene chloride to yield, upon evaporation, 0.3049 g (2.5 mmol) of a waxen solid. This was purified by sublimation 35° (20 mm) to give solid melting 108–116° (lit.[13] mp 103–106°) (*Anal.* Calcd % excess deuterium: 9.17 atom %. Found: 7.85 atom %). The nmr spectrum (CCl_4) of the deuterated cyclic ether had a doublet, J = 4.8 Hz, at 4.20 ppm.

The same deuterated cyclic ether (identical ir and nmr spectra) was prepared by refluxing cyclol with 15% deuteriosulfuric acid for 1 hr to give a 10% yield of the cyclic ether, mp 87–90° (*Anal.* Calcd % excess deuterium: 9.17 atom %. Found: 10.50 atom %).

The cyclic ether produced from a similar treatment of cyclol with sulfuric acid, mp 83–94°, had a quartet in its nmr spectrum (CCl_4) at 4.20 ppm (see Figure 1).

Addition to Norbornenes in Acetic Acid.—It was found that 2 mmol of unsaturated compound and 2 mmol of mercuric acetate could be combined in 1 ml of acetic acid to obtain a homogeneous solution. The nmr spectra of these solutions of mercury adducts could be used to determine their configurations. Table II lists the results for several norbornenes. The acetoxymercurials were isolated by precipitation with 25 ml of saturated sodium chloride solution.

TABLE II

Compound	δ, ppm[a,b]	$J_{2,3}$ Hz	Configuration
Norbornene	5.00	7.0	*cis-exo*
exo-5-Cyanonorbornene	5.06	6.8	*cis-exo*
endo-5-Cyanonorbornene	5.07	7.0	*cis-exo*
endo-5-Carbomethoxynorbornene	5.17	6.9	*cis-exo*

[a] External tetramethylsilane standard. [b] Chemical shift of the proton on the acetoxy-substituted carbon.

The product from norbornene, 0.6274 g (1.66 mmol, 83%) of a white solid mp 125.5–126°, gave on recrystallization from acetone–*n*-heptane white microneedles, mp 130.0–130.4° (lit.[24c] mp 130.8–131.8°).

The product from *exo*-5-cyano-2-norbornene, 0.7105 g (1.73 mmol, 86%) of a white solid, mp 146.8–147.2°, gave on recrystallization from chloroform–*n*-heptane a white crystalline solid, mp 150.0–151.0°.

Anal. Calcd for $C_{10}H_{12}O_2NHgCl$: C, 28.99; H, 2.92. Found: C, 28.82; H, 2.90.

The product from *endo*-5-cyano-2-norbornene, 0.6387 g (1.54 mmol, 77%) of a white solid, mp 170–171°, gave on recrystallization from chloroform–*n*-heptane a white crystalline solid, mp 171.5°.

Anal. Calcd for $C_{10}H_{12}O_2NHgCl$: C, 28.99; H, 2.92; Cl, 8.56. Found: C, 29.21; H, 2.68; Cl, 8.44.

The product from *endo*-5-carbomethoxy-2-norbornene, 0.7101 g (1.59 mmol, 80%) of a white solid, mp 145–149°, gave on recrystallization from chloroform–*n*-heptane a white crystalline solid, mp 150.5–151.0°.

Anal. Calcd for $C_{11}H_{15}O_4HgCl$: C, 29.54; H, 3.38. Found: C, 29.71; H, 3.21.

Addition to *endo*-5-Carbomethoxy-2-norbornene (X).—The reaction mixture of the unsaturated compound (0.3818 g, 2.5 mmol), mercuric acetate (0.7973 g, 2.5 mmol), and 20 ml of 25% acetone–water gave, after treatment with a solution of 0.5 g of sodium chloride and 0.5 g of sodium bicarbonate in 5 ml of water, 0.8456 g of a white solid, mp 203°. The ir and nmr spectra of this product were identical with those of *exo*-5-chloromercuri-*endo*-6-hydroxybicyclo[2.2.1]heptane-*endo*-2-carboxylic lactone (IV).

The reaction mixture of the *endo*-5-carbomethoxy-2-norbornene (0.3801 g, 2.5 mmol), mercuric acetate (0.7947 g, 2.5 mmol), and 20 ml of dry methanol (0.0074% water by Karl Fischer titration) gave, on work-up with 0.5 g of sodium chloride and 0.5 g of sodium bicarbonate, 1.1300 g of a clear viscous liquid. Its ir spectrum ($CHCl_3$) indicated the presence of an acetate group by the band at 5.79 μ. Its nmr spectrum ($CDCl_3$) indicates that the product consists of a mixture of acetate (XI) and methyl ether (XII) in approximately a 1:5 ratio. Although the doublet due to the acetate can be seen at 4.8 ppm (J = 7.0

(35) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1964.

(36) Since a quantitative yield of cyclic ether was obtained in the presence of 20% *exo*-5-hydroxymethyl-2-norobornene, the *endo* compound must react much faster (>100 times) than its *exo* isomer. Competition reactions with norbornene confirm this finding. Similar rate enhancement by neighboring-group participation was observed in the oxymercuration of 1-penten-5-ol.[23]

Hz), that due to the ether at ~4.5 ppm is obscured by the CH_3O—C(=O)- and CH_3—O- peaks. However, one can see its vicinal $Hg^{199}H$ side band 50 cps downfield which appeared as a doublet $J \cong 7.0$ Hz.

Addition to *endo*-5-Cyano-2-norbornene (XIII).—The reaction mixture of unsaturated compound (1.1908 g, 10.0 mmol) and mercuric acetate (3.1838 g, 10.0 mmol) in 100 ml of 25% acetone was worked up with a solution of 10 g of sodium chloride and 10 g of sodium bicarbonate in 200 ml of water. This mixture was continuously extracted with chloroform for 40 hr to yield 3.8236 g of a viscous orange oil. This product gave a precipitate with 2% ethanolic silver nitrate solution and a gray precipitate with ethanolic sodium borohydride. Its ir spectrum ($CHCl_3$) had bands at 2.79 and 5.79 μ (broad). Its nmr spectrum ($CHCl_3$) had doublets at 4.13 (J = 5.0 Hz), 3.98 (J = 6.8 Hz), and 5.0 ppm (J = 7 Hz). These were assigned to XVI, XV, and XIV, respectively. On standing in chloroform 3.1182 g of this product gave 1.7979 g of a white crystalline solid, mp 149.5–151.5°. Recrystallization from chloroform–*n*-heptane raised the melting point to 154–155°. Its ir spectrum (Nujol mull) had a band at 2.75 μ and showed no evidence of a carbonyl band. Its nmr spectrum (acetone-d_6) had a doublet at 3.94 ppm (J = 6.9 Hz), and therefore it was assigned structure XV.

Treatment of 0.3014 g of this product with 2 ml of acetic anhydride and 0.5 ml of dry pyridine yielded 0.2776 g of acetate (XIV), mp 170–170.2°, which was shown, by the method of mixture melting points and by exact correspondence of ir spectra, to be the same acetate obtained previously from the acetic acid–$Hg(OAc)_2$ treatment of *endo*-5-cyano-2-norbornene.

The reaction mixture from *endo*-5-cyano-2-norbornene (0.5979 g, 5.0 mmol), mercuric nitrate (1.7096 g, 5.0 mmol), and 50 ml of 20% acetone, after work-up with a solution of 1 g of sodium chloride and 1 g of sodium bicarbonate and extraction with chloroform, gave 2.1828 g of a gummy white solid. Slow crystallization from chloroform yielded 1.2679 g of alcohol XV, as indicated by the melting point (154–155°), mixture melting point, and ir and nmr spectra of the sample of alcohol previously obtained. The ir spectrum ($CHCl_3$) of the mother liquor had a carbonyl band at 5.83 μ. Its nmr spectrum showed a doublet at 4.12 ppm (J = 5.0 cps) and a multiplet at 7.65 ppm (olefin?). On the basis of this spectral evidence the lactam structure (XVI) was assigned to this residue (λ_{max} of γ-lactams, 5.88 μ). Further attempts to isolate this lactam by inducing crystallization or by chromatography on alumina (2% H_2O) failed to give a sample suitable for analysis.

Addition to Norbornene in Presence of Acetonitrile.—The reaction mixture of norbornene (0.3681 g, 4.0 mmol), mercuric nitrate (1.3516 g, 4.0 mmol), and 40 ml of 25% acetonitrile–water gave, after work-up with 1.2 g of sodium chloride and 1.2 g of sodium bicarbonate in 15 ml of water, 0.9517 g (69.4%) of 2-chloromercurinorborneol, mp 120–125° (lit.[24c] mp 131–131.5°). Chloroform extraction of the aqueous filtrate gave 0.3144 g (23%) more solid. The ir spectrum (Nujol mull) of this and the above product gave only a negligibly small carbonyl band, indicating less than 1% carbonyl-containing product present.

Registry No.—IV, 16487-00-6; VI, 16487-01-7; VII, 5257-51-2; VIII, 16487-03-9; IX, 16487-23-3; XI, 16487-24-4; XII, 16487-25-5; XIV, 16487-26-6; XV, 16487-27-7; XVI, 16487-28-8; product from *exo*-5-cyano-2-norbornene, 16487-04-0.

Acknowledgment.—The authors wish to thank the National Institutes of Health for a Postdoctoral Fellowship (A. F.), Varian Associates for several spectra, and the National Science Foundation for a grant (GP-242).

Oxymercuration of Strained Olefins.[1] The Effect of *syn*-7 Substituents

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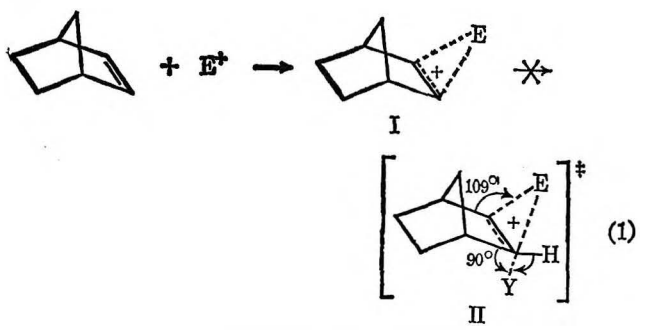
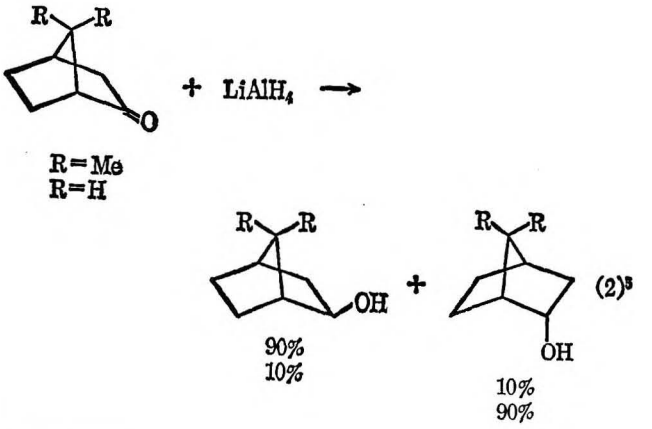
Received July 11, 1967

Oxymercuration of 1,4,7,7-tetramethylnorbornene produces 100% *cis-exo* product. Furthermore, *syn*-7-bromonorbornene oxymercurates completely *cis-exo*. These results are a strong indication that *cis-exo* electrophilic additions to norbornenes do not result from steric hindrance toward *endo* attack. Since the highly predominant *exo* attack on norbornenes by electrophiles is not of steric origin, it is concluded that it is an electronic effect.

The *cis* electrophilic additions to strained bicyclic olefins has been attributed to a twist strain introduced in the second step of the usual two-step *trans* addition.[3]



This postulate does not explain the highly selective *exo* attack by the electrophile to give I, and this selectivity is generally attributed to steric effects.[4] If this is true, then the addition to *syn*-7-substituted norbornene should occur *cis-endo*. Such substitution changes th stereochemistry of other reactions in the bicyclohepty system[4b] (eq 2 and 3).



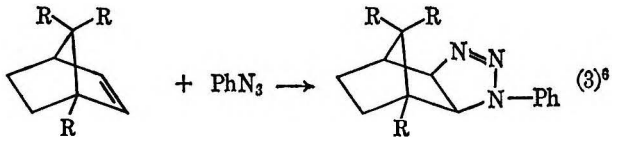
(1) Supported in part by the National Science Foundation, Grant GP-2829.

(2) National Institutes of Health Postdoctoral Fellow, 1964–1965.

(3) T. G. Traylor and A. W. Baker, *J. Amer. Chem. Soc.*, **85**, 2746 (1963).

(4) (a) See, *e.g.*, J. A. Berson, "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, p 166; (b) p 129; (c) H. C. Brown, *Chem. Brit.*, **2**, 199 (1966).

(5) R. Howe, E. C. Friedrich, and S. Winstein, *J. Amer. Soc.*, **87**, 379 (1965).

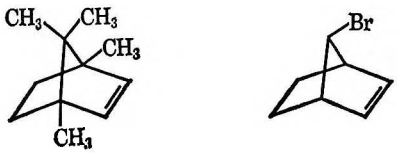


R = Me, no reaction
R = H, *exo* addition

An alternative suggestion is that $Hg(OAc)_2$, HOAc, or HBr can add to norbornene by a simple four-center transition state which would be similar in steric effects to eq 3. This would also predict that *syn*-7-substituted norbornenes should give substantial *cis-endo* oxymercuration products. We have, therefore, investigated the effect of *syn*-7 substituents on oxymercuration of norbornene.

Results

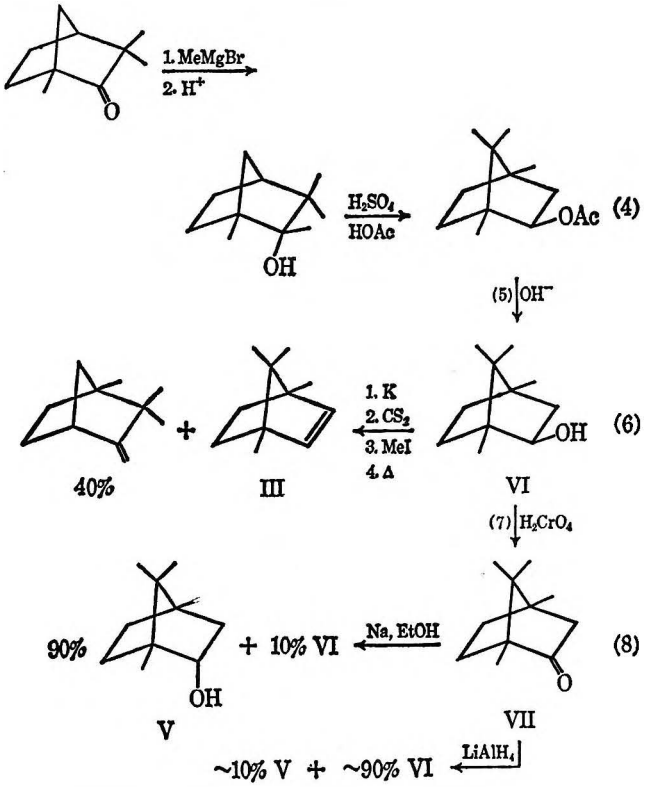
We have prepared 1,4,7,7-tetramethylnorbornene (III)[7] and *syn*-7-bromonorbornene (IV)[8] by known methods. The structure of III was confirmed by its nmr spectrum and by its chemistry, described below.



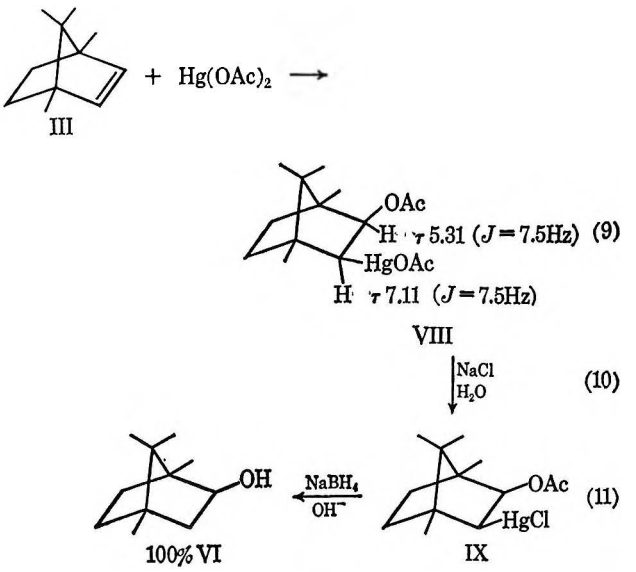
III IV

Preparation of the 4-Methylborneol (V) and 4-Methylisoborneol (VI).—The method of Shavrygin[7b] was used to prepare 4-methylisoborneol (VI) from fenchone. This alcohol was converted to 1,4,7,7-tetramethylnorbornene and to the ketone and thence to the isomeric alcohols V and VI as shown in Scheme I. The reductions of 4-methylcamphor (VII) to V with Na in ethanol[9] and to VI with $LiAlH_4$ confirm the assigned structures.[4b]

SCHEME I



Addition of Mercuric Acetate to III.—Combination of equimolar quantities of III and mercuric acetate in acetic acid and examination of the solution by nmr indicated formation of an acetoxymercuri acetate with the proton α to the OAc *cis* to the proton α to the HgOAc group as shown by clean doublets at τ 7.11 and 5.31 with coupling constants of J = 7.5 Hz.[3,10] (The nmr studies in this system are much simplified by the absence of 1,4,7,7 hydrogens.) The mercurial was isolated by dilution with aqueous sodium chloride and reduced with $NaBH_4$; the product was hydrolyzed and compared with V and VI by glpc. The alcohol proved to be VI and no trace of V was seen. The reactions just described therefore occur as is shown in eq 9–11.



III VIII 100% VI IX

The nmr spectrum of the reaction solution was identical with that of purified IX (except for the HgOAc hydrogens which are absent in IX and masked by the solvent peak in the reaction solution). Thus, not more than about 5% of isomeric mercurials was present. The positions of the sharp 7-methyl group resonances are very sensitive to 2 and 3 substitution.

In acetic acid the addition is slowly reversible. When an equimolar amount of norbornene was added to the solution of VIII, the nmr spectrum showed a reappearance of III, disappearance of norbornene, and formation of *exo*-3-acetoxy-*exo*-norbornylmercuric acetate.[3,11a-c] The half-life of this exchange was about 18 hr at 25°. Norbornene adds free mercuric acetate in acetic acid practically instantaneously. When a solution of VIII and norbornene was made 0.1 *M* in toluenesulfonic acid,[11d] the exchange half-time decreased to 30 min. On the other hand, an acetic acid solution of VIII was

(6) K. Alder, G. Stein, and S. Schneider, *Ann.*, **515**, 185 (1935).

(7) (a) A. I. Shavrygin, *Zh. Obshch. Khim.*, **9**, 516 (1939); *Chem. Abstr.*, **34**, 404 (1940). (b) A. I. Shavrysin, *Zh. Obshch. Khim.*, **18**, 49 9(1948); *Chem. Abstr.*, **42**, 7276*h* (1948).

(8) H. Kwart and L. Kaplan, *J. Amer. Chem. Soc.*, **76**, 4072 (1954).

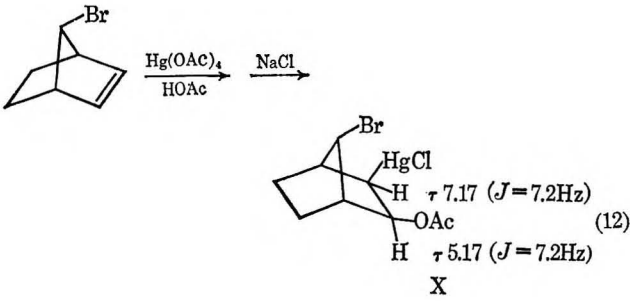
(9) S. Nametkin and A. Churchrikoff, *Ann.*, **432**, 207 (1923); see also S. Nametkin and L. Brüssoff, *ibid.*, **459**, 144 (1927).

(10) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961); P. Laszlo and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **85**, 2709 (1963); J. C. Davis, Jr., and T. V. Van Auken, *ibid.*, **87**, 3900 (1965).

(11) (a) T. G. Traylor and A. W. Baker, *Tetrahedron Lett.*, No. 19, 15 (1959). (b) T. G. Traylor, *ibid.*, **86**, 244 (1964). (c) A. Factor and T. G. Traylor, *J. Org. Chem.*, **33**, 2607 (1968). (d) Acid-catalyzed deoxymercuration has been studied by M. M. Kreevoy and M. A. Turner, *J. Org. Chem.*, **30**, 373 (1965), and previous papers.

found to retain its nmr spectrum for at least 50 days (65 half-lives). In the presence of toluenesulfonic acid, VIII isomerized to the other isomers, as shown by the disappearance of the original nmr absorptions and the appearance of new peaks at slightly different positions.

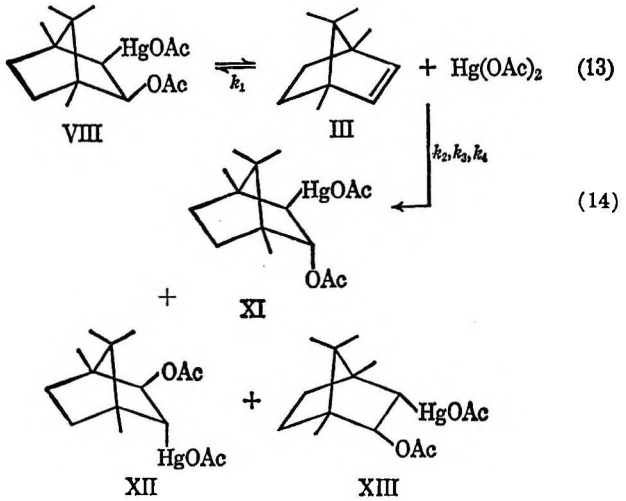
Addition of Mercuric Acetate to *syn*-7-Bromonorbornene.—The addition of equimolar mercuric acetate to *syn*-7-bromonorbornene[8] in acetic acid and pouring the resulting solution into aqueous sodium chloride produced an 86% yield of a mercurial whose melting point did not change upon recrystallization. The protons on carbons 2 and 3 exhibited simple doublets (J = 7.2 Hz) in the nmr spectrum. The fact that neither doublet was resplit by bridgehead protons (usually J = 4–5 Hz for *exo* protons) indicates that both protons were *endo*.[3,10] The splitting, J = 7.2 Hz, is also in agreement with the *cis-endo* configuration of these hydrogens. Thus addition occurred *cis-exo*.



This structure proof was not carried further because we feared the toxicity of the bromohydrin which would result from the reduction of X.[12] However, the nmr spectrum alone is quite definitive.[10]

Discussion

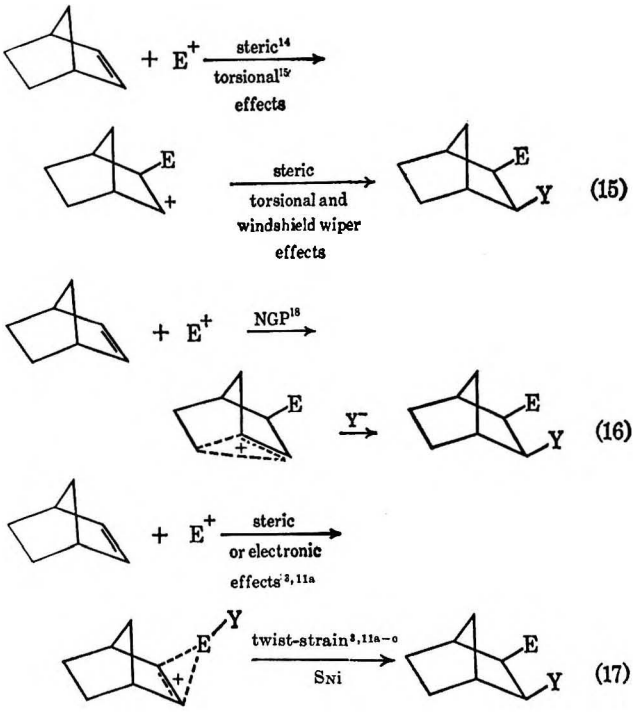
The high degree of stereospecific *cis-exo* addition to III was demonstrated by a kinetic comparison using the reversible oxymercuration scheme shown in eq 13 and 14.



We have determined the rate of elimination from VIII under oxymercuration conditions by trapping the mercuric acetate with norbornene. After 65 half-lives for elimination followed by readdition (reaction 13), the nmr spectrum revealed no isomeric products. (With added acid to accelerate reaction such isomers were detected.)

Because borneol is more stable than isoborneol, it is reasonable to conclude that VIII is the least stable of the isomers VIII, XI, XII, and XIII. We therefore suggest that the rates of formation of XI, XII, and XIII (reaction 14) are so much slower than that of VIII (k_1) that during 65 half-lives for exchange of VIII no detectable amounts of the other isomers are formed. If $k_2 = 10^{-2}\ k_1$ then at least 25% of XIII should have been formed. In addition, we could not detect V in the product of the reduction of VIII with sodium borohydride. (As much as 0.5% could have been found.) Thus the preference for *exo* addition (*exo*/*endo* > 10^3) rivals that displayed by the bornyl cation.

It has therefore been established that bicyclo[2.2.1]-heptenes react with electrophiles with high preference on the *exo* side *even in the presence of 7,7-dimethyl groups*.[13–15] Three different reasons have been offered for *exo* stereospecificity.



The literature abounds[3,11a–c] with evidence that resonance effects are not significant in oxymercuration and that oxymercuration does not proceed through classical carbonium ions such as that shown in reaction 15. Brown, Kawakami, and Ikegami[14a] have recently re-

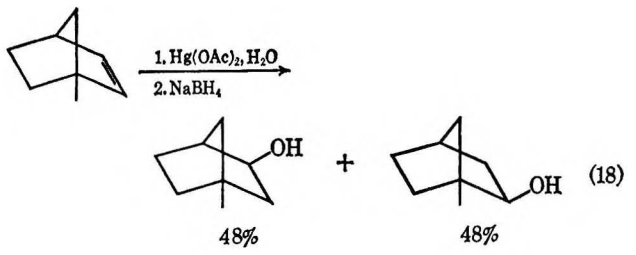
(12) S. Winstein, *J. Amer. Chem. Soc.*, **83**, 1516 (1961).

(13) Since this work was first submitted for publication, other examples of *cis-exo* electrophilic additions in the presence of 7,7-dimethyl groups have been reported[14a,b] and given interpretations[14a,b,15] with which the authors do not agree.[16] However, our priority in this discovery is acknowledged.[14a,15]

(14) (a) H. C. Brown, J. H. Kawakami, and S. Ikegami, *J. Amer. Chem. Soc.*, **89**, 1525 (1967); (b) H. C. Brown and K.-T. Liu, *ibid.*, 3900 (1967); (c) see ref 14b, footnote 15.

(15) (a) P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 701 (1967); (b) *ibid.*, **89**, 3901 (1967).

(16) NOTE ADDED IN PROOF.—Professor Thomas Bond (private communication) has observed exclusive *cis*-hydroxymercuration of bicyclo[2.2.1]-hexene. This result, predicted by the twist-strain theory of *cis* addition,[3,11a] is inconsistent with the proposals that torsional[15] or steric effects[14] are responsible for *cis* additions.

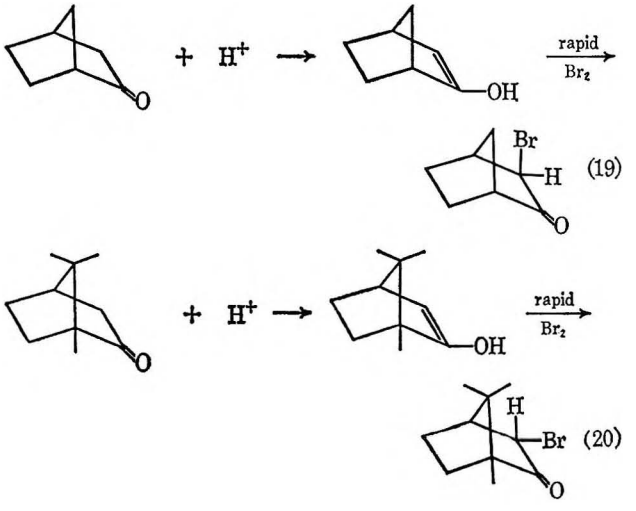


(18)

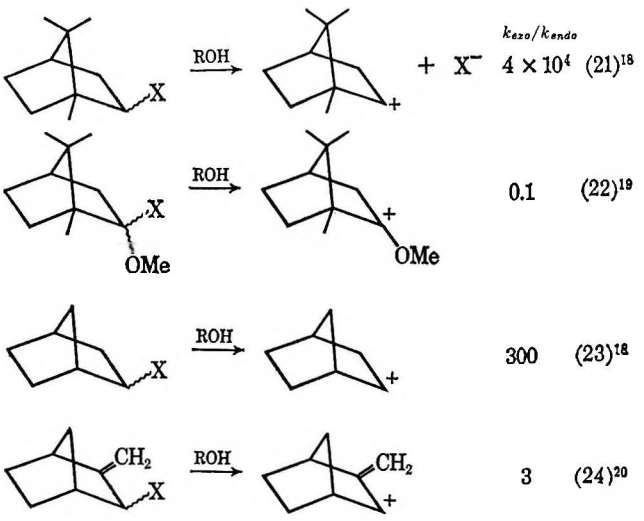
ported the result in eq 18 which reiterates these conclusions and indicates that resonance effects such as that shown in eq 16 do not account for *cis* oxymercuration of norbornenes. If oxymercuration involves neither reaction 15 nor 16, any discussion of classical *vs.* nonclassical carbonium ions can be omitted (see below).

The high stereospecificity in the addition to the sterically hindered olefins III and IV is not easily accommodated by reaction 17 which is similar to a molecular addition. Such processes either do not occur (phenylazide addition)[6] or lead to substantial *endo* product (hydroboration)[14c] when carried out on 7,7-dimethylbicyclo[2.2.1]heptenes. These observations seem to eliminate simple steric effects (which should have yielded some *endo* oxymercuration product) or torsional effects[15a] (according to which oxymercuration and hydroboration should give the same stereochemistry). It is therefore concluded that the stereochemistry in oxymercuration of bicycloheptenes is determined primarily by some electronic effect.

The acid-catalyzed brominations of camphor[17] and norcamphor[17a] agree with this postulate (with respect to the direction from which the electrophile attacks). In such brominations the rates are limited by enol formation, and the product is therefore determined kinetically.

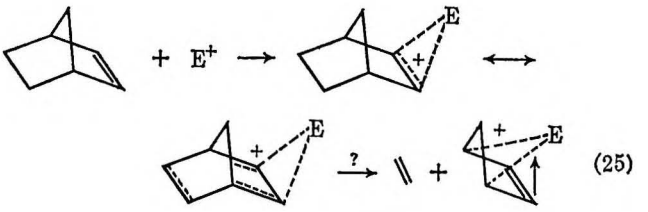


Such changes from *exo* to *endo* reactions upon external stabilization of positive charge have been observed previously.[18-20] There seems to be an electronic difference



in the *exo* and *endo* sides of the norbornene which is removed (swamped out)[20] by external stabilization. This high stereospecificity holds only for electrophilic additions and carbonium ion reactions.

If effects such as those shown in eq 15 or 16 cannot be used, then an additional possibility for a stereospecific electronic effect must be offered (with some reluctance). One such possibility might be an electrophilic catalysis of a partial reverse Diels–Alder reaction. Such a for-



(25)

mulation is symmetry allowed; it predicts neither rearrangement nor effects of 1-alkyl substitution but does require *exo* attack by electrophiles. However, neither this nor any other mechanism which has been suggested accommodates all the observations in a satisfactory manner, and the reason for the observed high *exo* stereospecificity in these *cis* electrophilic additions essentially remains obscure.

Effects of Added Sodium Acetate.—Of all the evidence against carbonium ion formation during oxymercuration the authors consider the effects of added sodium acetate[11a] to be the most decisive. When sodium acetate is included in an oxymercuration mixture in water or methanol, both *cis* and *trans* oxymercurations proceed more slowly owing to the reduced electrophilicity of the mercury salt. However this condition elicits completely different behavior from *cis* and *trans* oxymercurations. The inclusion of sodium acetate does not alter the *trans* oxymercuration product but causes *cis* oxymercurations to produce *cis*-acetoxyalkylmercury salts. Examples of both kinds of response are shown in Table I.[3,11b,21] These observations are not compatible with a mechanism of *cis* oxymercuration in which water and acetate ion compete for a carbonium ion. Rather they require that *cis* and *trans* oxymercurations involve different mechanisms.

We also observed that sodium acetate has a somewhat greater effect on product composition in oxy-

(17) (a) W. G. Woods and J. D. Roberts, *J. Org. Chem.*, **22**, 1124 (1957). (b) F. S. Kipping and W. J. Pope, *J. Chem. Soc.*, **73**, 576 (1893); (c) F. H. Lees, *ibid.*, **83**, 145 (1903).

(18) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 129, 131.

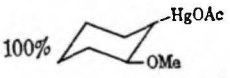
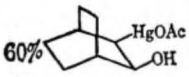
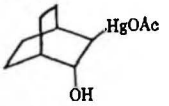
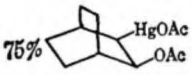
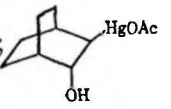
(19) T. G. Traylor and C. L. Perrin, *J. Amer. Chem. Soc.*, **88**, 4934 (1966).

(20) C. F. Wilcox, Jr., and R. G. Jesaitis, *Chem. Commun.*, 1046 (1967).

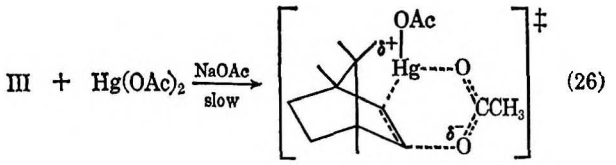
(21) M. J. Abercrombie, A. Rodgman, K. R. Bharucha, and G. F Wright, *Can. J. Chem.*, **37**, 1328 (1959).

TABLE I

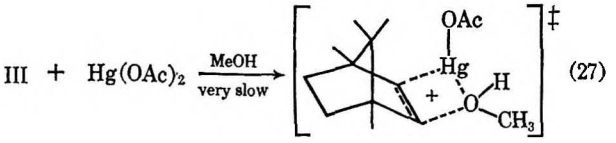
EFFECTS OF ADDED SODIUM ACETATE ON THE PRODUCTS OF OLEFIN OXYMERCURATIONS WITH $Hg(OAc)_2$

Olefin	Solvent	Concn of NaOAc, *M*	Products	Ref
Cyclohexene	MeOH	0.1	100% 	3
	H_2O–acetone	0	60%  + 40% 	11b
	H_2O–acetone	0.1	75%  + 25% 	11b
				
Norbornene	MeOH	0	60–80%	21, this work
Norbornene	MeOH	0.1	20–40%	21, this work
				
III	MeOH	0	70%	This work
III	MeOH	0.1	0	This work

mercuration of III than in oxymercuration of norbornene. This result at once confirms *cis* addition to III and suggests that methoxymercuration of norbornene proceeds through a four-center transition state. Such a four-center reaction would be retarded more by 7,7-dimethyl groups than would be the six-centered transition state for addition of the elements of mercuric acetate.[11a]



(26)



(27)

The *cis* additions of acids to norbornenes[22-24] have (with one exception)[14b] likewise been interpreted as rather polarized molecular additions. Unlike oxymercuration, acid additions are usually accompanied by some carbonium ion formation,[22,23] and this complicates the interpretations of such reactions.

Relationship to the Nonclassical Ion Problem.—The available data favor mechanisms of *cis-exo* additions in which both electrophile and nucleophile are strongly bonded to the respective carbons in the transition state. On the other hand, these results might be due to steric factors which respond only to electrophilic reagents and the intermediates might be classical carbonium ions which behave in a rather unprecedented manner. However, before these additions can be related to solvolysis reactions, it is necessary to prove that they indeed proceed through the same intermediates as those involved in solvolysis. Without this proof conclusions concerning the "need to reconsider the proposed σ-bonded intermediates"[14] derived from additions to olefins are invalid.

It might be asked whether the "polarized molecular addition" of eq 17 has a transition state whose charge distribution resembles that of the localized (eq 15) or σ-bridged (eq 16) carbonium ion. Equation 18 suggests that it resembles more closely the distribution in the localized (classical) carbonium ion, but this says nothing about the existence of nonclassical ions.

Experimental Section[25]

Reagents and Procedures.—Melting points were obtained using sealed capillaries in a Thomas–Hoover apparatus and are not corrected. Infrared spectra were determined in carbon tetrachloride solution using a Perkin-Elmer 137 Infracord spectrophotometer. Nmr spectra were determined on a Varian HR-60 instrument; chemical shifts are reported in units of τ and were calibrated by the side-banding technique. Tetramethylsilane was used as an internal standard in carbon tetrachloride solutions; alkyl resonances calibrated in this way were used as internal standards in acetic acid solutions. Gas chromatographic analyses and separations were carried out on a Wilkens "Autoprep" instrument using the columns named.

Acetic acid was purified by distillation from potassium permanganate followed by distillation from triacetyl borate.[26] Tetrahydrofuran was purified by stirring over potassium hydroxide and distilling from lithium aluminum hydride.[7]

Preparation of 1,4,7,7-Tetramethylnorbornene (III).[7]—Crude 4-methylisoborneol (VI) was prepared by treating Eastman Organic Chemicals fenchone (85% pure by glpc) with methylmagnesium bromide, treating the crude product of this reaction with acetic acid–sulfuric acid at 65° for 24 hr and saponifying the resulting acetate. A recrystallized sample of this product melted at 188.5–191 (lit.[7b] mp 190–191°). The crude alcohol

(22) (a) S. J. Cristol, W. R. Seifert, D. W. Johnson, and J. B. Jurale, *J. Amer. Chem. Soc.*, **84**, 3918 (1962); (b) S. J. Cristol, L. K. Gaston, and D. W. Johnson, *Tetrahedron Lett.*, 185 (1963).

(23) J. K. Stille, F. M. Sonnenberg, and T. H. Kinstke, *J. Amer. Chem. Soc.*, **88**, 4922 (1966).

(24) S. Winstein, private communication.

(25) Analyses were performed by Schwartzkopf Microanalytical Laboratory and by F. Pascher Microanalytical Laboratory.

(26) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955.

(27) K. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(338 g, 2 mol) was added to 82 g (2.1 g-atoms) of potassium metal in 1 l. of dry toluene and heated at reflux after the initial reaction subsided. The resulting solution was treated with 160 g (2.1 mol) of carbon disulfide in 2 hr, then with 269 g (1.9 mol) of methyl iodide and 300 ml of ether. After filtration and removal of solvent by distillation, the residue was distilled through a short-path column first at atmospheric pressure and temperatures up to 160° and then at aspirator pressure and 160° to give (after redistillation of foreruns and residues) 71.6 g of white solid (0.47 mol, 21% based on fenchone). There was also obtained in the distillation about 100 ml of a higher boiling liquid whose infrared spectrum showed no olefinic absorption.

The solid reaction product was recrystallized three times from acetonitrile to give 42 g of white solid (mp 115°) which was shown by glpc (on a 0.375-in column, packed with Carbowax 20M on Chromosorb P and operated at 100°) to consist of two components in the ratio 61:39 having retention times of 20 and 45 min. The first of these was collected and identified by its spectral properties as 1,4,7,7-tetramethylnorbornene (III): infrared spectrum, 6.15 μ (weak),[28,29] 14.00 (strong);[28,29] nmr (CCl_4) τ 9.38 (s, three protons of a 7-methyl group), 9.33 (s, three protons of a 7-methyl group), 9.00 (s, six protons of the two bridgehead methyl groups), 8.3–9.3 (m, four protons of the 2-methylene groups), 4.49 (s, two vinyl protons). Samples of this olefin used in later experiments were purified by glpc in this way.

The second component was assumed to be a trimethyl-*exo*-methylenenorbornane on the basis of its spectral properties: infrared spectrum 6.05 μ (strong),[30] 11.33 (strong);[30] nmr (CCl_4) τ 9.12 (s, three protons of a methyl group), 9.08 (s, three protons of a methyl group), 9.04 (s, three protons of a methyl group), 8–9 (m, four protons of two methylene groups), 7.57 (d, J = 4 cps, vague, one bridgehead proton), 5.81 and 5.63 (s, two vinyl protons of a terminal methylene group).

Oxidation of *exo*-1,4,7,7-Tetramethylnorborneol with Chromic Acid.—Chromium trioxide (2.5 g, 0.025 mol) was dissolved in 10 ml of water and 15 ml of actic acid was added. The alcohol (VI) (2.0 g, 0.0119 mol) was dissolved in 10 ml of acetic acid and cooled in an ice bath while the cooled chromic acid solution was added slowly to keep the temperature below 15°. The solution was stirred 4 hr while warming to room temperature and then was poured into 500 ml of water and filtered. The collected solid was dried in a desiccator to give 1.35 g (0.0081 mol, 68%) of a white solid, mp 149–168°. Recrystallization from petroleum ether (bp 30–60°) gave 0.106 g of material with mp 168.0–168.6° (lit.[9] mp 168–168.5°).

Reduction of 1,4,7,7-Tetramethylnorbornanone with Sodium in Alcohol.—The ketone (0.2 g, 0.0012 mol) was dissolved in 50 ml of absolute ethanol and sodium (0.6 g, 0.026 g-atom) was added with stirring in small pieces over a period of 24 hr. After the sodium was completely dissolved, the solution was poured into 500 ml of water which was then extracted twice with petroleum ether which was then removed on the rotary evaporator. The residue, a white solid (0.134 g, 0.0008 mol, 70%), was shown by ir spectroscopy to contain alcohol but no ketone and was assumed to be *endo*-1,4,7,7-tetramethylnorborneol. Recrystallization from acetonitrile yielded 4 mg of material, mp 167–178° (lit.[9] mp 183–184°), with the same infrareds pectrum as that of the crude material. Glpc analysis of crude alcohol indicated about 10% VI and 90% the *endo* isomer (V).

Reduction of 1,4,7,7-Tetramethylnorbornanone with Lithium Aluminum Hydride.—Reduction of this ketone (1.1 g) with ethereal lithium aluminum hydride produced 85% (VI) which melted at 182–187.5° before and 188.5–192.5° after recrystallization from acetonitrile. Glpc analysis of the crude alcohol indicates about 90% VI and 10% the *endo* isomer (V). These results agree with the usual *endo* attack on 7,7-disubstituted norbornanones.[4b]

Reaction of 1,4,7,7-Tetramethylnorbornene with Mercuric Acetate in Acetic Acid.—Pure 1,4,7,7-tetramethylnorbornene (0.0671 g, 0.000446 mol), dissolved by warming in acetic acid in an nmr tube, gave the characteristic spectrum of the olefin. Mercuric acetate (0.145 g, 0.000455 mol) was added and the tube was shaken 10 min until the solid dissolved. The nmr spectrum now corresponded exactly to that of the purified mercurial (see below). The contents of the tube were poured into sodium chloride solution which was extracted twice with methylene chloride. The methylene chloride layers were combined, washed with sodium bicarbonate, dried over Drierite, and evaporated to give a gum which gradually solidified to a white solid, mp 92–100° (0.137 g, 0.000308 mol, 69%), identified as *exo*-2-chloromercuri-*exo*-3-acetoxy-1,4,7,7-tetramethylnorbornane. One recrystallization from heptane–ethyl acetate gave 0.0485 g of stubby white crystals: mp 100–101.5° (second recrystallization from heptane raised the melting point to 101.8–103.2°); infrared spectrum 5.72 μ; nmr (CCl_4) τ 9.30 (s, three protons of a methyl group), 9.16 (s, three protons of a methyl group), 8.97 (s, three protons of a methyl group), 8.89 (s, three protons of a methyl group), 8.06 (s, three protons of the methyl group of the acetate), 9.1–8.4 (m, four protons of the two methylene groups), 7.11 (d, J = 7.5 Hz, one proton attached to mercury-bearing carbon), 5.31 (d, J = 7.5 Hz, one proton attached to acetoxy-bearing carbon).

Anal. Calcd for $C_{13}H_{21}HgO_2Cl$: C, 35.06; H, 4.75; Cl, 7.97. Found: C, 35.44; H, 5.18; Cl, 8.40.

Exchange Reaction between the Mercuric Acetate–1,4,7,7-Tetramethylnorbornene Adduct and Norbornene.—The addition of mercuric acetate to 1,4,7,7-tetramethylnorbornene in an nmr tube was carried out as before; then 1 equiv of norbornene was added giving the superimposed spectra of the unsubstituted olefin and the original mercurial. Addition of 0.2 equiv of toluenesulfonic acid led to complete disappearance (half-life, 30 min) of the spectra of norbornene and of the mercurial (VIII) and simultaneous regeneration of the spectrum of the tetramethylnorbornene (VI). In addition there appeared the typical spectrum of the addition product from norbornene.

Repetition of the above experiment without the addition of toluenesulfonic acid led to the same result but with the half-life lengthened to 18 hr.

The mercuric acetate–1,4,7,7-tetramethylnorbornene adduct (VIII) alone in acetic acid showed no change in its nmr spectrum after 50 days. When toluenesulfonic acid (0.2 M) was added, the two doublets at τ 7.11 and 5.31 slowly disappeared and were replaced by two doublets at slightly lower field (J = 10 Hz) and two doublets at slightly higher field ($J \cong 3$ Hz). While these isomers were not isolated, the nmr spectrum indicates that both *cis-endo* and *trans* products were formed.

Reduction of *exo*-2-Chloromercuri-*exo*-3-acetoxy-1,4,7,7-tetramethylnorbornane with Sodium Borohydride.—A purified sample of IX (0.924 g) in 2.5 ml of 2 N sodium hydroxide was treated with sodium borohydride (0.7 g) for 5 hr and extracted with ether; the ether was washed, dried, and evaporated to yield a mixture of acetate and alcohol. This mixture was treated with a refluxing solution of 0.5 N sodium hydroxide in 50% methanol for 2 hr, diluted with aqueous sodium chloride, extracted with ether, and the extract dried and evaporated to yield 82 mg (23%) of solid product, mp 176–193°. Glpc analysis (see below) of this product showed only VI and no trace of the *endo* product (V) was observable.

When the entire oxymercuration solution (containing VIII) was treated with enough base to neutralize the acetic acid, then reduced with sodium borohydride in ether, direct examination of the ethereal solution by glpc revealed an 8% yield of VI and no trace of V. The low yield of VI is not significant here because the exchange experiments, and the nmr results above establish that only one product was produced. However, Bordwell and Douglass[31] have greatly improved this reduction and Brown, Kawakami, and Ikegami[14a] have obtained greater than 98% yield of 7,7-dimethyl-*exo*-norborneol from oxymercuration of apobornylene followed by reduction.

Reaction of *syn*-7-Bromonorbornene with Mercuric Acetate in Acetic Acid.—*syn*-7-Bromonorobornene (IV) (1.10 g, 0.00635 mol), prepared by the method of Kwart and Kaplan,[8] was dissolved in 25 ml of glacial acetic acid in a 125-ml erlenmeyer flask and mercuric acetate (2.03 g, 0.00637 mol) was added with 10-min shaking to dissolve the solid. After standing 20 min the solution was poured into sodium chloride solution and let stand overnight. The solid was collected and dried in a desiccator to give white crystals (2.57 g, 86.3%), mp 123–124.5°, identified as *exo*-2-chloromercuri-*exo*-3-acetoxy-*syn*-7-bromonorbornane (X): (recrystallization from heptane–ethyl acetate gave mp 121.2–123.8°); infrared 5.74 and 5.80 μ; nmr ($CDCl_3$) τ 8.0–8.8

(28) Characteristic of 1,2-disubstituted olefins.[29]

(29) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp 36, 48.

(30) Characteristic of 1,1-disubstituted olefins: ref 29, pp 36, 51.

(31) F. G. Bordwell and M. L. Douglass, *J. Amer. Chem. Soc.*, **88**, 993 (1966).

(m, four protons of two methylene groups), 7.97 (s, three protons of the acetoxy methyl group), 7.35 (s, broad, two bridgehead protons), 7.17 (d, J = 7.2 Hz, proton on mercury-bearing carbon), 5.94 (s, broad, bridge proton), 5.17 (d, J = 7.2 Hz, proton on acetoxy-bearing carbon).

Anal. Calcd for $C_9H_{12}O_2HgClBr$: C, 23.09; H, 2.58; Hg, 42.85; Cl, 7.57; Br, 17.07. Found: C, 23.04; H, 2.57; Hg, 42.69; Cl, 7.82; Br, 16.94.

Effects of Sodium Acetate Addition.—A solution of III (0.075 g, 0.00050 mol) and mercuric acetate (0.159 g, 0.00050 mol) in 1.0 ml of absolute methanol was allowed to stand overnight, poured into 10 ml of sodium chloride solution (~0.5 M), and extracted with six 5-ml portions of methylene chloride. After drying over calcium chloride and evaporating to dryness the product weighed 0.06 g (30% yield). The infrared spectrum showed a carbonyl peak at 5.8 μ which, by comparison with the 3.4-μ absorption both in this product and in pure VIII, indicated about 30% VIII in the product. When this experiment was repeated with 0.1 M sodium acetate in the methanol, the crude product had a spectrum identical with that of the product obtained in acetic acid. When this latter experiment (0.1 M NaOAc) was carried out with norbornene, the reaction was very fast (complete in 10 min) and the product contained about 60% acetate and 40% methoxymercurial. This ratio was obtained by comparing the infrared spectrum of the product with those of various mixtures of 3-*exo*-chloromercuri-2-*exo*-norbornyl acetate and 3-*exo*-methoxy-2-*exo*-norbornylmercuric chloride.[11a]

Both III and norbornene were oxymercurated in the presence of 0.1 M sodium acetate at the same concentrations given above but using 50 vol. % water–tetrahydrofuran as solvent. The results corresponded rather closely to those obtained in methanol. Thus, the product from III was almost pure VIII but that from norbornene contained 40–50% hydroxymercurial.

Registry No.—III, 16487-05-1; VII, 10309-50-9; IX, 16487-07-3; X, 16487-08-4.

Acknowledgment.—We are grateful to the National Institutes of Health for a fellowship (T. T. T.) and to the National Science Foundation for an equipment grant (GP-2137) and other support (Grant GP-2829).

The Reaction of Sulfur Dichloride with Linear Diolefins. Stereochemical Aspects in the Formation of Cyclic Sulfides[1]

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Received January 9, 1968

Additions of sulfur dichloride to linear diolefins, such as pentadiene-1,4, hexadiene-1,5, diallyl sulfide, and diallyl ether, which lead to cyclic β,β'-dichlorosulfides is reported. Only in one case an alternative synthesis had been reported previously. Stereochemical aspects of that addition are discussed, which are characterized by the predominant formation of the *cis* products in that reaction. The addition reaction is compared with the hydrogen sulfide addition to several linear diolefins. An outstanding feature of the reaction is the influence of steric effects on the reaction products, which cause the formation of predominantly anti-Markovnikov products. In one example, ring expansion from a tetrahydrothiophene ring system to a thiacyclohexane system occurs both during oxidation and reduction of the sulfur dichloride addition product. An alternative synthesis to the cyclic β,β'-dichlorosulfides is provided by the addition of chlorine to the corresponding olefinic episulfides.

Although sulfur monochloride and 2,3-dimethylbutadiene were reported to give 3,4-dichloro-3,4-dimethyltetrahydrothiophene in a yield of 1%[2] and although transannular additions of sulfur dichloride to cyclic diolefins occur readily, the possibility that cyclic derivatives may result in reactions of sulfur dichloride with linear diolefins has not been investigated. This reaction is an approach to a variety of cyclic sulfides. In the absence of special geometric arrangements of the olefinic double bonds, which would favor such an intramolecular addition, the use of high dilutions of equimolar amounts of reagents is required to reduce the yield of intermolecular addition which leads to polymer formation.[3-6] In this report, only monomeric components of the addition reaction are investigated, which consist exclusively of cyclic β,β'-dichlorosulfides.

The products of that addition reaction are of mechanistic and stereochemical interest with respect to the size of the resulting heterocyclic ring system and the configuration of its substituents. In principle, three possible ring systems can be envisaged to result from that reaction with linear diolefins, which differ in the number of atoms in the sulfur-containing ring (Scheme I). In addition, and contrary to the reaction of sulfur dichloride with cyclic diolefins[3-6] where only a single stereoisomer was obtained, the reaction with linear diolefins could conceivably lead to two stereoisomers, one *meso* (*cis*) and a *dl* pair (*trans*). With one exception, the products described here have not been reported in the earlier literature.

Results and Discussion

The addition reaction of sulfur dichloride was investigated on seven diolefins. The structures of the isolated addition products were primarily assigned on the basis of their nuclear magnetic resonance spectra, specifically on the relative proportion of CH_2Cl and CHCl *vs.* CH_2S and CHS protons, which distinguishes the various ring systems.

Additional support for several of the assigned structures results from the reduction of the cyclic dichlorosulfides to known sulfides with lithium aluminum hydride. In addition, several of these sulfides can be synthesized in low yield by the reaction of hydrogen sulfide with the corresponding linear diolefins.[7,8]

The addition of sulfur dichloride to diallyl ether leads to **1** in a yield of 42%. No isomeric products of differ-

(1) Presented in part at the Intra-Science Research Symposium, Santa Monica, Calif., Nov 30, 1967.

(2) H. J. Backer and J. Strating, *Rec. Trav. Chim.*, **54**, 52 (1935).

(3) E. D. Weil, K. J. Smith, and R. J. Gruber, *J. Org. Chem.*, **31**, 1669 (1966).

(4) (a) F. Lautenschlaeger, *ibid.*, **31**, 1679 (1966); (b) F. Lautenschlaeger, The Princeton University Conference on the Chemistry of Sulfides, June 29, 1966.

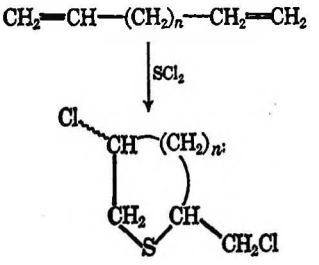
(5) E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1679 (1966).

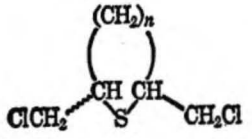
(6) F. Lautenschlaeger, *Can. J. Chem.*, **44**, 2813 (1966).

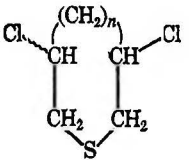
(7) D. Harman and W. E. Vaughn, *J. Amer. Chem. Soc.*, **72**, 631 (1950).

(8) C. S. Marvel and E. D. Weil, *ibid.*, **76**, 61 (1954).

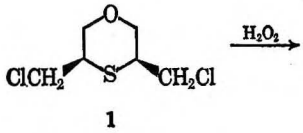
SCHEME I



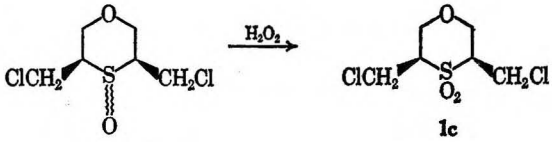




ent ring size were observed as evidenced by gas chromatographic analysis. The *cis* configuration for the dichlorosulfide **1** is suggested on the basis of the formation of two sulfoxides **1a** and **1b** on oxidation with hydrogen peroxide in glacial acetic acid, as shown by chroma-



1

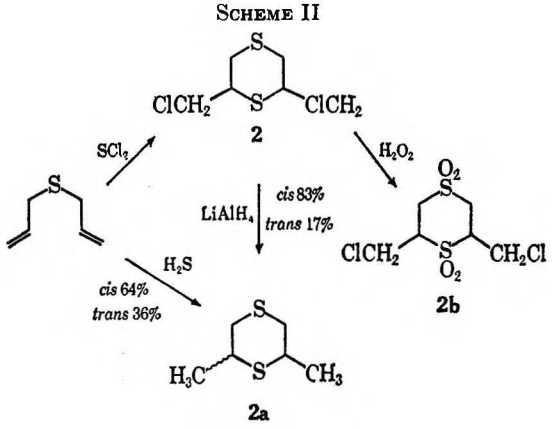


1a + 1b **1c**

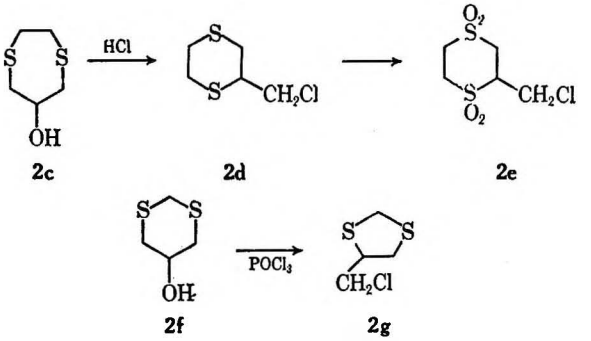
tographic analysis. Oxidation of a mixture of both sulfoxides leads to a single sulfone **1c** in a yield of 85%.

The dithian derivative **2** is obtained from diallyl sulfide in a yield of 44% (Scheme II). The isolation of

SCHEME II



that ring system is of interest since this corresponds to the head-to-head dimer of 3-chloropropylene sulfide. The dimerization of that episulfide has not been reported and, since only the head-to-tail isomer has been isolated from the dimerization of 3-chloropropylene oxide,[9] the formation of **2** from 3-chloropropylene sulfide would not be expected. The unsubstituted sulfide **2a** was obtained by the addition of hydrogen sulfide to diallyl sulfide. This addition in the presence of a secondary amine follows the rule of Markovnikov, which leads predominantly to the formation of a secondary carbon–sulfur bond in preference to the primary bond and, consequently, leads to the same ring system as the anti-Markovnikov addition of sulfur dichloride to the corresponding diolefin, as demonstrated in Scheme II. The only difference of these two approaches to **2a** appears in the *cis/trans* ratio of the two pathways, with the hydrogen sulfide addition showing an increased contribution of the *trans* isomer with a proportion of *cis/trans* of 64:36, whereas reduction of the dichlorosulfide **2** with lithium aluminum hydride leads to the *cis* and *trans* isomer of **2a** in a proportion of 83 *vs.* 17%. The predominance of the *cis* isomer in the reduction product suggests the *cis* configuration for **2**.

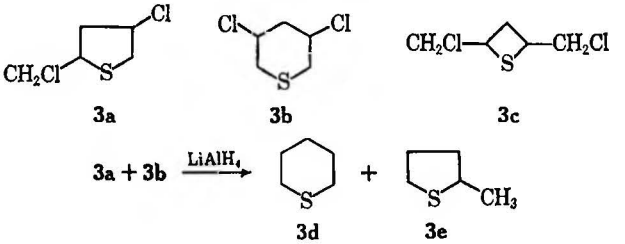


2c **2d** **2e** **2f** **2g**

The reaction of sulfur dichloride with pentadiene-1,4 leads to **3a** and **3b** in a proportion of 65:35 in a total yield of 39%. A gas chromatogram indicates the presence of both isomers of **3a** and **3b** by the appearance of two pairs of poorly separated peaks. Spinning-band distillation separates one isomer of **3a** of undetermined configuration.

Reduction of a mixture of **3a** and **3b** in a proportion of 74:26 with lithium aluminum hydride yields the sulfides **3e** and **3d** in a proportion of 82:18 and a total yield of 33% (Scheme III). In contrast, hydrogen sulfide

SCHEME III



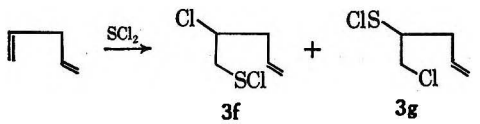
3a **3b** **3c** **3d** **3e**

addition to pentadiene-1,4 leads to **3e** exclusively, although only in a yield of approximately 1%, demonstrating that the initial addition of hydrogen sulfide to that terminal olefin proceeds to form the Markovnikov adduct, 4-mercaptopentene-1. This addition in the presence of amine is in contrast to the benzoyl peroxide catalyzed cyclization of 5-mercaptopentene-1, which, as expected from homolytic additions, leads predominantly to the anti-Markovnikov product **3d** (57–76%)

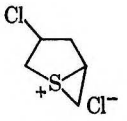
(9) J. D. McClure, U. S. Patent 3,140,296 (1964); *Chem. Abstr.*, **61**, P8318*d* (1964).

in preference to **3e** (15–42%).[10] Further examples in the report of these internal additions of olefinic mercaptans indicate the large steric effect on the mode of this cyclization reaction under homolytic conditions. These results indirectly support our conclusions derived from the sulfur dichloride addition, that steric factors play a dominant role in the formation of the alternative cyclic sulfides.

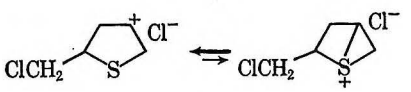
Whereas exclusively anti-Markovnikov products are isolated from the addition of sulfur dichloride to diallyl ether and diallyl sulfide, the formation of the corresponding anti-Markovnikov product **3c** in the reaction of pentadiene-1,4 is excluded for steric reasons. The first addition step would involve the formation of **3f** and **3g**, in analogy to the addition of sulfenyl chlo-



3f **3g**



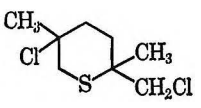
3i



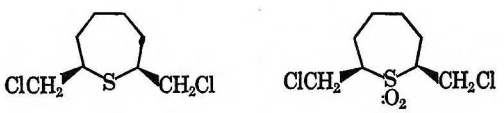
3j **3h**

rides to terminal olefins.[11] Intramolecular addition *via* the episulfonium intermediate **3h** is unlikely because of the steric requirements of that ion. The intermediate is therefore better represented by the open ion **3j**, which leads to **3a** and together with **3b** could also be obtained from **3i** or its open ion.

From a complex mixture of monomeric products, obtained from sulfur dichloride and 2,5-dimethylhexadiene-1,5 in a yield of 69%, product **4** was isolated in a yield of only 6%. The formation of several addition products indicates that even in the addition to this diolefin contribution from anti-Markovnikov additions are obtained.



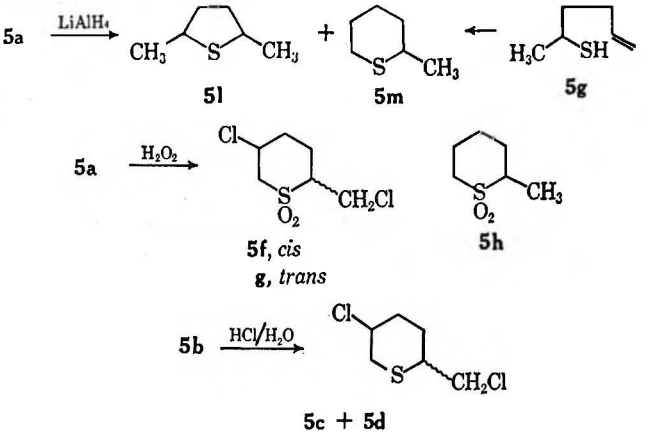
4



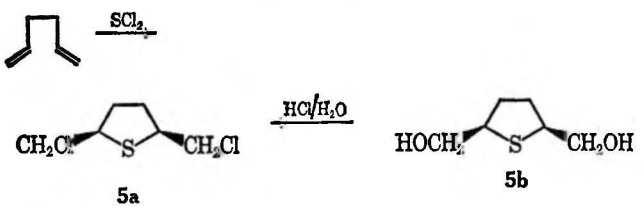
6 **6a**

In contrast, the addition of sulfur dichloride to hexadiene-1,5 leads to **5a** as the only product. The formation of **5a** is surprising in view of the reported formation of its isomeric ring system **5c** and **5d** by the treatment of the *cis* and *trans* isomers of **5b** with concentrated hydrochloric acid.[12] According to these earlier reports, both stereoisomers of **5b** were isolated from the reduction of the diethyl esters of *cis*- and *trans*-tetrahydrothiophene-2,5-dicarboxylic acid. It was reported that conversion of these diols to the dichlorosulfides **5c** and **5d** occurs by treatment with concentrated hydrochloric acid. In the light of our observation, this conclusion seems doubtful, although rearrangements of substituted cyclic sulfides are common. For example, this postulated ring rearrangement has analogies in the ring contraction of 3-hydroxy-1,5-dithiacycloheptane (**2c**) to 2-chloromethyl-1,4-dithiane (**2d**) in the presence of hydrochloric acid,[13] and also in the ring contraction of 2-phenyl-1,3-dithian-5-ol (**2f**) to 4-chloromethyl-2-phenyl-1,3-dithiolane (**2g**) with phosphorous chloride in the presence of pyridine.[14] These rearrangements proceed during substitutions of the β-carbon atom of the sulfides and therefore can be assumed to involve the intermediate episulfonium ion. Against this background, it is conceivable that both nonidentical chlorides **5c** and **5d** could be obtained from **5b** on treatment with hydrochloric acid and that oxidation with monoperphthalic acid leads to the sulfones **5f** and **5g** as has been claimed.[12] The products of the assumed structures **5f** and **5g** were converted into the known thiane dioxide **5h** by hydrogenation over Raney nickel[12] (Scheme IV). The six-membered cyclic structures **5c** and **5d**

SCHEME IV



were suggested for the sulfides only on the basis of the isolation of **5h**. In contrast to this, we have observed that the five-membered cycle **5a** represents the addition product of the sulfur dichloride to hexadiene-1,5 and that the corresponding diol **5b** can be obtained from **5a** with aqueous sodium carbonate. Furthermore, treatment of the diol **5b** with hydrochloric acid leads to **5a** without rearrangement. In contrast to earlier reports, we observe that oxidation of **5a** with hydrogen peroxide proceeds *via* rearrangement to the ring-expanded six-membered ring system **5f** or **5g**, the configuration of which we have not assigned. The fact that rearrangement with ring expansion occurs during oxidation and



5a **5b**

(10) J. M. Surzur, M. P. Crozet, and C. Dupuy, *C. R. Acad. Sci., Paris Ser. C*, t264 (Feb 13, 1967).

(11) W. H. Mueller and P. E. Butler, *J. Amer. Chem. Soc.*, **88**, 2866 (1966).

(12) J. Cerny and J. Hora, *Collect. Czech. Chem. Commun.*, **25**, 711 (1960); *Chem. Abstr.*, **57**, 13113*h* (1960).

(13) R. C. Fuson and A. J. Speziale, *J. Amer. Chem. Soc.*, **67**, 155 (1945.)

(14) E. Atkinson, R. J. S. Beer, D. Harris, and D. J. Royal, *J. Chem. Soc., Sect., C*, 638 (1967).

not during the treatment with hydrochloric acid, as had been suggested, is not surprising in view of the observation of these authors,[12] that the oxidation of the diacetate of **5b** leads to a ring-expanded diacetoxy sulfone.

Furthermore, although the same authors[12] suggest the involvement of an episulfonium intermediate in the conversion of the *trans*- and *cis*-diol **5b** to the rearranged sulfides **5c** and **5d**, it was suggested that this conversion is stereospecific in that both the *cis*- and *trans*-diol **5b** lead to either the *cis*- and *trans*-dichlorides **5c** and **5d**. If an episulfonium intermediate is assumed, this would be a common intermediate for both the *cis* and *trans* products and identical products should be expected. Therefore, either the nonidentity of the resulting postulated products **5c** and **5d** or the isolated products **5f** and **5g** or the episulfonium intermediate should be questioned. Spectroscopic data of products **5f** and **5g** as well as **5c** and **5d** were not reported. Physical constants of both **5c** and **5d** as well as their derivatives are nearly identical and do not permit distinguishing between them.

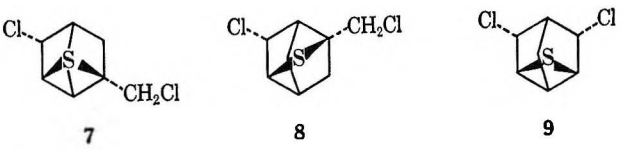
We assume that the ring expansion observed on **5a** on oxidation is due to the steric crowding of the β substituents and the oxygen attached to the sulfur atom, which is particularly critical if these substituents are *cis* with respect to one another. In this case, the sulfur–oxygen bonds in the sulfone would restrict the free rotation of the equatorial CH_2Cl groups. That this is not the only factor is evident from the absence of these rearrangements on ring systems **1**, **2**, and **4**.

The *cis* configuration is also assumed for the diol **5b** on the basis of its infrared absorption, which shows a band at 3630 cm^{-1} for the free O–H stretching frequency and a second band at 3580 cm^{-1} due to intramolecular hydrogen bonding in high dilution. Molecular models suggest that intramolecular hydrogen bonding can only be explained on the basis of a *cis* configuration. Although intramolecular bonding to the sulfur atom can be considered,[15] the characteristic frequency for that absorption had been observed at longer wavelength near 3524 cm^{-1}.

More significant stereochemical differences between the two approaches to the cyclic sulfide, the hydrogen sulfide addition and the sulfur dichloride addition with subsequent reduction, result in the reaction sequence arising from hexadiene-1,5. In both approaches, 2,5-dimethyltetrahydrothiophene **5l** and 2-methylthiacyclohexane **5m** are obtained in various proportions. It is interesting that, although only the tetrahydrothiophene ring system **5a** is isolated from the sulfur dichloride addition, reduction of that product leads to **5l** and **5m** in a proportion of 67 and 33%, indicating that ring expansion is not restricted to oxidation of **5a** but occurs also during reduction. The proportion of five- and six-membered-ring structure is not identical from both approaches; addition of hydrogen sulfide to hexadiene-1,5 favors the five-membered-ring system **5l** with a distribution of 97 *vs.* 3%. Also significant is the *cis*/*trans* ratio of **5l** obtained from the diolefin with hydrogen sulfide, which is 64:36 compared with the formation of only the *cis* isomer from the reduction of **5a**, which again suggests the *cis* configuration for **5a**. The larger predominance of the *cis* isomer in the reductions of both **5a** and **2** is therefore the most characteristic feature of the two alternative routes, the hydrogen sulfide and the sulfur dichloride addition to the diolefin. In comparison, ring closure of 2,6-dichlorohexane, obtained from hexadiene-1,5, leads to a smaller preponderance of the *cis* over the *trans* isomer of **5l**; a proportion of 58:42 was obtained.

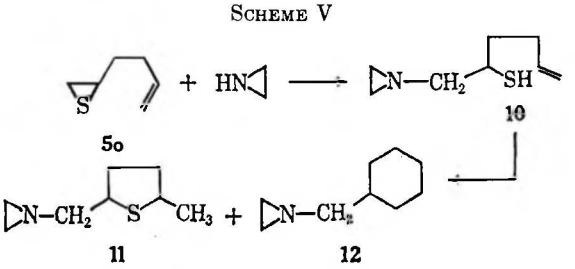
A cyclic addition product from octadiene-1,7 is obtained only in 13% yield. The structure **6** is suggested for the product on the basis of its nuclear magnetic resonance spectrum. Oxidation with hydrogen peroxide leads to the corresponding unrearranged sulfone **6a**.

The reaction with methylenenorbornene may lead to four intramolecular addition products. The structure **7** for the sulfide was tentatively assigned on the basis of the presence of a signal for a chloromethyl group in the nuclear magnetic resonance spectrum and on the basis of the unsymmetric shielding of the S=O group in the isomeric sulfoxides derived from **7**,[4b] which rules out the isomeric structure **8**. The formation of **7** is analogous to the reaction of sulfur dichloride with bicyclo[2.2.1]heptadiene in which the thietane ring system **9** was formed.



Studying the base-catalyzed formation of cyclic sulfides further, it was assumed that intramolecular addition of an olefinic mercaptan as proceeding in the hydrogen sulfide addition to linear diolefins should also result from the addition of a primary or secondary amine to an olefinic episulfide. Addition of ethyleneimine to the episulfide **5o** involves the formation of the intermediate mercaptan **10** which closes to the two isomeric sulfides **11** and **12** in a proportion of 50:50 and a total yield of 30% (Scheme V). This reaction shows,

SCHEME V



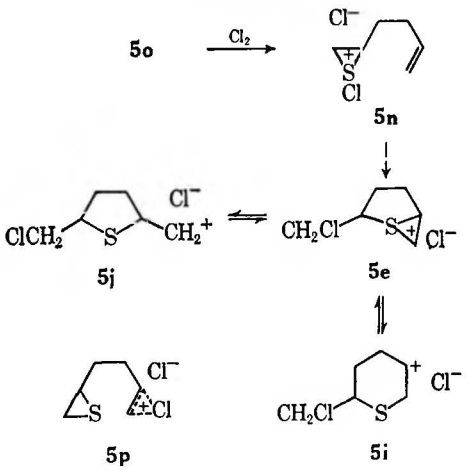
as expected, a larger contribution of the Markovnikov product **11**. In comparison with the cyclization of 4-mercaptopentene-1 in the presence of benzoyl peroxide, in which of the two alternative five- and six-membered-ring systems, the six-membered ring is predominant.[10] The formation of the methyleneaziridyl derivatives **11** and **12** in preference to products in which the aziridinyl group is attached to the thiane or tetrahydrothiophene ring suggests the opening of the episulfide group on the terminal carbon atom, as expected from the observations on the opening of propylene sulfide

(15) A Lüttringhaus, S. Kabuss, H. Prinzbach, and F. Langenbucher, *Ann.*, **653**, 195 (1952).

with secondary amines.[16,17] The presence of only a single doublet in the nuclear magnetic resonance spectrum for the methyl group in **12** suggests the formation of a single isomer in that cyclization reaction.

An alternative synthesis to several cyclic β,β'-dichlorosulfides is suggested by the assumption that the intermediate **5n** in the addition of chlorine to the episulfide **5o** should be identical with that obtained from sulfur dichloride and an olefinic compound (Scheme VI).

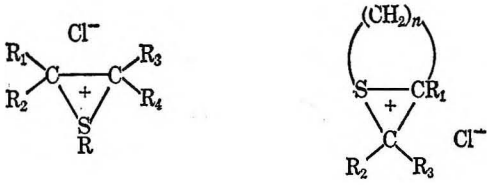
SCHEME VI



Consequently, in the case of an episulfide of such a diolefin in which intramolecular addition of sulfur dichloride occurs, the addition of chlorine should lead to the formation of a cyclic β,β'-dichloromonosulfide, identical with the sulfur dichloride addition product to the diolefin, and in contrast to the reported chlorine additions to episulfides,[18] which give β,β'-dichlorodisulfides, exclusively. This was indeed observed, addition of chlorine to **5o** leads to **5a** in a yield of 66%. Similarly, addition of chlorine to 1,5-cyclooctadiene monoepisulfide **13**[19] leads to the earlier[6] reported cyclic sulfide **14**. In the addition of chlorine to unsaturated episulfides, the product does not permit distinguishing between the initial approach of the chloronium ion to the sulfur atom as in **5m** or to the unsaturation as shown in **5p** because both lead to identical products.

Transannular additions to unsaturated sulfides should therefore provide a convenient synthesis to ring systems related to structures obtained by the addition of sulfur dichloride to diolefins.

If both the addition of sulfur dichloride to the diolefin and the intramolecular addition of the resulting unsaturated β-chlorosulfenyl chloride followed the rule of Markovnikov, the largest possible ring system would be formed in all cases of reactions with terminal diolefins. Such a product was detected only as a minor component in one case (**3b**). This observation is interesting in view of earlier studies on the stereochemical nature of sulfenyl chloride additions to unsaturated compounds. In these addition reactions, the assumption of an intermediate episulfonium ion has generally become accepted.[20] However, the possibility of contributions of open ions was not ruled out.[21] This becomes particularly relevant if the carbon–sulfur bonds in the three-membered ring are not symmetrical with R_1 to R_4 being nonidentical (I), either because of



I

stabilization of the carbonium ion by electronic effects of the various substituents or because of steric requirements. Both influences would favor a contribution of an open ion and could even act against the formation of an episulfonium ring structure. This steric influence is different from the steric approach effect, which affects the mode of opening of an unsymmetric episulfonium ion by an approaching nucleophile. Rearrangements of sulfenyl chloride addition products to olefins are therefore not surprising since kinetically and thermodynamically favored products could result, as demonstrated in the significant study of Mueller and Butler on the addition of sulfenyl chlorides to 1-alkenes,[11] which showed that predominantly anti-Markovnikov products are obtained at low temperatures, and rearrangement to Markovnikov addition products occurred at room temperature. Also, mixtures of both isomers were obtained by the addition of alkenesulfenyl chlorides to acrylic acid derivatives.[22]

Whereas the factors leading to these varying modes of additions are not yet understood, it is obvious from the observed additions of sulfur dichlorides to diolefins that steric factors appear to dominate and determine the product distribution. Specifically, the deciding factor is the formation of the five-membered sulfur-containing cycle in preference to the four- or six-membered isomer in case of **3a**, **3b**, and **5a**. The exclusive formation of the seven-membered ring in preference to the eight- or nine-membered ring in **6** and the exclusive formation of the six-membered in preference to the seven- or eight-membered ring in **1** and **2**, follow from similar considerations. In addition, the formation of the ring systems, **1**, **2**, **3a**, **5a**, **6**, and **7**, is further favored by the approach of the chloride ion from the least hindered site, although in view of the absence of **3c** this cannot be considered the overriding factor. These results become plausible if a contribution of open ions of the episulfonium intermediates are considered, in which case it is anticipated that the three carbon–sulfur bonds of the episulfonium ring structure are sterically nonequivalent and that steric effects determine which of the two possible ions, for example, **5i** and **5j**, predominates. The bicyclic episulfonium intermediate (I) would open and locate the carbonium ion in less strained ring system, whereby it could be anticipated that a contribution of such an episulfonium ion becomes smaller or negligible if n of $(CH_2)_n$ (I) approaches 1.

The significance of these steric factors becomes particularly apparent in a comparison of the products ob-

(16) N. S. Isaacs, *Can. J. Chem.*, **44**, 395 (1966).

(17) (a) S. D. Turk, R. P. Loutham, R. L. Cobb, and C. R. Bresson, *J. Org. Chem.*, **29**, 974 (1964). (b) A more recent investigation in the opening of episulfides was carried out by N. V. Schwartz, *ibid.*, in press.

(18) J. M. Stewart and H. P. Cordts, *J. Amer. Chem Soc.*, **74**, 5880 (1952).

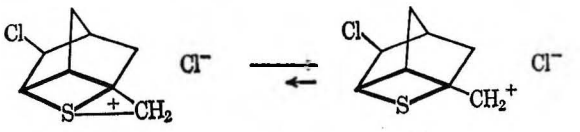
(19) French Patent 1,428,686 (to Dunlop Rubber Co. Ltd.) (1965).

(20) N. Kharasch and C. M. Buess, *J. Amer. Chem. Soc.*, **71**, 2724 (1949).

(21) A. Streitwieser, *Chem. Rev.*, **56**, 571 (1958).

(22) K. D. Gundermann and R. Huchting, *Chem. Ber.*, **95**, 2191 (1962).

tained from pentadiene-1,4 and methylenenorbornene. Whereas steric considerations exclude the formation of the thietane system **3c**, on the basis of similar considerations, the formation of the thietane system **7** should be favored in the reaction with strained bycyclic systems such as methylenenorbornene. It could be argued that, in the latter case, a large contribution of the open ion **7e** *vs.* the episulfonium intermediate **7d** is involved,



7d **7e**

since a symmetric episulfonium ion would require the two carbon–sulfur bonds of the three-membered cyclic ion to be of equivalent length, which is sterically impossible and may rule out such a cyclic intermediate.

The isolation of only the *cis* isomer in case of **1**, **2**, and **5a** follows from thermodynamic considerations, which requires isomerization *via* the episulfonium intermediate to the thermodynamically most stable ring system. The latter is expected to be the *cis* isomer in analogy to observations on 1,3-disubstituted cyclohexanes, for which the less stable isomer was shown to be a *dl* pair and therefore *trans*.[23] The increased stability of the *cis*-1,3 isomer results from the possibility of the *cis* isomer to exist in the favored diequatorial conformation, whereas the *trans* isomer would necessarily be equatorial–axial.[24] Isomerization through the episulfonium intermediates such as **5e** would readily allow the formation of the more stable product.

Experimental Section

Gas chromatographic analysis was carried out on a 3-, 6-, or 12-ft Apiezon column between 75 and 175° on a Perkin-Elmer 800 instrument. Infrared spectra were recorded on a Perkin-Elmer 422 spectrophotometer either neat or in potassium bromide pellets. Nuclear magnetic resonance spectra were recorded on a Varian A-60 instrument. Melting points were determined in a Gallenkamp block and are uncorrected.

2,6-Chloromethyl-1,4-oxathiane (1).—Solutions of 107 g (1.1 mol) of allyl ether and 103 g (1 mol) of sulfur dichloride were allowed to react as described previously[4a] to give 42% of **1** as shown by vpc analysis, which also indicates the presence of a single product. Separation from polymeric product by molecular distillation gave 60 g (30%) of crude product, which crystallized partially at room temperature. After sublimation, a product of mp 36–37.5° was obtained.

The product shows strong ir bands at 1106, 896, and 730 cm^{-1}. The nmr spectrum in carbon disulfide solution shows integration values of 2:2:1 for multiplets centered near 3.84, 3.55, and 2.84 ppm in agreement with the assigned structure **1**.

Anal. Calcd for $C_6H_{10}OCl_2S$: C, 35.8; H, 5.01; Cl, 35.3; S, 15.9. Found: C, 35.7; H, 4.99; Cl, 35.0; S, 15.8.

2,6-Chloromethyl-1,4-oxathiane Oxide (**1a** + **b**).—A solution of 2.9 g (0.04 mol) of 47% hydrogen peroxide and 8.04 g (0.04 mol) of **1** in 60 ml of acetone was allowed to stand at room temperature for 12 hr. The solution was evaporated to give 8.4 g (97%) of product, mp 60–92°. An analytical sample of the mixture of the isomers was obtained by sublimation at 60° (0.1 mm). Vpc analysis shows the absence of unchanged sulfide **1**.

Anal. Calcd for $C_6H_{10}O_2Cl_2S$: C, 33.18; H, 4.64; Cl, 32.67; S, 14.77. Found: C, 32.87; H, 4.34; Cl, 32.60; S, 14.74.

2,6-Chloromethyl-1,4-oxathiane 4,4-Dioxide (**1c**).—A solution of 0.5 g of the mixture of sulfoxides **1a** and **b** in 50 ml of glacial acetic acid was allowed to stand at 25° for 64 hr. The solution was then evaporated to 5 ml to give 0.25 g of **1c**, mp 129–130.5°. On complete evaporation, another 0.2 g of product was obtained: mp 128–129.5°; total yield 85%.

Anal. Calcd for $C_6H_{10}Cl_2O_3S$: C, 30.91; H, 4.32; S, 13.75; Cl, 30.43. Found: C, 31.26; H, 4.36; S, 13.91; Cl, 30.69.

2,6-Chloromethyl-1,4-dithiane (**2**).—The product was obtained as described for **1** and was purified by recrystallization from ethanol and subsequent sublimation. An analytical sample showed mp 49–51°.

The nmr spectrum shows four protons centered at 3.63 ppm for the group CH_2Cl and six protons centered at 2.97 ppm for the groups CH_2S and CHS. In the ir spectrum, major absorption bands are observed at 1412, 732, 690, and 670 cm^{-1}.

Anal. Calcd for $C_6H_{10}Cl_2S_2$: C, 33.2; H, 4.67; Cl, 32.62; S, 29.58. Found: C, 33.4; H, 4.72; Cl, 32.03; S, 29.53.

2,6-Chloromethyl-1,4-dithiane 1,1,4,4-Tetroxide (**2b**).—Oxidation of 1 g of **2** with hydrogen peroxide as described above gives 1.2 g (93%) of **2b**, mp 204–206°, soluble in hot acetic acid, hot hexachlorobutadiene, and cold pyridine. Recrystallization from acetic acid increased the melting point to 250° dec.

Anal. Calcd for $C_6H_{10}Cl_2O_4S_2$: C, 25.62; H, 3.58; S, 22.81; Cl, 25.22. Found: C, 25.97; H, 3.54; S, 23.05; Cl, 25.05.

The Reaction of Sulfur Dichloride with Pentadiene-1,4. 2-Chloromethyl-4-chlorotetrahydrothiophene and 3,5-Dichlorothiacyclohexane (**3a and b**).—Solutions of 50 g (0.735 mol) of pentadiene-1,4 and 75.7 g (0.735 mol) of sulfur dichloride in 500 ml of dry pentane were allowed to drop into 1 l. of dry pentane over a period of 2 hr. The reaction proceeded at room temperature. After 12 hr the solution was decanted from 50.1 g of insoluble product A. On evaporation of the solvent, 73.1 g of oily product B was obtained. Vpc analysis of B showed two components in a proportion of 65:35 which were further separated into four peaks at decreased column temperature. Fractionation of 60 g of B at 0.05 mm through a 10-in. Vigreux column gave following fractions: (1) bp 48–52°, 5.2 g; (2) bp 52–62°, 15.8 g, $n^{20}D$ 1.5545; (3) bp 62°, 13.7 g, $n^{20}D$ 1.5560; (4) bp 64–84°, 7.0 g.

Fraction 1 shows an isomer ratio of 16:1; fraction 4 of 2:3 by vpc analysis. Fractions 1 and 4 show similar elemental compositions.

Anal. Calcd for $C_5H_8Cl_2S$: C, 35.10; H, 4.71; Cl, 41.46; S, 18.74. Found: C, 35.52; H, 4.67; Cl, 41.03; S, 18.17.

Fractionation on a spinning-band column separated a single stereoisomer of **3a** of unidentified configuration: bp 47° (0.05 mm); $n^{20}D$ 1.5558.

Reduction of 3a and b with Lithium Aluminum Hydride (**3d and e**).—To a solution of 5.22 g (0.03 mol) of **3a** and **b** (of a proportion of 74:26) in 100 ml of diethyl ether was added 0.75 g (0.02 mol) of lithium aluminum hydride. After refluxing with stirring for 64 hr, the suspension was acidified with dilute sulfuric acid; the ether solution washed with water, dried ($MgSO_4$), and distilled to give 1.0 g of a mixture of **3d** and **e** (18:82), 33%, bp 40–41.5° (25 mm), $n^{20}D$ 1.4893. The components were identified by comparison of their vpc retention times with those of authentic materials.[25]

2-Chloromethyl-2,5-dimethyl-5-chlorothiacyclohexane (**4**).—Solutions of 92.5 g (0.84 mol) of 2,5-dimethylhexadiene-1,5 and 81.5 g (0.84 mol) of sulfur dichloride in 500 ml of pentane were allowed to react at room temperature by adding the solutions over a period of 30 min. After 12 hr, the solution was decanted from polymeric material and evaporated to give 123.4 g (76%) of product. Vpc analysis shows eight major products which only partially could be separated by distillation.

Fractionation through a 5-in. Vigreux column of 100 g of product at 0.001 mm gave following fractions: (1) bp 40–60°, 9.2 g; (2) bp 60–68°, 11.1 g; (3) bp 69–72°, 12.0 g; (4) bp 72–78°, 6.0 g; (5) bp 78–88°, 9.5 g; (6) bp 88–104°, 19 g.

Repeated crystallization of fraction 5 from hexane gave a sample of **4**, mp 65.5–67°.

Anal. Calcd for $C_8H_{14}Cl_2S$: C, 45.01; H, 6.67; Cl, 33.30; S, 15.05. Found: C, 45.02; H, 6.51; Cl, 32.83; S, 14.89.

The nmr spectrum of **4** shows two AB patterns for the groups CH_2Cl at 3.53 ppm (J_{AB} = 11 cps) and CH_2S at 2.77 ppm (J_{AB} = 15 cps) each corresponding to two protons. The nonequivalence of the two methyl groups is indicated by single peaks at 1.69 and 1.18 ppm.

(23) M. Mousseron and R. Granger, *Bull. Soc. Chim. Fr.*, [5] **5**, 1518 (1938).

(24) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(25) E. V. Whitehead, R. A. Dean, and F. A. Fiedler, *J. Amer. Chem. Soc.*, **73**, 3632 (1951).

2,7-Chloromethyl-1-thiacycloheptane (6).—Solutions of 82.7 g (0.75 mol) of octadiene-1,7 and 76.0 g (0.75 mol) of sulfur dichloride in 250 ml of hexane were added to 3 l. of hexane under stirring at 50° over a period of 3 hr. After an additional 8 hr at room temperature, the clear solution was decanted and evaporated to give 52.5 g (33%) of syrupy product. Vpc analysis indicates a total yield of 13% of **6**. Molecular distillation at 100° separated 17.2 g of volatile material, from which 7 g of **6** were separated by fractionation: bp 92–94° (0.1 mm); $n^{20}D$ 1.5432. Vpc analysis shows a single peak for that product.

Anal. Calcd for $C_8H_{14}Cl_2S$: C, 45.05; H, 6.62; Cl, 33.29; S, 15.02. Found: C, 45.90; H, 6.41; Cl, 32.86; S, 15.25.

The nmr spectrum for **6** shows four protons corresponding to CH_2Cl between 3.4 and 4.1 ppm in carbon disulfide solution.

2,7-Chloromethyl-1-thiacycloheptane 1,1-Dioxide (6a).—To a solution of 0.53 g of **6** (2.5 mmol) in 20 ml of acetone was added 0.34 g (5.6 mmol) of 47% aqueous hydrogen peroxide. After 12 hr the solution was allowed to evaporate, the crude crystalline material was washed with 10 ml of methanol to give 0.2 g of sulfone, mp 121–125°. After recrystallization from glacial acetic acid, mp 127–129° was obtained. Evaporation of the mother liquor gave another 0.2 g of product.

Anal. Calcd for $C_8H_{14}Cl_2O_2S$: C, 39.19; H, 5.76; S, 13.08; Cl, 28.92. Found: C, 38.87; H, 5.56; S, 13.08; Cl, 28.78.

The nmr spectrum in hexachlorobutadiene at 100° shows four protons corresponding to the groups CH_2Cl in the region between 3.4 and 4.2 ppm, two protons for the groups CHS between 2.8 and 3.4 ppm, and eight protons for the methylenic protons as a wide multiplet centered at 1.93 ppm.

2,5-Chloromethyltetrahydrothiophene (5a). **A.**—Solutions of 103 g (1 mol) of sulfur dichloride and 98 g (1.2 mol) of hexadiene-1,5 were allowed to drop into 2 l. of pentane over a period of 30 min at room temperature. After 8 hr the solution was decanted from 29 g of insoluble product. Evaporation of solvent gave 147 g (79.5%) of crude product. Vpc of the crude reaction product showed a single peak for **5a** in a yield of 61%.

Distillation through a Vigreux column at 0.1 mm gave following fractions: (1) bp 86–88°, 41.5 g; $n^{20}D$ 1.5504; (2) bp 88–93°, 26.2 g; (3) bp 93–97°, 19.2 g; $n^{20}D$ 1.5504.

Anal. Calcd for $C_6H_{10}Cl_2S$: C, 38.92; H, 5.39; Cl, 38.31; S, 17.32. Found: C, 38.93; H, 5.52; Cl, 38.19; S, 17.28.

Fraction 1 shows an nmr spectrum (in CS_2) in agreement with structure **5a**, with four protons due to the groups CH_2Cl between 3.3 and 4.2 ppm, two protons for the groups CHS centered at 2.8 ppm, and four protons for the methylenic hydrogens between 1.6 and 2.5 ppm.

No difference was obtained in the nmr spectrum of fractions 1 and 3 although fraction 3 shows additional weak peaks in its ir spectrum at 865, 788, 773, and 512 cm^{-1}.

B.—An amount of 2.95 g (0.02 mol) of the diol **5b** was dissolved in 50 ml of concentrated hydrochloric acid. The clear solution turned cloudy after several min, and was then extracted with pentane after 2 hr. The pentane solution was washed with water, dried ($MgSO_4$), and evaporated to give 3.7 g (100%) of dichlorosulfide **5a**, identified by its ir and vpc spectra.

C.—Into a solution of 10.4 g (0.09 mol) of hexadiene monoepisulfide dissolved in 50 ml of methylene chloride was passed 7.1 g (0.1 mol) of chlorine at −35° with rapid stirring. The solution was evaporated to give 17 g (97%) of crude product; vpc shows 66% **5a**. Distillation produced 10.8 g (61%) of **5a**, identified by its ir absorption.

Hexadiene 1,5-monoepisulfide (5o) was obtained from the corresponding epoxide by treatment with potassium thiocyanate[26] in a yield of 50%: $n^{20}D$ 1.4920; bp 62° (24 mm).

Anal. Calcd for $C_6H_{10}S$: C, 63.09; H, 8.83; S, 28.07. Found: C, 63.90; H, 8.69; S, 28.03.

2-Chloromethyl-5-chlorothiacyclohexane 1,1-Dioxide (5f or g).—To a solution of 3.7 g (0.02 mol) of **5a** in 50 ml of acetone was added 3.4 g (0.05 mol) of 50% aqueous hydrogen peroxide. The solution was allowed to stand for 5 days at room temperature and was then evaporated to give a partially crystallized product, which was suspended in 5 ml of methanol to give 1.7 g of crude product, mp 110–114°. Recrystallization increased this to 118–121° (lit.[12] mp 119.5–120°). Evaporation of the methanol solution produced an oily fraction, virtually identical by ir analysis with the purified sulfone. Crystallization of the oil from 10 ml of chloroform–hexane in a proportion of 1:1 at −20° yielded another 0.8 g of product: mp 110–117°; total yield 57%.

The nmr spectrum of the sulfone in $CDCl_3$ shows three protons arising from the groups CHCl and CH_2Cl between 3.4 and 4.5 ppm with the multiplet for CHCl at 4.32 ppm. Three protons due to groups CH_nSO_2 are observed between 3.4 and 3.6 ppm and four methylenic protons in the region of 1.8–2.5 ppm support the structure **5f** or **g**.

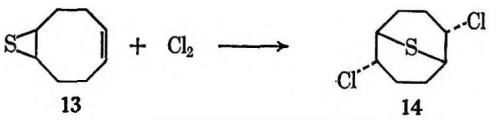
2,5-Hydroxymethyltetrahydrothiophene (5b).—A suspension of 9.25 g of **5a** (0.05 mol) in 100 ml of water containing 10.6 g (0.1 mol) of anhydrous sodium carbonate was stirred at 90° with a high-speed mechanical stirrer until a clear solution had formed after approximately 10 min. Extraction with diethyl ether (500 ml) and distillation after drying with magnesium sulfate gave 4 g of **5b**: bp 108° (0.1 mm); $n^{20}D$ 1.5459.[12]

The nmr spectrum in pyridine shows 4.0 protons corresponding to CH_2OH at 3.85 ppm, 4.0 methylenic protons at 2 ppm, and two protons at 2.85 ppm, corresponding to the group CHS.

The ir spectrum of **5b** was recorded on a Perkin-Elmer 421 instrument in an undetermined low concentration, obtained by stirring the alcohol with carbon tetrachloride and subsequent centrifugation. Further dilution did not affect the absorption peaks at 3630 and 3580 cm^{-1}. A neat sample shows strong absorption at 1020 and 3300 cm^{-1}.

Reduction of 2,5-Chloromethyltetrahydrothiophene.—To a solution of 5.55 g (0.03 mol) of **5a** in 100 ml of tetrahydrofuran was added 0.75 g (0.02 mol) of lithium aluminum hydride. After refluxing for 12 hr the vpc spectrum showed the absence of starting material. The suspension was poured into 1 l. of water, extracted with two portions of 100 ml of pentane, the pentane was washed with water and dried ($MgSO_4$). The vpc spectrum shows **5l** and **5m** in a proportion of 67:33. Distillation yielded 2.0 g of the mixture of **5l** and **5m**: bp 49° (38 mm); $n^{20}D$ 1.4788. The products were identified by comparison of their vpc retention times and physical constants[26] with those of authentic samples.

2,6-Dichloro-9-thiabicyclo[3.3.1]nonane (14). **From Cyclooctadiene 1,5-Monoepisulfide.**—Into a solution of 2.3 g (0.016 mol) of 1,5-cyclooctadiene monoepisulfide dissolved in 200 ml of methylene chloride was passed 1.14 g (0.016 mol) of chlorine at −40°. The solution was allowed to warm to room temperature and the solvent evaporated to give 3.45 g of semicrystalline material. Sublimation of 0.5 g of the crude product gave 0.47 g of **14** (94%), mp 80–87°. A sample was purified by crystallization as described earlier[6] to give a pure sample of mp 100–101° and was identified by mixture melting point and ir spectrum as identical with a product obtained from sulfur dichloride and *cis,cis*-cyclooctadiene-1,5.



13 14

***exo,exo*-2-Chloromethyl-5-chloro-9-thiatricyclo[2.2.1.1^{2,6}]octane** (7).—2-Methylene-5-norbornene (220 g, 2.07 mol) and 206 g (2 mol) of sulfur dichloride were allowed to react in hexane as described before[4] at −40°. While still at this temperature, the solution was decanted, the solvent evaporated to give 220 g (53%) of syrupy product. A portion of 42 g was distilled through a 2-in. Vigreux column to give 17 g of product, bp 87° (0.09 mm). Alternatively, the pure product can be obtained in comparable yield by steam distillation of the crude reaction product. An analytical sample was obtained by recrystallization from methanol and shows mp 44–46.5°.

Anal. Calcd for $C_8H_{10}Cl_2S$: C, 45.94; H, 4.82; Cl, 33.90; S, 15.33. Found: C, 45.89; H, 4.90; Cl, 33.99; S, 15.62.

2,5-Dimethyltetrahydrothiophene (5l) **from 2,5-Dichlorohexane and Sodium Sulfide.**—The reported procedure[26] was followed on a mixture of *meso*- and racemic 2,5-dichlorohexane, obtained by the addition of hydrogen chloride to diallyl. From 9.3 g (0.06 mol) of the dichloride, 4.1 g of **5l**, 59%, bp 53–54° (30 mm), $n^{20}D$ 1.4766, was obtained. The nmr spectrum in $CDCl_3$ shows the presence of two doublets for methyl groups at 1.33 and 1.31 ppm in a proportion of 58:42, whereby the lower field doublet is due to the *cis* isomer, as demonstrated by adding an authentic sample.

The Addition of Hydrogen Sulfide to Hexadiene-1,5 (5l and 5m).—A solution of 8.2 g of hexadiene-1,5 (0.1 mol), 1 g of di-

(26) H. R. Snyder, J. H. Stewart, and J. B. Ziegler, *J. Amer. Chem. Soc.*, **69**, 2672 (1947).

n-butylamine, and 3.75 g of hydrogen sulfide was allowed to react at 100° for 18 hr. Distillation of the product after washing with dilute hydrochloric acid gave **5l** and **5m**: yield 0.55 g (5%); bp 68–69° (45 mm); $n^{20}D$ 1.4799.[26] The nmr spectrum indicates the presence of both *cis* and *trans* isomers of **5l**, although the vpc spectrum shows the presence of 3% **5m**. Vpc analysis does not separate the *cis* and *trans* isomer of **5l**.

The Addition of Hydrogen Sulfide to Diallyl Sulfide. *cis*- and *trans*-2,6-Dimethyldithiane (2a).—Into a solution of 3 g of *n*-dibutylamine and 4.5 g (0.04 mol) of allyl sulfide in 25 ml of benzene was condensed 1.7 g (0.05 mol) of hydrogen sulfide. The solution was heated for 20 hr at 100° in a stainless steel bomb. The product was distilled to give 1.4 g (26%) of **2a**: bp 87° (13 mm); $n^{20}D$ 1.5411.[27]

A vpc spectrum shows two close peaks in a proportion of 34:66, the shorter retention time is assumed to be due to the *trans* isomer. The nmr spectrum supports structure **2a** with two doublets for CH_3 groups at 1.20 and 1.42 ppm in $CDCl_3$, corresponding to six protons.

The Reaction of Hydrogen Sulfide with Pentadiene-1,4.—Under conditions described above, approximately 1% of **3e** was obtained as shown by vpc analysis. The isomeric product **3d** was not observed.

The Reaction of Ethylenimine with Hexadiene 1,5-Monoepisulfide (5o). 2-Methyl-5-aziridinylmethyltetrahydrothiophene (11) and 2-Aziridinylmethyl-1-thiacyclohexane (12).—To a solution of 6.0 g (0.14 mol) of ethylenimine in 25 ml of benzene was added 11.4 g (0.1 mol) of hexadiene episulfide with stirring at 65°. The solution was kept at 65° for 17 hr, then decanted from polymeric residue, and distilled to give 4.7 g of product: bp 50° (0.004 mm); $n^{20}D$ 1.521. Gas chromatographic analysis shows the two components **11** and **12** in a proportion of 50:50 (±2).

Anal. Calcd for $C_8H_{15}NS$: C, 61.09; H, 9.61; N, 8.91; S, 20.39. Found: C, 61.01; H, 9.69; N, 9.13; S, 20.13.

The nmr spectrum of the mixture of **11** and **12** in deuteriochloroform shows a doublet for the methyl group at 1.27 ppm corresponding to 1.5 protons and suggesting the presence of **11** and **12** in equal proportions. Two doublets at 2.27 and 2.17 corresponding to 2.0 protons are assigned to the exocyclic CH_2N group.

Registry No.—**1**, 16728-39-5; **1a**, 16728-40-8; **1b**, 16728-45-3; **1c**, 16728-38-4; **2**, 16728-41-9; **2a** (*cis*), 16728-42-0; **2a** (*trans*), 16727-98-3; **2b**, 16728-43-1; **3a**, 16728-44-2; **3d**, 1613-51-0; **3e**, 1795-09-1; **4**, 16728-25-9; **5a**, 16728-26-0; **5b**, 16728-27-1; **5f** or **g**, 16728-28-2; **5l** (*cis*), 5161-13-7; **5l** (*trans*), 5161-14-8; **5m**, 5161-16-0; **5o**, 6766-70-7; **6**, 16728-32-8; **6a**, 16728-33-9; **7**, 16742-80-6; **11**, 16728-34-0; **12**, 16728-35-1; **14**, 16728-36-2; sulfur dichloride, 10545-99-0.

Acknowledgment.—The author is greatly indebted to the National Research Council, Ottawa, for supporting part of this project, and to D. Johnson and S. Rae for technical assistance.

(27) F. J. Glavis, L. L. Ryden, and C. S. Marvel, *J. Amer. Chem. Soc.*, **59**, 707 (1937).

The Reaction of Sulfur Dichloride with Cyclic Polyolefins

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Received February 29, 1968

Sulfur dichloride additions to cyclic polyolefins lead to novel sulfur-containing ring systems. The reaction with cyclooctatetraene, cycloheptatriene, and 1,5,9-cyclododecatrienes was investigated. Intramolecular addition products were obtained in moderate yield to give novel bicyclic sulfides. Of interest are rearrangment reactions of the sulfoxides and sulfones derived from the addition product of sulfur dichloride and cycloheptatriene.

The recently reported addition of sulfur dichloride to cyclic diolefins[1-5] was extended to cyclic tri- and tetraolefins and provides a general synthesis for several unsaturated bicyclic β,β'-dichlorosulfides. The observation that bicycloheptadiene leads to a transannular addition product in preference to products resulting from Wagner–Meerwein rearrangement[1] indicated that the reaction could be extended to conjugated cyclic polyolefins, such as cycloheptatriene and cyclooctatetraene. Intramolecular addition was observed in both cases. Results were summarized earlier[4] and details are reported here.[6] The formation of intramolecular addition products from conjugated ring systems in the reaction with sulfur dichloride again emphasizes the unique role of this inorganic sulfenyl chloride in comparison with its organic homologs such as alkylsulfenyl chlorides. For example, the reaction of sulfenyl chlorides with cyclooctatetraene was reported[7] and, although the product was insufficiently characterized, the structure **1** was assumed in analogy to products resulting from addition reactions of cyclooctatetraene involving skeletal rearrangements.[8]

Additions to cyclooctatetraene which proceed i tially or predominantly without rearrangement of t... carbon skeleton are still exceptions. Examples of this are the addition of cyanoimidogen,[9] carbene,[10] and dicyanocarbene,[11] the epoxidation with peracetic acid,[7,12] and the 1,2 cycloaddition of 1,1-dichloro-2,2-difluoroethylene.[13] Furthermore, the significant studies of Huisgen[14] demonstrated that, in the particular case of the addition of bromine to cyclooctatetraene, the reaction proceeds at −55° without skeletal rearrangement to give a 1,2-addition product, and that ring

(1) F. Lautenschlaeger, *J. Org. Chem.*, **31**, 1679 (1966).

(2) E. D. Weil, K. J. Smith, and R. J. Gruber, *ibid.*, **31**, 1669 (1966).

(3) E. J. Corey and E. Block, *ibid.*, **31**, 1663 (1966).

(4) F. Lautenschlaeger in "The Chemistry of Sulfides," A. V. Tobolsky, Ed., Interscience Publishers, New York, N. Y., 1968, p 73; F. Lautenschlaeger, The Princeton University Conference on the Chemistry of Sulfides, June 29, 1966.

(5) F. Lautenschlaeger, *Can. J. Chem.*, **44**, 2813 (1966).

(6) In an independent investigation just prior to the submission of this paper the reaction of 1 and 2 mol of sulfur dichloride with cyclooctatetraene was reported and the resulting structures were determined on the basis of their nmr spectra: P. Y. Blanc, P. Diehl, H. Fritz, and P. Schlapfer, *Experientia*, **23**, 896 (1967).

(7) H. Brintzinger and M. Langheck, *Ber.*, **86**, 557 (1953); H. Brintzinger and H. Ellwanger, *ibid.*, **87**, 300 (1954).

(8) See, for example, W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Ann.*, **560**, 1 (1948).

(9) A. G. Anastassiou, *J. Amer. Chem. Soc.*, **87**, 5512 (1965).

(10) T. J. Katz and P. J. Garratt, *ibid.*, **86**, 5194 (1964); E. Vogel, *Angew. Chem.*, **74**, 829 (1962).

(11) E. Ciganek, *J. Amer. Chem. Soc.*, **88**, 1979 (1966).

(12) A. C. Cope, P. T. Moore, and W. R. Moore, *ibid.*, **80**, 5505 (1958).

(13) G. Schroder and Th. Martini, *Angew. Chem. Intern. Ed. Engl.*, **6**, 806 (1967).

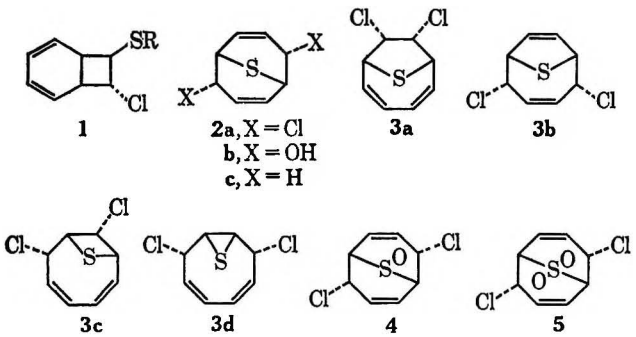
(14) G. Roche and R. Huisgen, *Tetrahedron Lett.*, No. 23, 1769 (1965); R. Huisgen, G. Boche, W. Hechtle, and H. Huber, *Angew. Chem. Intern. Ed. Engl.*, **5**, 585 (1966).

constriction occurs at 0° or in the presence of aluminum trichloride to form a bicyclic dibromide. Thus it was unambiguously demonstrated that tautomerization of cyclooctatetraene to bicyclo[4.2.0]octa-2,4,7-triene is not the initial reaction in addition reactions which ultimately proceed *via* rearrangement.

In our investigations of the reaction products which could conceivably consist of a number of novel ring systems, structural assignments were primarily based on nuclear magnetic resonance spectra and on the shielding effect of the sulfoxide oxygen in the spectrum of the derived sulfoxides and sulfones.

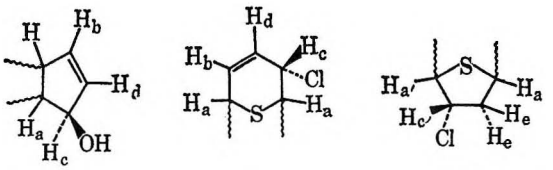
Sulfur dichloride reaction with cyclooctatetraene and cycloheptatriene is essentially one of equimolar proportion of reagents. At −10° in methylene chloride as solvent, only a 0.04 molar equiv of cyclooctatetraene remains unreacted. This suggests that unidentified polymeric products arise from an equimolar addition and that by-products corresponding to a reaction of sulfur dichloride with 2 molar equiv of tetraene analogous to the addition of sulfuryl chloride[7] contribute only to a negligible proportion.

The intramolecular reaction product **2a** is obtained in a yield of 31%. When the addition reaction was carried out at 30°, no isomeric product was obtained as evidenced by gas chromatographic analysis, although, in several cases of repeated additions, evidence for a second product with very close retention time and in a yield of less than 2% was observed. The symmetrical structure **2a** for the major reaction product is suggested by the observation that a single sulfoxide was obtained on oxidation with hydrogen peroxide and that the same sulfoxide was recovered after attempted inversion with triethyloxonium fluoroborate,[5,15] suggesting the symmetrical structure **4**. This structure is further supported by the nuclear magnetic resonance spectrum, where two multiplets with centers 0.22 ppm apart represent protons CHCl, of which the signal at higher field (4.81 ppm) corresponds to the chemical shift of that proton in the sulfide **2a**. This suggests deshielding of only one of the protons H_c and rules out the isomeric structures **3a** and **3b**. As anticipated, in the sulfone **5** the protons H_c are again identical but only 0.11 ppm downfield from their positions in the sulfide **2a**. This deshielding effect is smaller than in the oxidized derivatives of the earlier reported bi- and tricyclic β,β'-dichlorosulfides.[1,5]



1 **2a**, X = Cl; **b**, X = OH; **c**, X = H **3a** **3b** **3c** **3d** **4** **5**

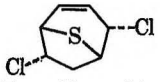
For the configurational assignments of **2a** and its hydrolysis product **2b**, a comparison with the nuclear magnetic resonance spectrum of the ring structure **6a** is



6a **6b** **6c**

of interest.[16] In the latter system, H_c is of opposite configuration with respect to H_a than it is in the six-membered section **6b** of structures **2a** and **2b**. Consequently, the spectrum of **6a** shows a quartet for H_c, resulting from coupling of H_c with H_a and H_d, a quartet for H_d, and a doublet for H_b. In the opposite configuration as shown in **6b**, H_c is represented by a doublet, resulting from coupling with only H_a. Proton H_d is represented by one and proton H_b by two perturbed doublets, whereby the splitting arises from coupling of H_b with both H_a and H_d. A significant difference between the ring system **6a** and the system **6b** is shown by the relative chemical shift of the olefinic protons. Whereas H_d is downfield from H_b in the ring system **6a**, inversion of these positions occurs in **6b** as the result of the proximity of the sulfur atom, which affects H_b to a larger extent than H_d.

Cycloheptatriene leads to the intramolecular addition product **7a** in a yield of 35%. In the nuclear



7a, $X_1 = X_2 = Cl$
b, $X_1 = X_2 = OH$
c, $X_1 = OH$; $X_2 = Cl$

magnetic resonance spectrum, the olefinic and allylic protons in **7a** and its hydrolysis product **7b** resemble those of product **2a** and **2b**. In addition, a sextet pattern observed for H_c' at 4.32 ppm corresponding to a single proton suggests the nonequivalence of both CHCl groups and rules out the hypothetical isomeric structures **17** and **18**. The magnetic equivalence of protons H_e[17] explains the sextet pattern for H_c' which was also observed on a similar ring system **6c**.[3] This result supports the *trans* configuration of the chlorine with respect to the sulfur atom in the five-membered ring of structure **7a**, which is further supported by a coupling of 4.5 cps between H_c' and the bridgehead proton H_a'.

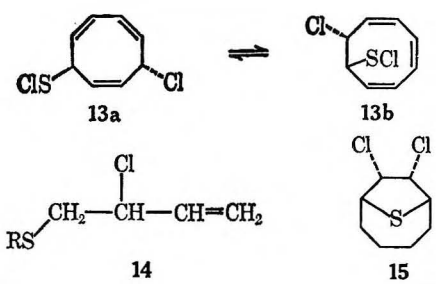
Nucleophilic substitution occurs very readily on the β,β'-dichlorosulfides **2a** and **7a**, although the products are obtained in lower yield than would be expected on the basis of the reaction of similar saturated cyclic chlorosulfides.[1-5] Substitution occurs without rearrangement as demonstrated by the isolation of **2b** and **7b**. The structure **7b** for the diol is supported by the characteristic pattern for the olefinic protons in the nmr spectrum for both dihydroxysulfides **2b** and **7b** and the chlorohydroxysulfide **7c**. The nonidentity of both groups CH–O, indicated by two doublets for these protons at 4.81 and 4.91 ppm, further supports the structure **7b** in preference to an isomeric symmetric structure. Reduction of the dichlorosulfide **2a** with lithium aluminum hydride leads to the novel olefinic sulfide **2c** in low yield.

(15) C. R. Johnson and D. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965).

(16) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, 1964, p 86.

(17) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

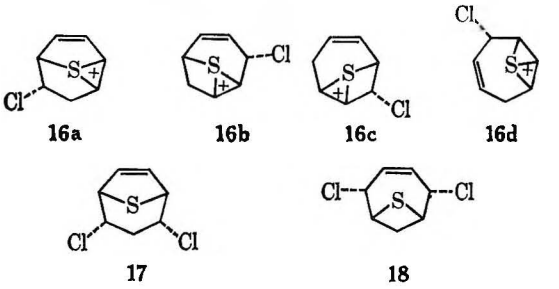
The *trans* or *endo* configuration for the allylic chlorine atom can be rationalized by the assumption of an intermediate episulfonium ion following from the stereochemistry of previously reported additions of sulfur dichloride to cyclic diolefins. The ease of conversion of the diols **2b** and **7b** to the corresponding dichlorides and vice versa supports the involvement of the sulfur atom in these replacement reactions. The stereospecificity of the sulfur dichloride addition and subsequent replacement reactions was particularly remarkable in the products obtained from cyclohexadiene-1,4[3] where in substitution reactions the nucleophile has to approach from the *endo* side of the bicyclic molecule. This is further emphasized on our ring systems **2** and **7**, where the episulfonium intermediate could conceivably compete with an allylic carbonium ion. Participation of such open ions would be expected to yield contribution of products resulting from an *exo* approach of the chloride ion, which was not observed. It is of interest to consider the various episulfonium ions which could be involved in the reaction with cyclooctatetraene and cycloheptatriene. After formation of the intermediates **13a** and **b** in the first addition step, the central location of the sulfur atom of the sulfenyl group in the eight-membered ring could in the second addition step lead to various intermediate ions. These ions can be envisaged by inspection of structures **2a** and **3a** to **3d** after removal of one chloride ion. In each case, the corresponding episulfonium ion or the open allylic carbonium ion are alternative possibilities. The probability of contributions of these various ions would be affected predominantly by the steric requirements of the carbon–sulfur bonds.[18] The formation of product **2a** suggests that the contribution of these intermediates is negligible. It is apparent that the strain required for the sulfur containing ring in the majority of these intermediates is not compensated by the conjugation of the remaining double bonds. Furthermore, it is of interest that, on the basis of the observed product, it cannot be decided whether the reaction of sulfur dichloride with cyclooctatetraene involves two consecutive 1,2 additions or two 1,4 additions *via* **13a** or **13b**, respectively. Our observation, that 1,2 addition proceeds with butadiene-1,3 to give **14**, suggests the first alternative to be more likely. This is further supported by the addition product from cyclooctadiene-1,3[2] for which the structure **15** was established, and which can only result from two consecutive 1,2 additions. The preference for the addition of sulfur dichloride to conjugated olefins in such a manner that the chlorine atom is located in the allylic position is also supported by the product **14** obtained from butadiene-1,3, which consists almost exclusively of the structure shown in preference to the isomeric 1,4 addition product.



13a 13b 14 15

(18) F. Lautenschlaeger, *J. Org. Chem.*, **33**, 2620 (1968).

The ambiguity of 1,4 *vs.* 1,2 addition does not exist in the addition to cycloheptatriene, where the alternative episulfonium intermediates should be different. Structures **16a** and **16c** result from two consecutive 1,2 additions and **16b** from an initial 1,4



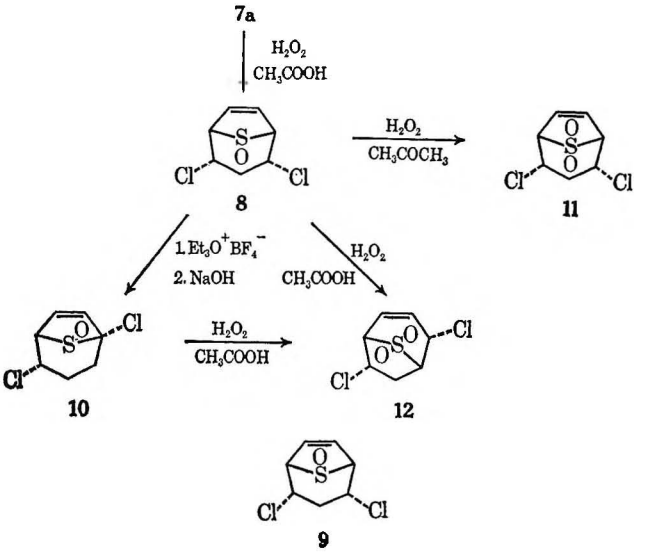
16a 16b 16c 16d 17 18

addition to a terminal double bond. A more strained intermediate, **16d**, results from an initial 1,4 addition to the central double bond of the triene. Therefore, the product can only be explained to result from 1,2 additions. Furthermore, the product obtained from cycloheptatriene can only be rationalized by an initial addition to the terminal olefinic site in preference to addition to the central double bond. Gas chromatographic analysis suggests the formation of isomeric products in a yield of less than 2%. Contributions of structures **17** and **18** could therefore only be small.

A sequence of unexpected rearrangements is observed in the series of oxidation products obtained from **7a** (Scheme I). Oxidation of the dichlorosulfide **7a** with hydrogen peroxide in glacial acetic acid leads to the rearranged sulfoxide **8** as the exclusive product in a yield of 97%. No evidence for the presence of an isomeric product was obtained. The structure of **8** is evident from its nuclear magnetic resonance spectrum, which shows a doublet for the olefinic protons at 5.63 ppm corresponding to two protons. A narrow multiplet of a half-width of 8 cps for both groups CHCl is exhibited at 4.99 ppm. The downfield chemical shift for these pro tons suggests their exposure to the deshielding by th sulfoxide group and therefore supports the sulfoxide configuration as shown in **8**.

Inversion of **8** with triethyloxonium fluoroborate is again accompanied by rearrangement and leads to **10** as the only isolated product. No evidence for the isomeric product **9** was observed. The structure of **10** is

SCHEME I



evident from its nuclear magnetic resonance spectrum which resembles **7a** except for the shielding and deshielding introduced by the sulfoxide group (Table I). The CHCl group in allylic position has shifted from

TABLE I

CHEMICAL SHIFTS OF DICHLORO-8-THIABICYCLO[3.2.1]OCTENE AND DERIVATIVES[a]

	H_b	H_d	H_c	$H_{c'}$
Dichlorosulfide **7a**	5.72	5.18	4.71	4.32
Dihydroxysulfide **7b**[b]	5.92	5.47	4.78	
Dichlorosulfoxide **8**	5.63		4.99	
Dichlorosulfone **11**	5.88		5.17	
Dichlorosulfoxide **10**	5.83	6.16	5.37	4.50
Dichlorosulfone **12**	5.98		5.32	4.91

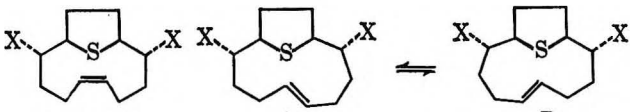
[a] Values in parts per million downfield from tetramethylsilane, recorded on a Varian A-60 spectrophotometer in deuteriochloroform as solvent. [b] Pyridine as solvent.

4.71 ppm in **7a** to 5.37 ppm in **10**. This deshielding of H_c is in opposite direction but of comparable magnitude as reported earlier in a similar bicyclic system.[1] In contrast, the effect on H_b is only 0.09 ppm, although both represent β hydrogens with respect to the sulfur atom. The large effect on H_c suggests the pseudo-axial position of that hydrogen and supports the assigned configuration of **7a**. Although the carbon atoms bearing protons H_b and H_c are nearly equidistant to the sulfoxide group, the different spatial arrangement of the carbon–hydrogen bonds leads to large differences in the deshielding of these protons. The largest deshielding is exhibited by H_d, which is spatially closest to the oxygen atom of the sulfoxide group. For the assignment of the position of the sulfoxide group, it is significant that chemical shifts for H_e and $H_{c'}$ in structure **10** are nearly identical with **7a**. The orientation of the S=O bond in isomer **10**, which is on the side of the olefinic unsaturation after inversion of isomer **8**, supports the opposite assignment of the S=O bond in **8**. The small deshielding actually observed on $H_{c'}$, which is located in line but on the back side of the sulfoxide bond, will be confirmed on a later example in this paper.

Further rearrangement is observed on oxidation of **8** to the oxidation state of the sulfone. If the oxidation is carried out with hydrogen peroxide in glacial acetic acid, an identical sulfone is obtained from both sulfoxides **8** and **10**, but oxidation with hydrogen peroxide in acetone leads to the nonidentical sulfones **11** and **12**, respectively. Although **11** is only isolated in a yield of 51%, **12** is obtained quantitatively from both sulfoxides.

The rearrangement of **7a** on oxidation and its exclusive formation provides a further example of rearrangement of carbon–sulfur bonds arising from steric interaction with electronegative substituents. In earlier examples, the β substituent was either an acetoxy group[19] or a chlorine group, for example, on oxidation of 2,5-chloromethyltetrahydrothiophene.[18] It is of interest that in the case of both ring systems substitution of the β substituent proceeds without rearrangement, whereas oxidation of the sulfides does involve it. In the rearrangement of **7a** to **8**, the predominant factor appears to be the repulsion of the peroxide molecule by the olefinic double bond, which prevents the formation of a sulfoxide with the sulfur–oxygen bond on the side of the olefinic double bond. The rearrangement on inversion of **8** to **10** suggests that the interaction with the olefinic site is partially relieved in **10**. The unusual aspect of this over-all reaction sequence is that the isolation of the sulfone **12** from its sulfide **7a** occurs *via* two rearrangements. These rearrangements are distinctly different from the base-catalyzed isomerizations of β-unsaturated sulfones to their α-unsaturated isomers.[20]

The reaction of sulfur dichloride with cyclic nonconjugated triolefins leads to bicyclic β,β'-dichlorosulfides in which the remaining unsaturation provides substances of synthetic interest. *trans,trans,cis*-Cyclododecatriene-1,5,9 leads to **19** in a yield of 69%, whereas the corresponding *trans,trans,trans* isomer leads to **20** in a yield of 41%. The structure of the products was assigned by analogy to the product obtained from the addition of sulfur dichloride to hexadiene-1,5, where of the possible five-, six- or seven-membered sulfur-containing ring the smallest possible ring system was formed.[18] Addition across the two *trans* bonds of the trienes is therefore assumed to lead to the 2,5-substituted tetrahydrothiophene structure as shown in **19** and **20**. The presence of the *cis* double bond in **19** and the *trans* double bond found in **20** follows from the infrared absorption spectra, which show the characteristic absorption for the remaining *trans* double bond in **20** at 980 cm^{-1} and for the *cis* unsaturation in **19** at 728 cm^{-1}. Substitution reactions proceed readily on the dichlorosulfides and products **21** and **22** were isolated by using the appropriate nucleophiles. The structure of the product **22** is further supported by its nuclear magnetic resonance spectrum which shows a single signal for both acetoxy groups, indicating that both groups are in identical environment whereby this identity arises from free rotation of the olefinic site to include the conformations A and B.



19, X = Cl
21, X = CN
20, X = Cl
22, X = $OCOCH_3$

In structures such as **2a** in which two olefinic sites are available for further addition reactions, a second intramolecular addition of sulfur dichloride was achieved and the addition product was obtained in a yield of 20%.[6] For the resulting product three tricyclic structures can be envisaged, with a further multiplicity arising from the various possible configurations of the carbon–chlorine bonds. The structure is evident from considerations of the resulting sulfoxides. A single monosulfoxide is formed by oxidation with hydrogen peroxide in acetic acid, indicating the formation of **23** or **24** and also that the four six-membered rings are of identical configuration. Such a configuration results from two consecutive *trans* additions, in agreement with the mechanism of addition of sulfenyl chlorides and sulfur dichloride to olefinic sites. However, the isolation of a single sulfoxide does not permit us to distinguish between these alternative ring systems **23** and **24**. The

(19) J. Hora and J. Czerny, *Collect. Czech. Chem. Commun.*, **25**, 711 (1960); *Chem. Abstr.*, **54**, 13113*h* (1960).

(20) R. C. Krug and D. E. Boswell, *J. Heterocycl. Chem.*, **4**, 309 (1967).

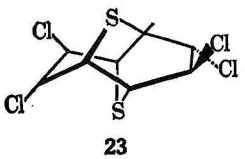
TABLE II

CHEMICAL SHIFTS OF TETRACHLORODITHIAADAMANTANE AND DERIVATIVES[a]

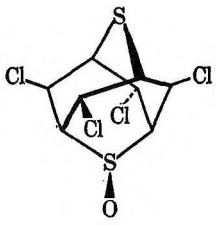
Compound	CHCl	$CH_aSCH_{a'}$	$CH_aSCH_{a'}$
Sulfide **24**	5.68 (4)[b]	...	3.04 (4)
Monosulfoxide **25**	5.88 (1), 5.68 (2), 5.11 (1)	4.15 (2)	3.32 (1), 3.13 (1)
Disulfoxide **26**	5.95 (2) 5.14 (2)	4.27 (1), 4.16 (1), 4.07 (1)	

[a] Values are in part per million downfield from tetramethylsilane, recorded on a Varian HA-100 spectrophotometer in deuterioacetic acid as solvent at 27.5° ($\delta \pm 0.01$ ppm). [b] Numbers in parentheses indicate the number of protons as shown by integration values.

further observation that a single disulfoxide is formed confirms the stereochemical conclusions evident from the monosulfoxide and in addition can only be explained on the basis of the highly symmetrical structure **24**. In addition, the nuclear magnetic resonance spectra of the sulfide **24**, the monosulfoxide **25**, and the disulfoxide **26** are readily interpreted by the aid of shielding and deshielding effects of the sulfoxide groups and reliable quantitative data of this effect can be obtained from the spectra of these rigid tricyclic structures (Table II). In the sulfide **24**, the protons adjacent to sulfur (H_a and $H_{a'}$) are represented by a multiplet at 3.04 ppm and protons adjacent to chlorine (CHCl) by a multiplet at 5.68 ppm. On conversion to the monosulfoxide **25**, one of the protons adjacent to chlorine is shifted upfield by 0.57 ppm, in very good agreement with that



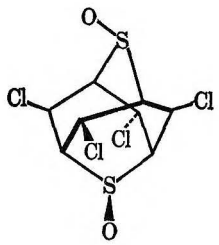
23



24

shielding effect on a similar rigid tricyclic system[1] where a shift of 0.53 ppm was observed. In the same monosulfoxide **25** a proton corresponding to a second CHCl group, which is located in line with the sulfoxide group behind the sulfur atom, is deshielded to a smaller extent (0.20 ppm). The remaining two CHCl protons remain unaffected if their chemical shift is compared with the corresponding sulfide **24**, since both are not located within the range of the magnetic anisotropy of the sulfoxide group.

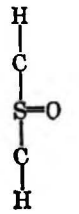
In the disulfoxide **26** the nuclear magnetic resonance spectrum shows similar symmetry as in that of **24**.



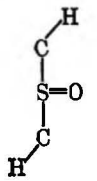
26

Two groups CHCl are shielded by 0.54 ppm compared with their position in **24** and the remaining two groups CHCl which are located in line with the sulfoxide group behind the sulfur atom are shielded by 0.27 ppm in good agreement with the observation on **25**.

Further evidence for structure **24** in preference to isomeric structures results from the inspection of the hydrogen atoms in α position with respect to sulfur.



Ia



Ib

Molecular models indicate that only in the dithiaadamantane structure **24** these hydrogen atoms are in a W-shaped relationship within the group HCSCH and are therefore symmetrically oriented with respect to the sulfoxide bond (Ia). In the alternative transannular sulfur dichloride addition products **23**, both groups of HCSCH are arranged as shown in Ib, where one of these hydrogens is *syn* with respect to the sulfoxide group and the second is *anti*. As a consequence, one proton should be in the region of deshielding of the sulfoxide group in structures containing the arrangement as shown in Ib. Therefore, these protons should be nonidentical in the nuclear magnetic resonance spectrum. Although structures **24**–**26** are clearly evident from previous considerations, it was observed that the protons of the group CHSCH in **25** and of both groups CHSOCH in **26** are magnetically nonequivalent (Table II). Inspection of molecular models indicates that this nonidentity arises from a deshielding of one of these protons within these groups by the sulfoxide oxygen atom attached to the nonadjacent sulfoxide group. The magnitude of this effect is remarkable when one considers the fact that the deshielded proton is attached to a carbon in γ position with respect to this sulfoxide group.

The study of the magnetic anisotropy of the sulfoxide group in these polycyclic sulfides provides a convenient method for structural analysis of polycyclic products obtained from sulfur dichloride additions to cyclic polyolefins.

Experimental Section

Nucler magnetic resonance spectra were recorded on a Varian A-60 instrument; chemical shifts are measured downfield from tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 422 grating instrument in potassium bromide pellets. Gas chromatography spectra were obtained on a Perkin-Elmer Model 800 chromatograph. Melting points were measured on a Hallenkamp block and are uncorrected.

The Reaction of Sulfur Dichloride with Cyclooctatetraene. 2,6-Dichloro-9-thiabicyclo[3.3.1]3,7-nonadiene (2a). A.—A solution of 103 g (1 mol) of freshly distilled sulfur dichloride dissolved in 500 ml of methylene chloride was added with stirring to a solution of 104 g (1 mol) of cyclooctatetraene at an internal temperature of −20 to −10°. The solution was kept at −20° for 12 hr. Gas chromatographic analysis indicated the presence of 0.04 mol of unreacted tetraene although a test for sulfenyl chloride was negative. Evaporation of the solvent and distillation yielded 44% of crude product **2a** which partially turns into a tarry material. Recrystallization from hexane yielded an analytical sample, mp 101–102°, in a yield of 31%. *Anal.*

Calcd for $C_8H_8Cl_2S$: C, 30.99; H, 2.60; Cl, 45.73; S, 20.68. Found: C, 31.15; H, 2.65; Cl, 45.65; S, 20.50. The ir spectrum of **2a** shows strong absorption at 1043, 796, 724, 714, 737, and 703 cm^{-1}.

B. From 2b and Hydrogen Chloride.—A solution of 0.17 g (0.001 mol) of **2b** was dissolved in 10 ml of concentrated hydrochloric acid. Precipitation occurred at once. Filtration of the crystalline product after 30 min, drying over calcium chloride, and sublimation provided 0.07 g (36%) of **2a**, mp 101–102°, identified by mixture melting point and its ir spectrum.

2,6-Dihydroxy-9-thiabicyclo[3.3.1]nonadiene-5 (2b).—A suspension of 3 g of the dichlorosulfide **2a** in 50 ml of water containing 6.0 g of sodium carbonate was stirred rapidly at 80° for 5 min, traces of tarry material were filtered off and the aqueous solution was continuously extracted with diethyl ether to give 1.15 g of diol **2b**, mp 176–179°. *Anal.* Calcd for $C_8H_{10}O_2S$: C, 56.47; H, 5.93; S, 18.87. Found: C, 56.30; H, 5.99; S, 18.70. The ir spectrum of **2b** shows major absorption peaks at 3280, 1035, 1011, and 839 cm^{-1}.

Bicyclo-9-thia[3.3.1]2,6-nonadiene (2c).—A solution of 10.3 g (0.05 mol) of **2a** in diethyl ether was refluxed with 1.14 g (0.03 mol) of lithium aluminum hydride until a gas chromatogram indicated the absence of starting material. The suspension was treated with 50 ml of dilute sulfuric acid and filtered; the organic layer was taken up with 20 ml of benzene, washed with water, dried ($MgSO_4$), and evaporated to give 4.6 g of product. Distillation at 75° (0.02 mm) gave 1.0 g of **2c**, $n^{20}D$ 1.5742. *Anal.* Calcd for $C_8H_{10}S$: C, 69.57; H, 7.30; S, 23.19. Found: C, 69.40; H, 7.59; S, 22.86.

The ir spectrum shows strong absorption at 3020, 2880, 1641, 1422, and 700 cm^{-1} and the nmr spectrum ($CDCl_3$) shows four olefinic protons in the region of 5.4–6.3 ppm and the protons due to the groups CHS are represented as a multiplet at 3.40 ppm.

2,6-Dichloro-9-thiabicyclo[3.3.1]nonadiene 9,9-Dioxide (5).—To a solution of 0.72 g (0.0035 mol) of **2a** in 20 ml of glacial acetic acid was added 0.6 g of 50% aqueous hydrogen peroxide. The solution was allowed to evaporate at room temperature to 5 ml and 0.15 g of product was filtered off. The mother liquor on complete evaporation gave another 0.75 g of product. Sublimation of both products provided a pure material, mp 143–145°. *Anal.* Calcd. for $C_8H_8Cl_2O_2S$: C, 40.2; H, 3.38; S, 13.38; Cl, 29.7. Found: C, 40.4; H, 3.42; S, 13.30; Cl, 29.7.

2,6-Dichloro-9-thiabicyclo[3.3.1]nonadiene 9-Oxide (4).—Sulfide **2a** (3 g, 0.0145 mol) was allowed to react with 1 g of 50% aqueous hydrogen peroxide as described under the preparation of **5**. Sulfoxide (3.1 g) was obtained which was purified by recrystallization from water until mp 131.5–133.5° was obtained. *Anal.* Calcd for $C_8H_8Cl_2OS$: C, 43.08; H, 3.62; Cl, 31.80; S, 14.3. Found: C, 43.06; H, 3.64; Cl, 31.86; S, 14.4.

Attempted Inversion of 4 with Triethyloxonium Fluoroborate.—To a solution of 0.22 g (0.001 mol) of **4** in 5 ml of methylene chloride was added 0.19 g (0.001 mol) of triethyloxonium fluoroborate. After the solution had been kept at room temperature for 12 hr, the solvent was partially evaporated to 2 ml to give 0.17 g of adduct, mp 133° dec. On further evaporation, another 0.13 g of product was obtained. *Anal.* Calcd for $C_{10}H_{13}BCl_2F_4O$: C, 35.43; H, 3.86. Found: C, 35.61; H, 3.61.

To a solution of 0.25 g of sodium hydroxide in 5 ml of water was added 0.125 g of the adduct. After stirring for 5 min, the crystalline product was filtered off, washed with water, and air dried to give 0.06 g of **4**, mp 133.5–135°. The product was identified by mixture melting point and by its infrared absorption.

The Reaction of Sulfur Dichloride with Cycloheptatriene. 2,6-Dichloro-8-thiabicyclo[3.2.1]3-octene (7a). A.—Solutions of 257.6 g (2.8 mol) of freshly distilled cycloheptatriene and 288.4 g (2.8 mol) of sulfur dichloride in 500 ml of methylene chloride were allowed to react by approximately equivalent addition into 500 ml of methylene chloride, which was maintained at −20°. After the reaction was complete, gas chromatographic analysis showed 6% of the cycloheptatriene to be unreacted. After evaporation of solvent, gas chromatographic analysis on the residue showed 41% product **7a**. Distillation at 86–88° (0.003 mm) gave 191 g (35%) of **7a**, which slowly crystallizes at room temperature. Recrystallization from hexane increased the melting point to 47.5–49°.

B.—To 30 ml of concentrated hydrochloric acid was added 0.9 g (0.006 mol) of diol **7b**. The mixture was stirred for 1 hr, kept at +5° for 12 hr, and filtered to give 0.85 g of **7a**, mp 46–48.5°. Sublimation did not increase the melting point of the product. *Anal.* Calcd for $C_7H_8Cl_2S$: C, 43.10; H, 4.13; S, 16.41; Cl, 36.36. Found: C, 43.13; H, 4.27; S, 16.32; Cl, 36.21.

In the nmr spectrum (deuteriochloroform) the perturbed quartet arising from H_b is located at 5.72 ppm and the doublet corresponding to H_d at 5.12 ppm. A small coupling of approximately 1 cps is observed on H_b and H_c.

2,6-Dihydroxy-8-thiabicyclo[3.2.1]3-octene (7b).—An amount of 40 g of the crude reaction product of sulfur dichloride and cycloheptatriene, which contained 41% **7a**, was added in 5-g portions to a boiling solution of 38.2 g of sodium carbonate in 500 ml of water. After high-speed stirring for 15 min, the suspension was allowed to cool and then shaken with 200 ml of diethyl ether to extract ether soluble portions of the separated oily layer. Subsequently, the decanted aqueous solution was continuously extracted for 24 hr with diethyl ether to give, after evaporation, 6.0 g of **7b**, mp 179–181°. Recrystallization from chloroform increased the melting point to 188.5–190°. *Anal.* Calcd for $C_7H_{10}O_2S$: C, 53.16; H, 6.37; S, 20.23. Found: C, 53.37; H, 6.50; S, 20.22.

In the nmr spectrum of **7b** (pyridine) the perturbed quartet of H_b is located at 5.92 ppm and the doublet due to H_d at 5.47 ppm.

2-Hydroxy-6-chloro-8-thiabicyclo[3.2.1]3-octene (7c).—From the water-insoluble portion of the hydrolysis of **7a** described above, 1.2 g of **7c** was obtained by extraction with 250 ml of hexane, and chilling of the extract, mp 95.5–98°. Sublimation did not increase the melting point further. *Anal.* Calcd for C_7H_9ClOS: C, 47.6; H, 5.14; S, 18.12; Cl, 20.8. Found: C, 47.61; H, 5.78; S, 17.76; Cl, 19.82.

In the nmr spectrum of **7c** (deuteriochloroform) the perturbed doublet due to H_b is located at 5.80 ppm and the doublet for H_d at 4.49 ppm.

Oxidation of 2,6-Dichloro-8-thiabicyclo[3.2.1]3-octene with Hydrogen Peroxide. 2,4-Dichloro-8-thiabicyclo[3.2.1]6-octene 8-Oxide (8).—To a solution of 4.4 g (0.0225 mol) of **7a** in 25 ml of glacial acetic acid was added 1.6 g (0.0225 mol) of hydrogen peroxide (50%). The solution was allowed to evaporate to give 4.6 g (97%) of product, mp 90–95°. Recrystallization from heptane increased the melting point to 102–103.5°. *Anal.* Calcd for $C_7H_8Cl_2OS$: C, 39.82; H, 3.82; Cl, 33.59; S, 15.28. Found: C, 40.49; H, 3.73; Cl, 33.38; S, 15.29.

The ir spectrum shows major bands at 1223, 1058, 792 and 773 cm^{-1} and is identical in detail in both the crude oxidation product of **7a** and the purified sample **8**. The nmr spectrum of **8** (hexachlorobutadiene, 80°) shows a doublet for the olefinic protons at 5.63 ppm, multiplets for the groups CHCl at 4.99 ppm, for CHS at 3.7 ppm and for the methylenic protons at 2.75 ppm, each corresponding to two protons.

2,6-Dichloro-8-thiabicyclo[3.2.1]3-octene 8-Oxide (10).—To a solution of 4.4 g (0.02 mol) of **8** in 50 ml of methylene chloride was added 3.8 g (0.02 mol) of triethyloxonium fluoroborate. After standing at room temperature for 5 hr, the solution was evaporated to 25 ml and chilled to −20°; 2.5 g of adduct A, mp 138° dec, was filtered off. *Anal.* Calcd for $C_9H_{13}BF_4Cl_2OS$: C, 33.03; H, 3.98; S, 9.79; Cl, 21.71. Found: C, 32.88; H, 4.04; S, 10.25; Cl, 22.09. On complete evaporation of the solvent, another 5.0 g of adduct was obtained (B).

A.—A suspension of 2.0 g (0.005 mol) of A was stirred for 2 min with 25 ml of 5% aqueous sodium hydroxide. The suspension was filtered and air dried to give 1.0 g (94%) of crude **10**, mp 103–107°. Recrystallization from 80 ml of water increased the melting point to 115–116°. *Anal.* Calcd for $C_7H_8Cl_2OS$: C, 39.82; H, 3.82; Cl, 33.59; S, 15.28. Found: C, 39.56; H, 3.41; Cl, 33.63; S, 15.40.

The infrared spectrum shows major peaks at 1068 cm^{-1} for the sulfur–oxygen stretching mode and 794 and 776 cm^{-1} for the carbon–chlorine stretching mode. Medium intensity peaks are observed at 1300, 887, 874, and 703 cm^{-1}.

B.—A suspension of 5.0 g of B in 50 ml of 5% aqueous sodium hydroxide was stirred for 5 min, filtered, the residue washed with water and air dried to give 2.3 g of product, mp 85–100°. The nmr spectrum of the crude product showed only signals due to **10**. The ir spectrum of the crude product is identical with that of the purified material.

2,6-Dichloro-8-thiabicyclo[3.2.1]3-octene 8,8-Dioxide (12). A.—To a solution of 0.42 g (0.002 mol) of **10** in (20 ml) glacial acetic acid was added 0.3 g of hydrogen peroxide (45% in water). The solution was kept at 60° for 24 hr and was then evaporated to 10 ml to give 0.1 g of **12**, mp 140–142°. Complete evaporation of the mother liquor yielded another 0.35 g of **12**, mp 141–142°,

total yield 99%. *Anal.* Calcd for $C_7H_8O_2Cl_2S$: C, 37.00; H, 3.55; Cl, 31.24; S, 14.12. Found: 37.24; H, 3.41; Cl, 31.27; S, 14.04. The compound shows strong infrared absorption at 1320, 1183, 1112, and 792 cm^{-1}. In the nmr spectrum ($CDCl_3$) the olefinic protons are represented by a narrow multiplet at 5.98 ppm, the allylic CHCl group signal (doublet) is located at 5.32 ppm and the second CHCl group at 4.91 ppm.

B.—To a solution of 0.42 g (0.002 mol) of **8** in 20 ml of glacial acetic acid was added 0.3 g of hydrogen peroxide (45% in water). The solution was heated at 60° for 10 hr and evaporated to dryness and the residue, 4.5 g, mp 123–126°, was recrystallized from ethanol to give a product of mp 138–139.5°. Sublimation provided an analytical sample, mp 142–143°.

The ir spectrum of the purified material is in detail identical with that of the crude reaction product. Mixture melting point with the product obtained from **10** is not depressed.

2,4-Dichloro-8-thiabicyclo[3.2.1]-6-octene 8,8-Dioxide (11).—To a solution of 0.42 g (0.002 mol) of **8** in 20 ml of acetone was added 0.3 g of hydrogen peroxide, the solution was refluxed for 4 hr and then evaporated to dryness to give 0.45 g of partially crystalline material, which was stirred with water, filtered, dried over phosphorus pentoxide, and showed mp 96–99°; the yield was 0.22 g (51%). Sublimation produced an analytical sample, mp 102–103°. *Anal.* Calcd for $C_7H_8Cl_2O_2S$: C, 37.00; H, 3.55; Cl, 31.24; S, 14.12. Found: C, 37.17; H, 3.40; Cl, 31.35; S, 14.00. The infrared spectrum shows major absorption peaks at 1020, 1108, 840 cm^{-1} with medium intensity peaks at 1490, 1425, 1271, 1225, 1158 and 928 cm^{-1} and is not identical with **12**.

The Reaction of Sulfur Dichloride with Butadiene-1,3 (14).—Into a 2-l. round-bottom flask containing 800 ml of dry methylene chloride and cooled to −60 to −70° was condensed 378 g (7 mol) of butadiene. An amount of 348 g (3.38 mol) of sulfur dichloride was added dropwise, maintaining the internal temperature at −60°. After standing at −20° for 12 hr the volatile portions were evaporated to give 670 g (94%) of product. *Anal.* Calcd for $C_8H_{12}Cl_2S$: C, 45.50; H, 5.69; Cl, 33.63; S, 15.16. Found: C, 45.45; H, 5.55; Cl, 33.69; S, 15.30.

The nmr spectrum of **14** shows 2.0 protons for the group CH_2S, 1.95 protons for the group CH=CH, and 0.9 protons for CHCl in close agreement with the proposed structure **14**.

2,9-Dichloro-13-thiabicyclo[8.2.1]-5-tridecene (*cis*) (19).—To a solution of 810 g (5 mol) of *trans,trans,cis*-cyclododecatriene in 2000 ml of methylene chloride was added a solution of 103 g (1 mol) of sulfur dichloride in 500 ml of methylene chloride at −20° with stirring. After the addition was complete, the suspension was allowed to reach room temperature, insoluble product was filtered off and the filtrate was distilled to remove solvent and unreacted triolefin. Recrystallization of the residue from hexane gave 182 g (69%) of **19**, mp 139.5–141.5°. *Anal.* Calcd for $C_{12}H_{18}Cl_2S$: C, 54.34; H, 6.79; S, 12.07; Cl, 26.8. Found: C, 54.42; H, 6.68; S, 12.02; Cl, 26.7.

2,9-Dicyano-13-thiabicyclo[8.2.1]-5-tridecene (*cis*) (21).—To a solution of 9.0 g (0.2 mol) of potassium cyanide in 150 ml of 95% ethanol was added 10.1 g (0.038 mol) of **19** over a period of 30 min at an internal temperature of 40–45°. The solution was treated with 500 ml of water and filtered to give 8.0 g (87%) of crude **21**, mp 134–147, which was washed with pentane and recrystallized from alcohol to give a sample of mp 153–155.5°. *Anal.* Calcd for $C_{14}H_{18}N_2S$: C, 68.29; H, 7.32; N, 11.38; S, 13.01. Found: C, 68.17; H, 7.37; N, 11.42; S, 13.31. The ir spectrum shows strong absorption peaks at 3005, 2920, 2235, 1445, 727, and 695 cm^{-1}.

2,9-Dichloro-1,3-thiabicyclo[8.2.1]-5-tridecene (*trans*) (20).—Under conditions described for the synthesis of **19**, a yield of 41% of **20** was obtained, mp 108–109°. *Anal.* Calcd for $C_{12}H_{18}Cl_2S$: C, 54.34; H, 6.79; S, 12.07; Cl, 26.8. Found: C, 54.48; H, 6.85; S, 12.18; Cl, 26.9. The ir spectrum shows strong absorption at 2965, 2920, 1428, 979, 653, and 638 cm^{-1}.

2,9-Diacetoxy-1,3-thiabicyclo[8.2.1]-5-tridecene (*trans*) (22).—To a solution of 2.65 g (0.01 mol) of **19** in 100 ml of glacial acetic acid was added 1.8 g (0.022 mol) of sodium acetate. The solution was heated on the steam bath for 1 hr and then poured into 1 l. of water. After standing at room temperature for 8 hr the product was filtered off and allowed to dry to give 2.5 g (80%) of **22**, mp 97–99°. After sublimation, mp 104–106° was obtained. *Anal.* Calcd for $C_{16}H_{24}O_4S$: C, 61.5; H, 7.74; S, 10.26. Found: C, 61.7; H, 7.25; S, 10.14. The nmr spectrum ($CDCl_3$) shows a single peak for the group $OCOCH_3$ at 2.0 ppm.

3,5,7,9-Tetrachloro-1,10-dithiaadamantane (24).—To a solution of 10.4 g (0.05 mol) of **2a** in 100 ml of benzene was added a solution of 7.8 g (0.075 mol) of sulfur dichloride and the solution was refluxed until the red color of sulfur dichloride disappeared. After evaporation of benzene the residue crystallized partially. Recrystallization from acetic acid gave 3.1 g of **24** (20%). Sublimation afforded an analytical sample, mp 224–225°. *Anal.* Calcd for $C_8H_8Cl_4S_2$: C, 31.0; H, 2.60; Cl, 45.73; S, 20.68. Found: C, 31.35; H, 2.62; Cl, 45.50; S, 20.58. The ir spectrum shows strong absorptions at 1320, 801, 686, 594, and 380 cm^{-1} and medium-intensity bands at 1270, 1253, 1221, and 939 cm^{-1}.

3,5,7,9-Tetrachloro-1,10-dithiaadamantane 1-Oxide (25).—To a solution of 0.31 g (0.001 mol) of **24** in 75 ml of warm acetic acid was added 1 molar equiv of hydrogen peroxide (45% in water). After 48 hr at 60° the solution had evaporated to 20 ml and 0.07 g of unchanged **24** was filtered off. Complete evaporation of the solvent left 0.23 g of a crystalline product, which was dried over phosphorus pentoxide and recrystallized from heptane to give an analytical sample, mp 215–216° (hot stage). *Anal.* Calcd for $C_8H_8Cl_4OS_2$: C, 29.47; H, 2.47; Cl, 43.49; S, 19.66. Found: C, 29.46; H, 2.22; Cl, 43.14; S, 19.58.

The ir spectrum is distinguished from that of the sulfide **24** by strong absorption peaks at 822, 1058 and 1084 cm^{-1}. The spectrum of the purified product is identical with the crude reaction product's spectrum before recrystallization and suggests therefore the absence of isomeric products.

3,5,7,9-Tetrachloro-1,10-dithiaadamantane 1,10-Dioxide (26).—To a solution of 0.5 g (0.0016 mol) of **24** in 100 ml of warm acetic acid was added with rapid stirring 0.243 g (0.00322 mol) of hydrogen peroxide (45% in water). The solution was kept at 70° for 12 hr and was then allowed to evaporate to half volume, 0.25 g of crude **26** was filtered off, mp 140° dec. Complete evaporation and drying of the residue afforded another 0.3 g of product.

An analytical sample, mp 258°, was obtained by sublimation of the crude material. *Anal.* Calcd for $C_8H_8Cl_4O_2S_2$: C, 28.08; H, 2.36; Cl, 41.46; S, 18.74. Found: C, 28.10; H, 2.35; Cl, 41.50; S, 18.70.

The ir spectrum is distinguished from that of the monosulfoxide **25** and sulfide **24** by the absence of an intense peak at 802 cm^{-1} and the presence of strong peaks at 820 and 1076 cm^{-1}, arising from the carbon–chlorine and sulfur–oxygen stretching frequency. The spectrum is identical with that of the crude reaction product obtained by evaporation of the reaction mixture.

Registry No.—**2a**, 16831-97-3; **2b**, 16831-98-4; **2c**, 16831-99-5; **4**, 16832-00-1; **4** adduct, 12271-16-8; **5**, 16832-01-2; **7a**, 16832-02-3; **7b**, 16832-03-4; **7c**, 16832-04-5; **8**, 16832-05-6; **10**, 16832-06-7; **10** (adduct A), 12271-15-7; **11**, 16832-07-8; **12**, 16832-08-9; **14**, 16832-09-0; **19**, 16832-10-3; **20**, 16832-16-9; **21**, 16832-11-4; **22**, 16832-12-5; **24**, 16832-15-8; **25**, 16832-13-6; **26**, 16832-14-7; sulfur dichloride, 10545-99-0.

Acknowledgment.—The author is greatly indebted to The National Research Council for financial support of part of this investigation and to M. Myhre and D. Johnson for technical assistance.

Radical Reactions of Tetrafluorohydrazine. Cyclic Olefins[1]

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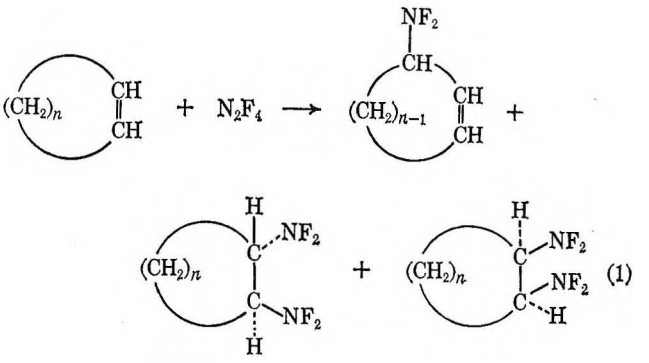
Received January 16, 1968

The reaction of tetrafluorohydrazine with cyclic olefins yields the normal adducts as the major products. Another reaction involving hydrogen abstraction from the α-methylenic carbon atom occurs to varying degrees with cyclopentene and cyclohexene resulting in the formation of mono(difluoramines). Reactions were conducted under various experimental conditions and the effect upon the distribution of products was noted.

Several reports[2-6] pertaining to the addition of tetrafluorohydrazine (N_2F_4) to olefins describe the formation of vicinal bis(difluoramines) *via* a radical mechanism. Hydrogen abstractions are known[7-9] in reactions of tetrafluorohydrazine with various substrates; however, it has been noted[6] that hydrogen abstraction by the difluoramino radical does not occur in the N_2F_4–olefin addition as is often observed in reactions involving radical reagents with olefinic substrates. Under more drastic conditions at elevated temperatures, hydrogen abstraction occurs readily even with saturated hydrocarbons.[10] These results prompted a further study of the reaction of N_2F_4 with cyclic olefins under various experimental conditions to determine the site of attack by the difluoramino radical, since cyclic olefins such as cyclohexene often yield both addition and substitution products when treated with radical reagents.[11-14] Formation of 3-(difluoramino)-substituted cyclic olefins would establish the allylic substitution reaction and represent the first reported example of hydrogen abstraction from olefins by NF_2 radicals. Cyclopentene, cyclohexene, and cyclooctene were employed in this study.

Reactions of the cyclic olefins with N_2F_4 were conducted in a flow reactor at 200–300° and in static reactors (neat and solution) at 30–100° to give similar product mixtures with cyclopentene and cyclohexene (eq 1). Cyclooctene gave only a mixture of *cis–trans* adducts. Absence of the mono(difluoramine) is not surprising in view of the lower reactivity of cyclooctene to hydrogen abstraction by radical reagents.[15]

The products were the same under all conditions, varying only in their percentage of the total product mixture, with the exception that in isolated instances small quantities (<2%) of other products were detected by glpc. These minor products were never present in sufficient quantity for thorough characterization. The addition–substitution product ratios



(1)

(Table I) were greater for those reactions carried out under normal conditions, *i.e.*, low reaction temperatures. Cyclohexene gave consistently slightly higher ratios than cyclopentene, particularly when the reactions were conducted neat, where only minor quantities of the substitution product were isolated. Only in reactions carried out under flow conditions at elevated temperatures did the substitution products predominate. It may be noted that in all instances the ratio of *cis/trans* adduct was greater than 1.0, indicating a slight preference for *cis* addition. A similar preference for *cis* addition was observed[2] in reaction of N_2F_4 with 2-butene and stilbene. The *cis/trans* ratio was greatest for reactions performed on the neat olefin where a qualitative rate enhancement was observed. These product ratios showed little variation in any series of reactions conducted under similar experimental conditions.

Products from the reactions were separated by fractional distillation at reduced pressure or by preparative gas chromatography. Characterization of each was accomplished by their infrared, F^{19} and H^1 nmr spectra, and elemental analysis. These data gave support to the structural assignments. Assignment of the *cis* or *trans* structure to the isomeric bis(difluoramines) was made by analogy of their physical properties with other known cyclic olefin adducts. In general, the *cis–trans* isomers may be distinguished by differences in boiling point, refractive index, density, etc.; the *trans* isomer usually displays the lower values. For instance, *trans*-1,2-dichlorocyclohexane[14] and the *trans*-1-iodo-2-per-

TABLE I

PRODUCT DISTRIBUTION IN CYCLIC OLEFIN–N_2F_4 REACTION

	Product ratios			
	Cyclopentene		Cyclohexene	
Reaction conditions	Addition–substitution	*cis/trans*	Addition–substitution	*cis/trans*
Flow	0.68	1.11	0.77	2.2
Neat (static)	10.9	3.72	53.2	3.0
Solution (90°)	5.4	1.09	7.08	1.11
Solution (30°)	9.6	1.11	11.7	1.10

(1) This work was carried out under the sponsorship of the U. S. Army Missile Command, Redstone Arsenal, Ala., under Contract DA-01-021-ORD-11909(Z).

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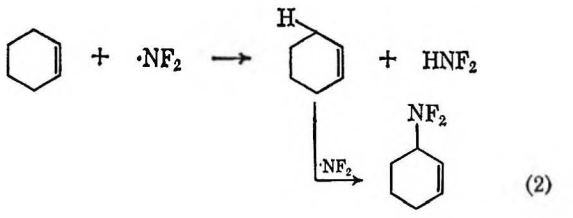
flouoroalkylcyclohexanes[16] exhibit lower values for these properties. In addition, the *trans* isomers normally show shorter retention times on glpc, and bis(difluoroamines) are known[6] to resemble the corresponding dichloro compounds in such physical properties as boiling point, solubility, and retention times on gas chromatography columns.

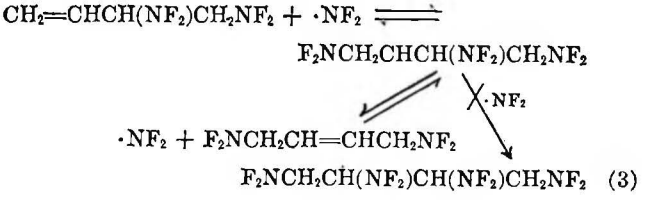
Addition of tetrafluorohydrazine to olefins has been described[2-4,6] as a radical reaction involving the attack of a difluoramine radical on the carbon–carbon double bond of the olefin followed by coupling of the intermediate difluoraminoalkyl radical with $\cdot NF_2$ to give the bis(difluoramine). It has been demonstrated that the reaction with cyclic olefins proceeds to a large extent in the same manner to yield the isomeric adducts. However, the reaction with the cyclic olefins, cyclopentene and cyclohexene, has been shown to occur to some extent by an alternate course involving hydrogen abstraction from the allylic position with the ultimate formation of 3-(difluoramino)-substituted cyclic olefins by coupling of the 3-cycloalkenyl radical (I) with $\cdot NF_2$ (eq 2 for cyclohexene). The presence of difluor-



(2)

amine as a reaction product was difficult to establish although mass spectra of many residual gas fractions were obtained. Its fate is unknown; however, its loss at the higher temperatures under which the flow reactions were conducted is not surprising, nor is the failure to detect its presence as a minor component in the other reactions. In order to substantiate to a degree hydrogen abstraction in reactions of N_2F_4 with cyclic olefins, advantage was made of the higher reactivity of 1,4-cyclohexadiene[17,18] to hydrogen abstraction when subjected to attack by radical reagents. In these reactions which occurred readily in solution at ambient temperatures (explosively when conducted neat) difluoramine was found in large quantities by mass spectral analysis. Although not isolated, it was obtained in yields of 30–40% based on olefin. Unfortunately, the difluoroamino-containing products from these reactions could not be isolated and characterized owing to slow but immediate decomposition of the liquid product mixture.

Another point of interest was the failure to obtain the tiis(difluoramines) from reactions yielding the 3-difluoramino-substituted cyclic olefins, particularly in those reactions carried to near completion with excess N_2F_4 present. In several instances the reaction of N_2F_4 with allyldifluoramines produces tris(difluoramines).[19] The difference in reactivity between the cyclic olefins and their 3-difluoramino derivatives to N_2F_4 addition is probably associated with the stability or steric conformation of the intermediate radical in the 3-difluoraminocyclohexene–N_2F_4 addition as compared with the corresponding intermediate radical for cyclohexene. This latter intermediate, although existing in equilibrium with cyclohexene and $\cdot NF_2$, is relatively more stable and readily couples with $\cdot NF_2$ to give the normal adduct. In the case of the intermediate radical for the 3-difluoramino derivative, its formation is considered probable since polar factors operating in this instance should be similar to those in the simple allyl difluoramines[19] and its final conversion into the tris(difluoramine) is prevented by steric considerations attributed to the conformation of the intermediate and/or to a rapid equilibrium between the intermediate and the reactants. It is known[6] that the N_2F_4 addition reaction is reversible as exemplified by the isomerization of 3,4-bis(difluoramino)butene-1 to 1,4-bis(difluoramino)butene-2 when treated with N_2F_4 and the failure to saturate these olefins under the usual reaction conditions (eq 3). Furthermore, conformational effects



(3)

have been shown[20] to influence reactions with substituted cyclic olefins proceeding through ionic intermediates. The influence of polar and conformation effects on the radical additions to 3-substituted cyclohexenes or cyclopentenes has not been studied. In most reactions of these cyclic olefins with radical reagents where hydrogen abstraction occurs with subsequent formation of 3-substituted derivatives, the presence of trisubstituted derivatives has not been noted. Even in the radical chlorination of cyclic olefins[14] the trichloro derivative, which would normally result from the addition of chlorine to 3-chlorocyclohexene, has not been reported. It is reasonable to assume that similar factors inhibit its formation.

This study has demonstrated the ability of the difluoramino radical to abstract hydrogen atoms from the α-methylenic carbon atom of cyclic olefins and represents the first reported instance of this reaction. Surprisingly, hydrogen abstraction occurs at relatively low temperatures with limited reaction taking place at ambient temperature (30°). Major products in most instances were the normal addition products represented by the *cis–trans* isomers of the cyclic olefins.

It is of paramount importance to conduct these reactions with care since mixtures of N_2F_4 and organic materials in the presence of air constitute explosive hazards. All experimental work was carried out in remote areas employing remote control devices insofar as possible. In addition care should be exercised in the handling of the products since in many instances difluoramines are known to be thermal and impact sensitive materials.

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Experimental Section[21]

Cyclic olefins were purchased from a commercial source and employed as received. They were found to be of at least 98% purity by gas chromatography. The tetrafluorohydrazine employed was known to contain approximately 5% of volatile C–F compounds. F^{19} nmr spectra were obtained with a Varian Associates Model V-3000-B high-resolution spectrometer using a 40-Mc probe. The proton nmr spectra were obtained on a Varian Associates Model A-60 spectrometer and exhibited absorption as expected; however, owing to their complex nature they have not been discussed in this paper. Infrared spectra were obtained with Perkin-Elmer Infracord spectrophotometer. Gas chromatographic work was carried out on an Aerograph Instrument, Model 100-C, using a 5′-dinonyl phthalate on Chromosorb column at 50–100° unless otherwise noted.

Tetrafluorohydrazine–Cyclopentene Reaction.—A solution of 5.8 g (85 mmol) of cyclopentene in 30 ml of methylene chloride was introduced into a thick-walled glass Aerosol tube of 100-ml capacity. The tube was connected to a high-pressure stainless-steel manifold and the solution degassed by alternately pressurizing to 500 psi with nitrogen and evacuating to low vacuum. The system was then pressurized to an equilibrium pressure of 160 psi with tetrafluorohydrazine and heated to 90°. This temperature was held over a period of 2 hr while the tetrafluorohydrazine pressure was maintained over the range of 160–330 psi by frequently recharging as necessary. After cooling to ambient temperature the excess tetrafluorohydrazine was vented, the reactor tube removed from the manifold, and its contents were transferred to a 100-ml round-bottom flask. The methylene chloride was removed by distillation, bp 39°. The distillation was continued through an 18-in. Holtzman column to give the following fractions: (A) 1.80 g, bp 47–50° (82 mm); (B) 5.1 g, bp 60–63° (42 mm); and (C) 5.7 g, bp 63–68° (17 mm). Examination of each fraction by gas chromatography showed incomplete separation of the three components. Each fraction was separately redistilled to give (A) 1.24 g, bp 49° (81 mm); (B) 4.62 g, bp 56° (36 mm), $n^{20}D$ 1.3912, d^{25}_4 1.316; and (C) 5.03 g, bp 67° (16 mm), $n^{20}D$ 1.3987, d^{25}_4 1.350. This represents yields of 12.1, 31.5, and 35.5% of the three products, respectively. Fraction A was identified as 3-(difluoroamino)-cyclopentene by infrared and F^{19} nmr spectral data and elemental analysis. The F^{19} nmr spectrum displayed a doublet at ϕ −48.2 and −47.8. The infrared spectrum was characterized by strong absorption bands in the 800–1000-cm^{-1} region typical of NF_2 compounds. Vinyl proton absorption was noted in the H^1 nmr spectrum in the region of τ 3.8–4.2.

Anal. Calcd for $C_5H_7F_2N$: C, 50.42; H, 5.88; F, 31.93; N, 11.76. Found for A: C, 50.71; H, 5.66; F, 31.85; N, 12.23.

Fractions B and C were identified in a similar manner as isomeric 1,2-bis(difluoroamino)cyclopentanes. Their infrared spectra showed strong absorption in the 800–1000-cm^{-1} region. The F^{19} nmr spectra showed typical ABX patterns with the AB portion represented by a series of four doublets.[22] The secondary NF_2 groups exhibited absorption in the usual range of ϕ −30 to −55.

Anal. Calcd for $C_5H_8F_4N_2$: C, 34.88; H, 4.65; F, 44.19; N, 16.28. Found for B: C, 35.06; N, 4.81; F, 44.60; N, 16.80. Found for C: C, 34.16; H, 4.96; F, 44.20; N, 16.63.

In a similar reaction conducted at 25–30° for 24 hr yields of 8% (A), 35% (B), and 39% (C) were obtained upon distillation.

In reactions conducted under flow conditions, the system was composed of feed lines for tetrafluorohydrazine and helium connected through separate calibrated flow meters into a single line to the reactor, a copper coil 0.25 in. in diameter and 12 ft in length. The cyclopentene was introduced into the feed line from a calibrated power driven syringe at a point prior to its entrance to the reactor. The reactor was completely enclosed in an electrical furnace and the temperature measured by means of thermocouples placed within the furnace immediately adjacent to the reactor coil. The exit line from the reactor was passed through a series of cold traps cooled in the order −80, −130, and −196°. In practice the organic materials from the reactor were always collected in the −80° trap while excess or unreacted tetrafluorohydrazine and other volatile gases were collected in the −196° trap. The reactions were initiated by first flushing the system at a given temperature with helium and, while maintaining the helium flow at the desired level, both tetrafluorohydrazine and cyclopentene flows were started. For instance at a reactor temperature of 250° and a constant helium flow of 25 ml/min, tetrafluorohydrazine was introduced at the rate of 140 ml/min and cyclopentene at 0.2 ml/min. The reaction was continued for 50 min with the helium flow being continued for an additional 15-min period. The −80° trap contained the major part of the organic materials. These materials were transferred from the trap into another series of cold traps cooled to −80, −130, and −196° in order to ensure removal of any dissolved tetrafluorohydrazine. After opening to the air, the contents of the trap were transferred to a distillation assembly and the products isolated by distillation. From this reaction there were obtained 2.05 g of A, 0.96 g of B, and 1.05 g of C whose physical properties were identical with those previously described. This represents ~25% conversion of cyclopentene into products and increased the relative yield of A to ~50%.

In another reaction 6.8 g (100 mmol) of deaerated cyclopentene was condensed through a glass manifold into an evacuated 1-l. stainless-steel cylinder fitted with pressure gauge and valve. Tetrafluorohydrazine, 10.4 g (100 mmol), was condensed into the cylinder, the valve closed, and the cylinder allowed to warm to ambient temperature (30°). After standing for a period of 48 hr the contents of the cylinder were removed and collected in a series of cold traps cooled in the order −80, −130, and −196°. The −196° trap was found to contain 1.87 g (18 mmol) of tetrafluorohydrazine and a trace of cyclopentene. The −80° trap contained 14.9 g of liquid residue. Distillation of this residue gave 0.75 g (6.3%) A, 2.5 g (14.5%) of B, and 9.3 g (54%) of C. This was one instance where the ratio of the bis isomers was decidedly different.

Tetrafluorohydrazine–Cyclohexene Reaction.—Reactions of tetrafluorohydrazine with cyclohexene were conducted under similar conditions employing the three experimental techniques. For instance, when a solution of 5.8 g (71 mmol) of cyclohexene in 30 ml of methylene chloride contained in the glass Aerosol tube was heated to 90° for 2 hr under 330–160-psi tetrafluorohydrazine pressure the products isolated by fractional distillation were 3(difluoramino)cyclohexene (D), bp 45° (24 mm), $n^{20}D$ 1.4138, 1.08 g (11.5%); a mixture of isomeric bis(difluoramino)-cyclohexanes [E, bp 56° (12 mm), $n^{20}D$ 1.4099, d^{25}_4 1.305, 5.06 g (38%), and F, bp 58° (11 mm), $n^{20}D$ 1.4123, d^{25}_4 1.337, 5.64 g (42%)]. The infrared spectrum of D showed strong N–F absorption in the 800–1000-cm^{-1} region. Its F^{19} nmr spectrum displayed a doublet at ϕ −43.6 and −43.1 typical of the >$CHNF_2$ group. Vinyl proton absorption was noted in the H^1 nmr spectrum at τ 3.8–4.2.

Anal. Calcd for $C_6H_9F_2N$: C, 54.14; H, 6.77; F, 28.57; N, 10.53. Found for D: C, 53.97; H, 6.61; F, 27.8; N, 10.91.

The identity of products E and F as being *cis–trans* isomers was based on similar data. Their infrared spectrum displayed strong absorption in the 800–1000-cm^{-1} region typical of N–F compounds. The fluorine resonance of the two isomers occurred as a typical ABX pattern.

Anal. Calcd for $C_6H_{10}F_4N_2$: C, 38.71; H, 5.38; F, 40.86; N, 15.05. Found for E: C, 38.51; H, 5.49; F, 40.56; N, 15.51. Found for F: C, 38.96; H, 5.41; F, 40.93; N, 15.69.

In a similar reaction conducted at 30° the products were D (7%), E (39%), and F (43%).

When the reaction was conducted in the flow reactor under the following conditions [200°, helium (25 ml/min), N_2F_4 (140 ml/min), cyclohexene (0.2 ml/min), time, 50 min], 7.69 g of liquid was collected in the −80° trap. Distillation gave 5.8 g of cyclohexene, bp 83°, 1.95 g of 3-(difluoramino)cyclohexene (D), and 0.69 (E) and 1.46 g (F) of the bis(difluoramino)cyclohexanes. This represents a conversion of approximately 26% under these experimental conditions with a ratio of the mono- to bis(difluoramines) of close to 1:1.

The reaction of 8.2 (100 mmol) of cyclohexene with 15.42 g (148 mmol) of tetrafluorohydrazine in a 1-l. stainless-steel cylinder at 30° for 4 hr gave 0.15 g of D, 3.16 g of E, and 8.73 g of F. This ratio of products was similar to that found in the case of cyclopentene.

Tetrafluorohydrazine–Cyclooctene.—When 5.5 g (50 mmol) of cyclooctene in 30 ml of methylene chloride was treated with tetrafluorohydrazine (350–150 psi) at 90° for 6 hr in a glass Aerosol tube the only products isolated was a mixture of the *cis–trans*-bis(difluoramino)cyclooctenes which were not separated. There was no evidence for the presence of the mono(difluoramino)-

(21) All boiling points are uncorrected.

(22) F. A. Johnson, C. Haney, and T. E. Stevens, *J. Org. Chem.*, **32**, 466 (1967).

cyclooctene. The isomers, 10.62 g (67%), were isolated by distillation: bp 50° (0.85 mm); $n^{20}D$ 1.4342; d^{25}_4 1.265. The presence of the two isomers in a ratio near 1:1 was established by gas chromatography using a 5-ft Dow Corning silicone 11 on Fluoropak column. The F^{19} nmr spectrum of the mixture showed the typical ABX pattern.

Anal. Calcd for $C_8H_{14}F_4N_2$: C, 44.86; H, 6.54; F, 35.51; N, 13.08. Found: C, 44.20; H, 6.62; F, 35.60; N, 14.42.

Registry No.—Tetrafluorohydrazine, 10036-47-2; fraction A, 16666-28-7; fraction B (*cis*), 16666-34-5; fraction C (*trans*), 16666-35-6; fraction D, 16666-29-8; fraction E (*cis*), 14182-81-1; fraction F (*trans*), 16666-31-2; *cis*-1,2-bis(difluoramino)cyclooctane, 16666-32-3; *trans*-1,2-bis(difluoramino)cyclooctane, 16666-33-4.

Acknowledgment.—Measurement and interpretation of the nmr spectra by Mrs. Carolyn Haney and Dr. F. A. Johnson are greatly appreciated. Technical assistance was rendered by Mr. J. O. Woods.

The Addition of N,N-Dichloro Carbamates to Conjugated Dienes

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Received December 14, 1967

The addition of N,N-dichloro carbamates (methyl, isopropyl, and bisethylene glycol) to a series of conjugated dienes (butadiene, isoprene, 2,3-dimethyl-1,3-butadiene, chloroprene, and piperylene) has been found to give high yields of the corresponding N-chloro-ω-chlorocrotyl carbamates. The mode of addition of these pseudo-halogens has been shown to be primarily 1,4 with minor amounts of other adducts also being formed. The N-chloro function of the adducts can be reduced in high yield with sodium sulfite to give the corresponding carbamates. Spectral data pertinent to the proof of structures are presented. A possible mechanism for the addition is discussed.

The addition of the pseudo-halogen, N,N-dichlorourethan, to a number of olefins has been reported.[2,3] The reaction is reported to give anti-Markovnikov adducts with terminal olefins.[2] With the isomeric-2-butenes[3c] and *trans*-3-hexene[2] mixtures of the *erythro* and *threo* isomers are formed. The initial adducts

$$RCH{=}CHR' + C_2H_5OCNCl_2 \longrightarrow RCH(Cl)CH(R')N(Cl)COC_2H_5 \longrightarrow RCH(Cl)CH(R')NHCOC_2H_5$$

β-chloro-N-chloro carbamates were not isolated but were reduced to the β-chloroethyl carbamates with either sodium bisulfite[2] or potassium iodide followed by thiosulfate solution.[3]

As part of a continuing study in this laboratory[4] of the chemistry of unsaturated hydrocarbons, the reaction of N,N-dichloro carbamates with a series of conjugated dienes has been examined.

The particular N,N-dichloro carbamates employed were methyl,[5] isopropyl, and a novel difunctional species, N,N,N′,N′-tetrachloroethylene glycol biscarbamate. These materials were prepared in fair to good yields by chlorination of the corresponding carbamate in aqueous sodium acetate solution.[2]

$$ROCNH_2 + 2Cl_2 \xrightarrow{NaOAc} ROCNCl_2 + 2HCl$$

R = CH_3, i-C_4H_7, $-(CH_2)_2-$

Results

The addition reactions could be performed in a number of ways. The N,N-dichloro carbamate could be added dropwise to a cooled solution of the diene or vice versa. With gaseous butadiene it was found to be particularly advantageous simply to distil the material, after dilution with nitrogen, into a chilled solution of the N,N-dichloro carbamate. Removal of the solvent afforded near quantitative yields of monoadduct.

The crude products were analyzed by a combination of gas chromatography (gc) and nuclear magnetic resonance spectroscopy (nmr). The products were then further purified by distillation *in vacuo*. The yields of analytically pure product along with pertinent physical data are recorded in the Experimental Section. The nmr parameters of the adducts are tabulated in Table I.

The reduction of the N-chloro group of the adducts could be effected in good yield with sodium sulfite to give the corresponding crotyl carbamates. The nmr parameters of these materials are tabulated in Table I.

An examination of the infrared and nmr spectra of the N-chloro adducts and their corresponding reduction products clearly indicate that the principal mode of addition is 1,4. As an example, the infrared spectrum of the butadiene adduct shows strong absorptions for the *trans*-disubstituted double bond. In the nmr spectra, the chemical shift of the CH_2Cl grouping was essentially the same in the N-chloro adduct and its corresponding reduction product. On the other hand, the chemical shift of the CH_2–N group was very sensitive to changes in chemical environment. Upfield shifts of the magnitude of 0.4–0.5 ppm were observed for this signal upon reduction of the N-chloro group ($-CH_2-NCl- \rightarrow CH_2-NH-$). Further substantiation of this assignment is found in the fact that this signal appears as a doublet (J = 5–7 Hz) in the reduction product due to NH–CH< coupling.[6] Exchange of the amide proton with

(1) Analytical Research Division.

(2) T. A. Foglia and D. Swern, *J. Org. Chem.*, **31**, 3625 (1966).

(3) (a) K. Schrage, *Tetrahedron Lett.*, 5795 (1966); (b) *Tetrahedron*, **23**, 3033, 3039 (1967).

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TABLE I.—NUCLEAR MAGNETIC RESONANCE PARAMETERS OF N,N-DICHLORO CARBAMATE–UNSATURATE ADDUCTS GROUP ASSIGNMENTS[a]

Unsaturate	Registry no.	ROCN(X)—O X	Structure 1	2	3	4	5	R[b] CH_3	R[b] $(CH_3)_2$	R[b] CH	R[b] NX	Chemical shift, ppm 1	2	3	4	5	Coupling constant,[a] J, cps
Butadiene	16487-86-8	Cl	$-CH_2-$	$-CH=$	$=CH-$	$-CH_2Cl$		3.78 s	...	...	...	4.15 m	.....5.88 m.....		4.15 m		
	16487-79-9	H	$-CH_2-$	$-CH=$	$=CH-$	$-CH_2Cl$		3.81 s	...	...	...	3.76 m	.....5.78 m.....		4.05 m		
	16487-72-2	H	$-CH_2-$	$-CH(Cl)-$	$-CH=$	$=CH_2$		3.63 s	...	...	...	3.45 m	4.47 q	5.93 ddd	5.32 dd		$J_{2,3} = 7.2$; $J_{3,4} = 16.5$ (t); 9.5 (c); $J_{4g} = 2.0$
															5.19 dd		
	16487-87-9	Cl	$-CH_2-$	$-CH=$	$=CH-$	$-CH_2Cl$		...	1.27 d	4.92 hp	...	4.14 m	.....5.87 m.....		4.14 m		$J_R = 6.5$
	16487-80-2	H	$-CH_2-$	$-CH=$	$=CH-$	$-CH_2Cl$		...	1.20 d	4.85 hp	5.52 b	3.75 m	.....5.77 m.....		4.02 m		$J_R = 6.3$
Isoprene	16487-88-0	Cl	$-CH_2-$	$-C(CH_3)=$	$=CH-$	$-CH_2Cl$		3.78 s	...	...	...	4.17 s	1.73 s	5.66 t	4.11 d		$J_{3,4} = 7.5$; $J_{3,g} = 1.2$; $J_{1,3} = 1.4$
	16487-81-3	H	$-CH_2-$	$-C(CH_3)=$	$=CH-$	$-CH_2Cl$		3.62 s	...	...	5.90 t	3.68 d	1.73 s	5.57 t	4.07 d		$J_{3,4} = 7.9$
	16487-89-1	Cl	$-CH_2-$	$-C(CH_3)=$	$=CH-$	$-CH_2Cl$		...	1.27 d	4.93 hp	...	4.15 s	1.73 bs	5.63 t	4.12 d		$J_R = 6.3$
	16487-82-4	H	$-CH_2-$	$-C(CH_3)=$	$=CH-$	$-CH_2Cl$		...	1.24 d	4.94 hp	5.1	3.76 d	1.73 bs	5.61 t	4.09 d		$J_R = 6.3$; $J_{3,4} = 7.8$; $J_{NH^{-1}} = 6.5$
	16487-93-7	Cl	$-CH_2-$	$-C(Cl)=$	$=CH-$	$-CH_2Cl$		3.77 s	...	...	...	4.29 s	1.77 s	1.85 s	4.11 s		
2,3-Dimethyl-1,3-butadiene	16487-43-7	H	$-CH_2-$	$-C(CH_3)=$	$C(CH_3)$	CH_2Cl		3.62 s	...	...	5.35 b	3.78 d	1.82 bs	1.82 bs	4.04 s		
	16487-90-4	Cl	$-CH_2-$	$-C(CH_3)-$	$C(CH_3)-$	CH_2Cl		...	1.33 d	5.02 hp	...	4.34 s	1.82 bs	1.82 bs	4.16 s		
	16487-83-5	H	$-CH_2-$	$-C(CH_3)-$	$C(CH_3)-$	CH_2Cl		...	1.23 d	4.92 hp	4.55 b	3.82 d	1.82 bs	1.82 bs	4.08 s		
Piperylene	16487-92-6	Cl	$-CH_2-$	$-CH=$	$-CH(Cl)-$	$-CH_3$		3.77 s	...	...	...	4.15 m	.....ca. 5.6 m.....		4.55 m	1.58 d	$J_{1,3} = 6.8$
	16487-74-4	Cl	$-CH-$	$-(CH_2)-$	$-CH=$	$-CH_2Cl$		3.77 s	...	...	...	5.06 m	1.33 d	..... ca. 5.8.....		4.05 m	$J_{1,2} = 6.3$
	16487-75-5	Cl	$-CH_2-$	$-CH(Cl)-$	$-CH=$	$-CH_3$		3.77 s	...	...	...	...	4.45 m	.....5.75 m.....		1.73 d	$J_{3,4} = 5.5$
	16487-85-7	H	$-CH-$	$-CH=$	$-CH(Cl)-$	$-CH_3$		3.63 s	...	...	...	6.10 b	3.75 m	..... ca. 5.7 m.....	4.55 m	1.55 d	$J_{4,5} = 6.5$
	16487-76-6	H	$-CH-$	$-(CH_2)-$	$-CH=$	$-CH_2Cl$		3.63 s	...	...	...	6.10 b	4.26 m	1.23 d	.....5.74.....	4.03 m	$J_{4,5} = 7.0$
	16487-77-7	H	$-CH_2-$	$-CH(Cl)-$	$-CH=$	$-CH_3$		3.63 s	...	...	...	6.10 b	~4.4 m	..... 5.78.....		1.72 d	$J_{4,5} = 5.5$
Chloroprene	16487-93-7	Cl	$-CH_2-$	$-C(Cl)=$	$-CH=$	$-CH_2Cl$		3.81 s	...	...	...	4.43 s	...	6.06 t	4.27 d		$J_{1,3} = 1.0$; $J_{1,4} = 0.7$; $J_{3,4} = 7.3$
	16487-44-8	H	$-CH_2-$	$-C(Cl)=$	$-CH=$	$-CH_2Cl$		3.71 s	...	...	...	5.79 b	4.02 d	...	6.03 t	4.22 d	
									(R = $-CH_3$)								
	16487-94-8	Cl	$-CH_2-$	$-C(Cl)=$	$-CH=$	$-CH_2Cl$		...	4.43 s	...	...	4.43 s	...	6.06 t	4.23 d		$J_{1,4} = 7.2$
	16487-84-6	H	$-CH_2-$	$-C(Cl)=$	$-CH=$	$-CH_2Cl$		...	4.21 s	...	~4.1 b	3.93 d	...	6.05 t	4.25 d		$J_{NH^{-1}} = 6.0$

[a] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, hp = heptet, b = broad, g = geminal, (c) = *cis*, (t) = *trans*. [b] R = methyl, isopropyl, or $(CH_2)_2$.

deuterium oxide caused the doublet to coalesce to a singlet. These data are compatible only with the 1,4 assignment for the adducts.

N,N-Dichloromethyl Carbamate Additions. Butadiene.—The reaction of N,N-dichloromethyl carbamate (DMC) proceeded smoothly to afford a nearly quantitative yield (>98%) of 86% of 1,4 adduct and 14% of the 1,2 adduct. The nmr spectrum of the crude product shows peaks due to both isomers. Integration of the relative amounts of protons of the respective —CH=CH— and $=CH_2$ groups allowed a calculation of the isomer ratio. Analysis of the crude product by gc indicated a 90:10 ratio of 1,4 to 1,2 adduct, the 1,2 adduct being eluted first.

In the 1,4 adduct, the olefin protons and the allylic methylene groups form a tightly coupled ABC_2D_2 system. The olefinic protons of the internal double bond appear as a complex two-proton multiplet at 5.88 ppm while the methylene groups which have nearly the same chemical shift appear as a four-proton multiplet at 4.15 ppm. Strong double irradiation of the olefin region collapses the methylene multiplet into a broad singlet. *trans* stereochemistry of the double bond in the major isomer is shown by characteristic bands at 3000 [=C—H stretching (str)] and 963 cm^{-1} [=C—H out of plane deformation (def)].[7a] Other bands due to the carbamate group were found at 1715 cm^{-1} (C=O str).[7b]

The minor isomer, the 1,2 adduct, was characterized by the typical resonance pattern of a terminal vinyl group which appears between 5.1 and 6.1 ppm. Signals due to other protons were coincident with those of the major isomer.

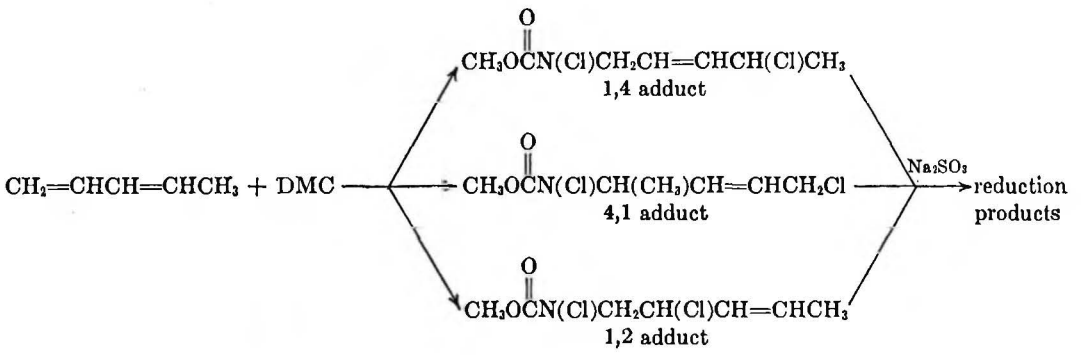
The ratio of isomers was independent of the solvent employed in the reaction. A 90:10 mixture of 1,4 and 1,2 adducts (determined by gc analysis) was obtained whether the reaction was run in pentane, benzene, methylene chloride, carbon tetrachloride, ether, or neat. In ether some chlorination of the solvent occurred; however, the ratio of the adducts formed was still 90:10. Furthermore, the same ratio of adducts was obtained when the reaction was performed in the dark under a nitrogen atmosphere. However, when the reaction was conducted in the dark under an oxygen atmosphere, addition was not observed and only starting material was recovered.

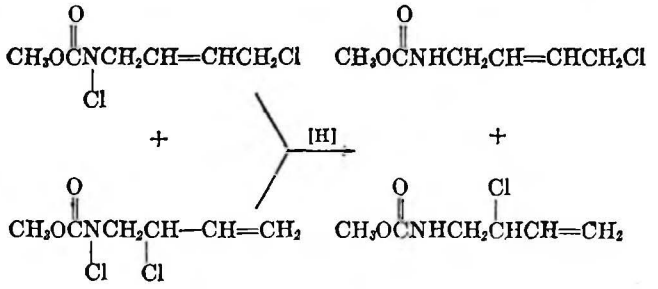
A number of reagents were examined for the reduction of the N-chloro group. The use of aqueous sodium bisulfite solution[7] afforded a 66% yield of reduced product. The ratio of 1,4 and 1,2 adducts in the crude reduction product remained at 90:10 so that no allylic rearrangement occurred during reduction.

The reduction of the N-chloro group by an exchange reaction with methyl carbamate was also attempted. It has been reported[8] that the reaction of equimolar

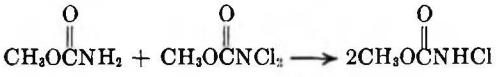
(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1959: (a) p 34; (b) p 222; (c) p 219.
(8) R. L. Datta and D. Gupta, *J. Amer. Chem. Soc.*, **37**, 569 (1915).

Scheme I





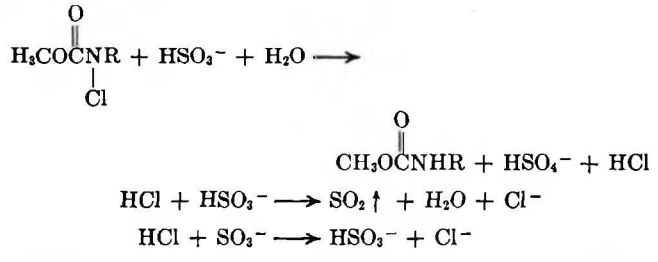
amounts of methyl carbamate and N,N-dichloromethyl carbamate results in the formation of N-chloromethyl carbamate.



The reaction of equimolar amounts of methyl carbamate and the isomeric mixture of N-chloro adducts was examined by nmr spectroscopy. No detectable amount of reduction product was observed after 125 hr at room temperature or after subsequent heating at 60° for 4 hr.

The reagent of choice for the reduction of the N-chloro group was found to be sodium sulfite. Stirring a methylene chloride solution of adduct with a 3 *M* excess of aqueous sodium sulfite solution at room temperature for 0.5 hr resulted in an 89% yield of reduction product.

The superiority of the sulfite method probably resides in the ability of the sulfite to buffer the acid generated in the reduction reaction. When bisulfite is used as a



reducing agent, the pH of the aqueous solution at the end of the reaction is about 3 as monitored by pH paper. In addition, sulfur dioxide is liberated. The acid generated may then hydrolyze part of the product lowering the yield. On the other hand, with sulfite qualitatively less sulfur dioxide is liberated. Also, the pH of the aqueous solution remains near neutral indicating a more effective buffering action.

In one experiment, the mixture of reduction products was distilled to effect a partial separation of the isomers.

The infrared spectrum of the 1,4 isomer has a prominent band at 960 cm^{-1} (=CH— out of plane def)[7a] that strongly supports the proposed *trans*-disubstituted olefin structure. The nmr data are in agreement with this infrared assignment. Conversion into the N—H group results in a shielding of the adjacent methylene group. It now is chemically shifted from the methylene group next to chlorine and is a multiplet at 3.76 ppm. The —CH_2Cl protons of the reduced adduct show up as a multiplet at 4.05 ppm while the olefin protons are a multiplet at 5.78 ppm. The interaction of these three groups was confirmed by a field sweep double resonance experiment. Irradiation at the center of the olefin multiplet collapsed either multiplet to a singlet.

Infrared and nmr analysis of the reduced 1,2 isomer confirms the structure of the original product. Prominent infrared bands at 1000 and 925 cm^{-1} [7a] (=C—H, $=CH_2$ out of plane def) are characteristic for the terminal vinyl group. Bands due to the carbamate group are at 1245 (C—O str), 1705 (C=O str[7b]), and 1525 cm^{-1} [7c] (N—H + C—N combination band). The nmr data support the infrared assignments. The vinylic methine proton is a doublet of a double doublet at 5.93 ppm. It is coupled to the nonequivalent terminal methylene protons at 5.19 and 5.32 ppm and to the allylic methine proton at 3.45 ppm. This proton is a quartet due to nearly equivalent coupling with both the vinyl proton and the methylene group adjacent to nitrogen. In the reduced product, the methoxy protons are slightly upfield at 3.63 ppm while the N—H proton (removable by deuterium oxide) shows a broad resonance peak at 5.90 ppm.

Other Dienes.—The addition of DMC to isoprene, chloroprene, and 2,3-dimethyl-1,3-butadiene was also examined. The nmr spectrum of the isoprene adduct indicated at least an 85% selectivity for the 1,4-addition product. The remainder of the material presumably resulted from 4,1 addition as evidenced by the presence of a broad singlet at 1.84 ppm for the vinylic methyl group (=C—CH_3) of this adduct and the lack of terminal olefin ($=CH_2$) absorption (4,3 adduct) or a signal for a tertiary methyl group adjacent to chlorine (1,2 adduct). The latter signal would be expected to be in the 1.5–1.65-ppm region. These isomers could not be separated by gc under a variety of conditions. The reaction of DMC with the latter two dienes led exclusively to the formation of 1,4 adducts (see Table I, p 2638).

Piperylene.—The reaction of piperylene with DMC results in a 95% yield of the three isomeric adducts formed by 1,2 (26%) and 1,4 (44% 1,4 and 30% 4,1) addition to the conjugated system (Scheme I).

The structure of each isomer was established by a detailed study of the nmr spectrum of the crude reaction mixture. These data were supported by infrared and nmr double irradiation studies. The results of the latter technique were invaluable in assigning chemical shifts to overlapping protons and confirming tentative assignments.

Each isomer was characterized by the nmr signal for its methyl group in the piperylene moiety. These groups have well known[9,10] shifts being adjacent to chlorine (1.58 ppm), nitrogen (1.33 ppm), or the double bond (1.73 ppm), respectively. Integration of these signals on an expanded scale allowed quantitative determination of each isomer.

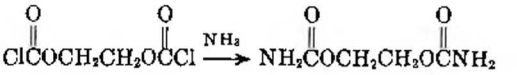
Irradiation of the chloromethine area at 4.55 ppm collapsed the methyl group doublet (J = 6.6 Hz) adjacent to chlorine of the 1,4 adduct to a singlet confirming that this group was coupled to an allylic methine proton (α to chlorine) rather than to an olefinic proton. Likewise strong irradiation in the olefin region collapsed the two-proton methylene signal at 4.15 ppm to a singlet. Reduction of the N-chloro group resulted in a diamagnetic shift of the adjacent methylene group 0.40 ppm upfield establishing its position α to nitrogen. In the reduced product, the position of the methyl group and methine proton adjacent to chlorine did not shift significantly. The doublet could be decoupled easily by irradiation again at 4.55 ppm.

In regard to the 4,1 adduct, irradiation of the olefinic area collapsed the methylene group adjacent to chlorine at 4.05 ppm (the position of this group did not change on reduction of the N-chloro group) to a singlet. Also, irradiation at 5.06 ppm, the position of the allylic methine proton adjacent to nitrogen, collapsed the methyl doublet (J = 6.3 Hz) to a singlet. On reduction, the position of this methine proton moved upfield 0.80 ppm (confirmed by double resonance) as expected. The structure of the 1,2 adduct was shown in a similar manner, although its low concentration in the isomer mixture hindered our decoupling experiments.

The vinylic nature of the methyl group (1.73 ppm) of the 1,2 adduct was shown by strong irradiation of the olefinic area at 5.75 ppm and the resulting collapse of the doublet (J = 5.5 Hz) to a singlet. This confirmed the partial structure, —CH=CH—CH_3. The position of the methyl group did not change in the reduced product. The signal for the methine proton on the carbon bearing the chlorine was found overlapped with several other signals at about 4.45 ppm while the adjacent methylene group's absorption was completely buried. On reduction the signal for the methine group remained constant whereas the multiplet for the methylene group next to nitrogen moved upfield to about 4.4 ppm.

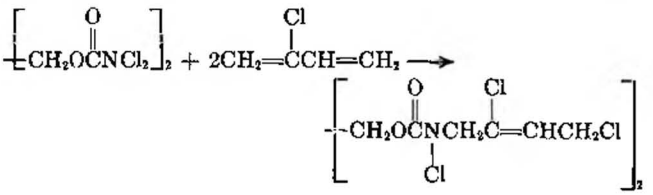
N,N-Dichloroisopropyl Carbamate Additions.—The reaction of isopropyl carbamate with chlorine in aqueous sodium acetate solution afforded a 75% yield of product. The addition of this reagent to three dienes, butadiene, isoprene, and 2,3-dimethyl-1,3-butadiene, was examined. The yields of adducts and the isomer ratios are very similar to those obtained with the methyl analog. The reduction of the N-chloro adducts with sulfite proceeded smoothly to afford high yields of crystalline reduction products.

N,N,N′,N′-Tetrachloroethylene Glycol Biscarbamate.—The reaction of ethylene glycol bischloroformate with ammonia gave the biscarbamate[11] in 93% yield.



This material was then converted by the standard procedure to the crystalline N,N,N′,N′-tetrachloro carbamate. The crude product was obtained in about 50% yield and was used directly without further purification. The nmr spectrum of the crude product exhibited a single resonance at 4.57 ppm. An acceptable chlorine analysis was also obtained on the crude product.

A quantitative yield of 1,4 adduct was obtained when this material was treated with 2 equiv of chloroprene. The adduct was obtained as a syrup and resisted all attempts at crystallization. The crude product was homogeneous on thin-layer chromatograms. The nmr spectrum of the material supports the proposed structure (see Table I). Treatment of the diadduct with sodium sulfite gave a 71% yield of crystalline bis-reduction product.



Discussion

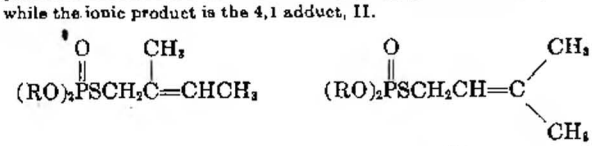
The data obtained indicate that the addition reaction proceeds by a radical-chain mechanism. The high preference for 1,4 addition has been observed in the radical addition of a number of reagents to conjugated dienes.[12,13] For example, a 90% or better selectivity for 1,4 addition has been reported for the addition of aliphatic and aromatic thiols to conjugated dienes.[14] The same order of selectivity has also been reported for the addition of protonated N-chlorodialkylamines to butadiene.[15] The ratio of 1,4 and 1,2 adducts resulting from the radical addition of chlorine to butadiene has been reported to be 78:22 while the ratio arising from purely ionic addition is 45:55.[16] Further support for

(9) W. H. Mueller and P. E. Butler, *Chem. Commun.*, 646 (1966).

(10) W. H. Mueller, R. M. Rubin, and P. E. Butler, *J. Org. Chem.*, **31**, 3537 (1966).

(11) W. Baird, P. Gaubert, and A. Lowe, British Patent 614,295 (1948).

(12) When a reagent may add by either an ionic or radical mechanism to a conjugated diene the position of attack of what would be the chain-carrying species in a radical reaction determines whether the addition is 1,4, 1,2, 4,1, etc. For example, thiophosphoric acids may add to conjugated dienes by either a radical or ionic mechanism.[13] With an unsymmetrical diene such as isoprene the adducts are not the same. The radical product is the 1,4 adduct, I, while the ionic product is the 4,1 adduct, II.



I II

(13) A. A. Oswald, W. H. Mueller, and F. A. Daniher, Abstracts 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967, p A055.

(14) A. A. Oswald, K. Griesbaum, W. A. Thaler, and B. F. Hudson, Jr., *J. Amer. Chem. Soc.*, **84**, 3897 (1962).

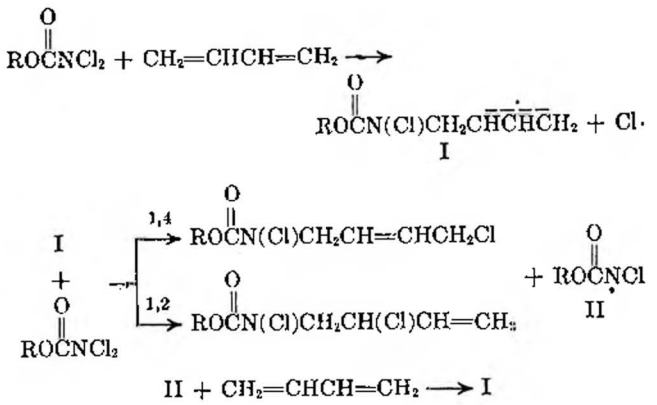
(15) R. S. Neale and R. L. Hinman, *ibid.*, **85**, 2666 (1963).

(16) M. L. Poutsma, *J. Org. Chem.*, **31**, 4167 (1967).

the radical nature of the reaction is the inhibition of addition by oxygen.

The spontaneity and exothermicity displayed by the reaction coupled with the mild conditions and lack of initiators required for the addition are characteristic of a spontaneous initiated radical–chain reaction. The phenomenon of spontaneous initiation with active halogen reagents has been observed by Walling[17] in the reaction of *t*-butyl hypochlorite and bromite with styrene and 2-butyne and also by Poutsma in the addition of chlorine to cyclohexene[18] and butadiene.[16]

The probable steps for the chain reaction are shown below using butadiene as an example.



In the initiation step, N,N-dichloro carbamate and diene combine to give the allylic radical (I) and a chlorine atom. In the propagation steps radical I reacts with another molecule of N,N-dichloro carbamate to give product and the N-chloro carbamate radical, II. Radical II can then react with another molecule of diene to regenerate I.

The abstraction of a chlorine atom from the N,N-dichloro carbamate by the allylic radical occurs preferentially at the least substituted carbon to yield the more thermodynamically stable product.[14] In the case of piperylene, little selectivity is noted since all of the adducts formed apparently are of equal stability, all being substituted 2-pentenes.

Experimental Section

The crude products were analyzed by gas chromatography using an Aerograph Model 1520B gas chromatograph. The column of choice was a 5-ft, 0.25-in.-o.d. column packed with 5% SE30 on 60–80 Chromosorb W. Nuclear magnetic resonance spectra were run on a Varian A-60 spectrometer as *ca.* 50% solutions in carbon tetrachloride with tetramethylsilane as an internal standard unless otherwise noted. Infrared spectra were recorded on a Beckman Model IR-10 infrared spectrophotometer.

Starting Dienes.—The dienes used in this study were commercial samples of the highest purity available. The butadiene (99+% purity) was obtained from the Matheson Co. The isoprene and piperylene were from Matheson Coleman and Bell. The 2,3-dimethyl-1,3-butadiene was obtained from the Borden Co. All of the above dienes were distilled prior to use with the exception of butadiene which was used without further purification. The chloroprene was obtained as a 50% solution in xylene from the E. I. du Pont de Nemours and Co., Inc., Elastomer Chemicals Department, Wilmington, Del. It was separated from the xylene by fractional distillation and then used immediately.

Alkyl Carbamates.—The methyl and isopropyl carbamates were obtained from commercial sources. The ethylene glycol biscarbamate was prepared by a modification of a patent procedure.[11] Ammonia was bubbled into an ice-cold, stirred solution of 60 g of ethylene glycol bischloroformate in 550 ml of dry toluene at such a rate so as to maintain the internal temperature between 5 and 10°. After the absorption of ammonia ceased, the addition was stopped and the reaction mixture allowed to stand at room temperature overnight. The reaction mixture was filtered and the cake washed with pentane and air dried. The residue was slurried with 500 ml of water and filtered, and the residue was dried under high vacuum to give 43 g (93%) of product, mp 163–165°.

N,N-Dichloro Carbamates.—The N,N-dichloro carbamates were prepared by reacting the corresponding carbamates with chlorine in aqueous sodium acetate according to the method of Swern.[2] With this procedure the following N,N-dichloro carbamates were prepared: $CH_3O_2CNCl_2$,[6] bp 47–48° (14 mm), $n^{25}D$ 1.4670, 70%; *i*-$C_3H_7O_2CNCl_2$, bp 58–59° (25 mm), $n^{25}D$ 1.4509, 79% (*Anal.* Calcd for $C_4H_7Cl_2NO_2$: Cl, 41.22. Found: Cl, 40.95); $(-CH_2OCNCl_2)_2$, mp 40–43° (*Anal.* Calcd for $C_4H_4Cl_4N_2O_4$: Cl, 49.60. Found: Cl, 49.18).

General Procedure for the Reaction of N,N-Dichloro Carbamates with Conjugated Dienes.—The N,N-dichloro carbamate (0.1 mol) was added dropwise to a stirred, nitrogen-purged solution of conjugated diene (0.1 mol) in 25 ml of methylene chloride cooled to between −10 and −20° by means of a Dry Ice–isopropyl alcohol bath. The rate of addition was such that the internal temperature was maintained between −5 and 5°. After addition was complete, the reaction mixture was allowed to warm slowly to room temperature. The solvent was then removed at water aspirator pressure at ambient temperature. The residue was then analyzed for its isomer content by a combination of gc and nmr. The adducts were then vacuum distilled. The structure, yield of isolated analytically pure material, isomer ratio of adducts (nmr), boiling point, $n^{23}D$, and analytical data for the products are given below: $CH_3OCON(Cl)CH_2CH{=}CHCH_3Cl$, 91%, 86:14, bp 52–56° (0.005 mm), $n^{23}D$ 1.4930 (*Anal.* Calcd for $C_6H_9Cl_2NO_2$: C, 36.28; H, 4.58; N, 7.07. Found: C, 36.27; H, 4.73; N, 6.98); *i*-$C_3H_7OCON(Cl)CH_2CH{=}CHCH_2Cl$, 85%, 85:15, bp 75–77° (0.006 mm), $n^{23}D$ 1.4762 (*Anal.* Calcd for $C_8H_{13}Cl_2NO_2$: C, 42.49; H, 5.80; N, 6.20. Found: C, 42.53; H, 5.85; N, 6.32); $CH_3OCON(Cl)CH_2C(CH_3){=}CHCH_2Cl$, 82%, 85:15, bp 72–74° (0.065 mm), $n^{23}D$ 1.4964 (*Anal.* Calcd for $C_7H_{11}Cl_2NO_2$: C, 39.64; H, 5.23; N, 6.60. Found: C, 39.55; H, 5.35; N, 6.63); *i*-$C_3H_7OCON(Cl)CH_2C(CH_3){=}CHCH_2Cl$, 94%, 85:15, 87° (0.007 mm), $n^{23}D$ 1.4814 (*Anal.* Calcd for $C_9H_{15}Cl_2NO_2$: C, 52.55; H, 7.84; N, 6.81. Found: C, 55.32; H, 8.16; N, 6.81); $CH_3OCON(Cl)CH_2C(CH_3){=}C(CH_3)CH_2Cl$, 80%, 100, bp 83° (0.006 mm), $n^{23}D$ 1.4996 (*Anal.* Calcd for $C_8H_{13}Cl_2NO_2$: C, 42.49; H, 5.80; N, 6.19. Found: C, 42.41; H, 5.99; N, 6.12); *i*-$C_3H_7OCON(Cl)CH_2C(CH_3){=}C(CH_3)CH_2Cl$, 82%, 100, bp 83° (0.003 mm), $n^{23}D$ 1.4850 (*Anal.* Calcd for $C_{10}H_{17}Cl_2NO_2$: C, 47.25; H, 6.75; N, 5.51. Found: C, 47.30; H, 7.06; N, 5.30); $CH_3OCON(Cl)C_5H_8Cl$, 84%, 40:33:27, bp 65° (0.01 mm), $n^{23}D$ 1.4852 (*Anal.* Calcd for $C_7H_{11}Cl_2NO_2$: C, 39.64; H, 5.23; N, 6.60. Found: C, 39.28; H, 5.23; N, 6.23); $CH_3OCON(Cl)CH_2C(Cl){=}CHCH_2Cl$, 82%, 100, bp 78° (0.003 mm), $n^{23}D$ 1.5095 (*Anal.* Calcd for $C_6H_8Cl_3NO_2$: C, 30.99; H, 3.47; N, 6.02. Found: C, 31.06; H, 3.90; N, 6.05); $[CH_2OCON(Cl)CH_2C(Cl){=}CHCH_2Cl]_2$, 100%, 100, oil (*Anal.* Calcd for $C_{12}H_{14}Cl_6N_2O_4$: C, 31.12; H, 3.05; N, 6.05. Found: C, 30.74; H, 3.25; N, 6.08).

The order of addition may be reversed so that the diene is added to a chilled solution of the N,N-dichloro carbamate.

A number of other solvents, which were mentioned in the text have also proved satisfactory for this reaction.

General Procedure for the Reaction of Butadiene with N,N-Dichloro Carbamates.—Butadiene (0.1 mol) was condensed into a Pyrex pressure tube fitted with a Teflon needle valve. The tube was then connected by way of a T-joint to a nitrogen source. The butadiene container was opened and distilled with nitrogen dilution into a stirred, cooled solution of N,N-dichloro carbamate at such a rate so as to maintain the internal temperature at 0–5°. After addition of the butadiene was complete, the reaction was treated as described above.

General Procedure for the Reduction of N,N-Dichloro Carbamate–Conjugated Diene Addicts.—A solution of 0.1 mol of adduct in 100 ml of methylene chloride was vigorously stirred at

(17) C. Walling, L. Heaton, and D. D. Tanner, *J. Amer. Chem. Soc.*, **87**, 1715 (1965).

(18) M. L. Poutsma, *ibid.*, **87**, 2161, 2172 (1965), and references cited therein.

ambient temperature with a solution of 0.3 mol of sodium sulfite in 150 ml of water for about 30 min, until the organic layer failed to give a positve test with potassium iodide–starch paper. The layers were separated and the aqueous layer extracted with methylene chloride. The organic extracts were combined, washed with water, and dried over sodium sulfate. The methylene chloride was evaporated at aspirator pressure at ambient temperature to give the reduced carbamate which was then purified by distillation or recrystallization. The following carbamates were prepared: $CH_3OCONHCH_2CH{=}CHCH_2Cl$, 89%, bp 84–88° (0.009 mm) (*Anal.* Calcd for $C_6H_{10}ClNO_2$: C, 44.38; H, 6.16; N, 8.56. Found: C, 44.05; H, 6.20; N, 8.44); *i*-$C_3H_7OCONHCH_2CH{=}CHCH_2Cl$, 78%, mp 61–62° (*Anal.* Calcd for $C_8H_{14}ClNO_2$: C, 50.13; H, 7.36; N, 7.31. Found: C, 49.99; H, 7.45; N, 7.45); $CH_3OCONHCH_2C(CH_3){=}CHCH_2Cl$, 76%, mp 31–32° (*Anal.* Calcd for $C_7H_{12}ClNO_2$: C, 47.33; H, 6.81; N, 7.88. Found: C, 47.29; H, 7.04; N, 7.89); *i*-$C_3H_7OCONHCH_2C(CH_3){=}CHCH_2Cl$, 81%, mp 51–52° (*Anal.* Calcd for $C_9H_{16}ClNO_2$: C, 52.55; H, 7.84; N, 6.81. Found: C, 52.32; H, 8.16; N, 6.81); $CH_3OCONHCH_2C(CH_3){=}C(CH_3)CH_2Cl$, 84%, mp 52–53° (*Anal.* Calcd for $C_8H_{14}ClNO_2$: C, 50.13; H, 7.36; N, 7.31. Found: C, 50.01; H, 7.30; N, 7.17); *i*-$C_3H_7OCONHCH_2C(CH_3){=}C(CH_3)CH_2Cl$, 86%, mp 59–61° (*Anal.* Calcd for $C_{10}H_{18}ClNO_2$: C, 54.66; H, 8.34; N, 6.38. Found: 54.43; H, 8.26; N, 6.50); $CH_3OCONHCH_2C(Cl){=}CHCH_2Cl$, 78%, mp 58–59° (*Anal.* Calcd for $C_6H_9Cl_2NO_2$: C, 36.38; H, 4.58; N, 7.07. Found: C, 36.32; H, 4.55; N, 7.18); $[CH_2OCONHCH_2C(Cl){=}CHCH_2Cl]_2$, 71%, mp 98–100° (*Anal.* Calcd for $C_{12}H_{16}Cl_4N_2O_4$: C, 36.57; H, 4.09; N, 7.11. Found: C, 36.19; H, 4.09; N, 7.20); $CH_3OCONHC_5H_5Cl$, 82%, bp 84–86° (0.004 mm) (*Anal.* Calcd for $C_7H_{12}ClNO_2$: C, 47.33; H, 6.81; N, 7.88. Found: C, 46.84; H, 6.20; N, 7.95).

Registry No.—*i*-$C_3H_7OCON(Cl)CH_2C(CH_3){=}C(CH_3)CH_2Cl$, 16487-91-5; $CH_3O_2CNCl_2$, 16487-46-0; *i*-$C_3H_6O_2CNCl_2$, 16487-47-1; $(-CH_2OCONCl_2)_2$, 16487-45-9.

Acknowledgment.—The authors wish to thank Joseph J. Clemens and Dominick S. DeCaro for their competent technical assistance. The assistance of Peter Paterson in the decoupling work is also appreciated. The elemental analyses were performed by Mr. T. J. Kielty, Jr., and his staff.

Monoadducts of Sulfenyl Chlorides and Conjugated Diolefins[1]

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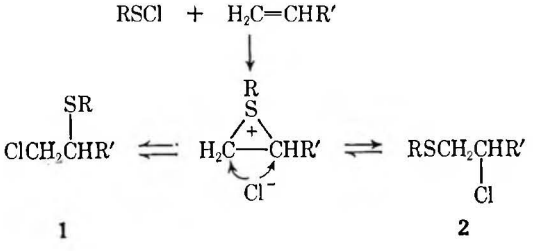
Received March 13, 1968

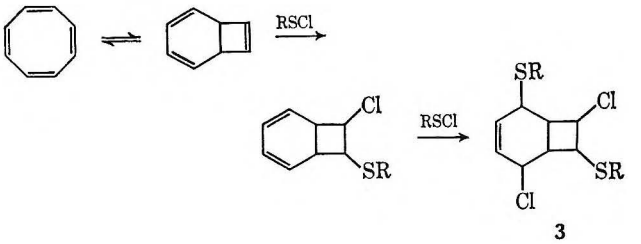
Methane- or benzenesulfenyl chloride afforded predominantly Markovnikov oriented 1,2 adducts with conjugated dienes under kinetic control. Strong preference for attack on the terminal double bond, *i.e.*, unsubstituted double bond, was found with chloroprene, piperylene, and 4-methyl-1,3-pentadiene. The reaction with isoprene, however, showed little selectivity, the substituted double bond being the slightly more favored reaction site. The kinetically controlled major adducts from methanesulfenyl chloride and piperylene, 4-methyl-1,4-pentadiene, or isoprene isomerized to their corresponding thermodynamically more stable 1,4 products. None of the benzenesulfenyl chloride adducts was found to isomerize. The mechanism of such additions and, in particular, the factors influencing the transition states most likely involved in the addition and subsequent rearrangement are discussed.

A mechanism involving an episulfonium ion intermediate to explain the Markovnikov[4] oriented *trans* addition of 2,4-dinitrobenzenesulfenyl chloride to olefins was first postulated by Kharasch and Buess.[5] More recently episulfonium ion intermediates have been proposed to account for the *trans* stereochemistry and *anti*-Markovnikov orientation of adducts obtained from methane- or benzenesulfenyl chloride and terminal olefins.[6] It has been found that, with these sulfenyl chlorides, ring opening of the cyclic intermediate by the chloride ion is strongly dependent on the nature of R′. When R′ is an alkyl substituent, the kinetically controlled ring opening occurs predominantly at the less sterically hindered terminal carbon giving the anti-Markovnikov products (1). These adducts then rearrange to the thermodynamically more stable Markovnikov products (2). When R′ is phenyl, however, the Markovnikov adduct (2) is the kinetically and thermodynamically favored isomer. Thus steric factors appeared to be quite important for the ring opening of episulfonium ions from nonconjugated olefins while the results from phenyl-substituted olefins suggested strong electronic effects in the case of conjugated olefins.



1 2

Earlier workers had tentatively proposed 1,4 addition of sulfenyl chlorides to cyclopentadiene and cyclooctatetraene.[7] The formation of diadduct **3** from cyclooctatetraene has been postulated.



3

(1) A preliminary account of part of this work has appeared: W. H. Mueller and P. E. Butler, *Chem. Commun.*, 646 (1966).

(2) To whom inquiries should be directed.

(3) Analytical and Information Division.

(4) Structures which have the chlorine on the most substituted carbon (the least hydrogen containing carbon) have been designated "Markovnikov" oriented while the opposite isomers, the "anti-Markovnikov" adducts, bear the chlorine on the least substituted (greatest number of hydrogens) carbon atom.

(5) N. Kharasch and C. M. Buess, *J. Amer. Chem. Soc.*, **71**, 2724 (1949).

(6) W. H. Mueller and P. E. Butler, *ibid.*, **88**, 2866 (1966); **90**, 2075 1968.

(7) H. Brintzinger and H. Ellwanger, *Chem. Ber.*, **87**, 300 (1954).

TABLE I.—PHYSICAL-ANALYTICAL DATA FOR METHANE- AND BENZENESULFENYL CHLORIDE-DIENE ADDUCTS

Diene	Sulfenyl chloride	Monoadduct[a] summary formula	Bp uncor, °C (mm)	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
Butadiene	CH_3SCl	C_5H_9SCl	60 (13)	43.95	6.59	23.44	43.80	6.70	23.92
	C_6H_5SCl	$C_{10}H_{11}SCl$	81–82 (0.25)	60.45	5.54	16.12	60.27	5.63	16.39
Isoprene	CH_3SCl	$C_6H_{11}SCl$	68–69 (14)	47.83	7.36	21.28	47.80	7.33	21.38
	C_6H_5SCl	$C_{11}H_{13}SCl$	77–79 (1×10^{-3})	62.10	6.16	15.07	62.31	6.37	15.32
Piperylene	CH_3SCl	$C_6H_{11}SCl$	81–82 (14)	47.83	7.36	21.28	47.62	7.44	21.52
	C_6H_5SCl	$C_{11}H_{13}SCl$	82 (1×10^{-3})	62.10	6.16	15.07	62.09	6.34	15.35
4-Methyl-1,3-pentadiene	CH_3SCl	$C_7H_{13}SCl$	71.5–73 (6)	51.04	7.96	19.47	51.31	8.03	19.79
Chloroprene	CH_3SCl	$C_5H_8SCl_2$	76–76.5 (7)	35.10	4.71	18.74	34.82	4.82	19.13
Cyclopentadiene	CH_3SCl	C_6H_9SCl	74–74.5 (8)	48.48	6.06	21.55	48.21	6.39	21.70

[a] Mixture of isomeric monoadducts.

TABLE II.—NUCLEAR MAGNETIC RESONANCE PARAMETERS OF SULFENYL CHLORIDE–DIOLEFIN ADDUCTS

Olefin	RSCl R	Group assignments 1	2	3	4	5	6	Chemical shift (ppm), multiplicity[a] 1	2	3	4	5	6	Coupling constant,[b] cps
Butadiene	CH_3	CH_3S	CH_2	CH(Cl)	CH	$=CH_2$		2.08 s	2.73[c] 2.92	4.42 dt	5.75 ddd	5.25 m 5.16 m		$J_{2,3} = 7.5, 6.5$; $J_{2g} = 13.5$; $J_{3,4} = 7.5$ $J_{4,5c} = 9.5$; $J_{4,5tr} = 16.8$
	C_6H_5	C_6H_5S	CH_2	CH(Cl)	CH	$=CH_2$		7.38 m	3.14[c] 3.44	4.46 dt	5.97 ddd	5.15 m		$J_{2,3} = 8.4, 6.0$; $J_{2g} = 14.0$ $J_{3,4} = 8.0$; $J_{4,5tr} = 16.8$; $J_{4,5c} = 10.0$
Isoprene	CH_3	CH_3S	CH_2	C(Cl)	(CH_3)	CH	$=CH_2$	2.10 s	2.91 s		1.59 s	6.00 dd	5.22 dd 5.03 dd	$J_{5,6c} = 10.0$; $J_{5,6tr} = 16.6$ $J_{6g} = 1.5$
		CH_3S	CH_2	CH(Cl)	$C(CH_3)$	$=CH_2$		2.04 s	2.86 d	4.47 t	1.74 m	5.00[d] 4.87		$J_{2,5} = 7.5$; $J_{5g} = 1.5$
	C_6H_5	C_6H_5S	CH_2	C(Cl)	(CH_3)	CH	$=CH_2$	7.25 m	3.38 s		1.65 s	6.01 dd	5.22 dd 5.03 dd	$J_{5,6c} = 10.0$; $J_{5,6tr} = 16.6$ $J_{6g} = 1.5$
		C_6H_5S	CH_2	CH(Cl)	$C(CH_3)$	$=CH_2$		7.25 m	3.12[c] 3.38	4.44 dd	1.65 s	5.08[e] 4.88		$J_{2,3} = 8.7, 6.5$; $J_{2g} = 13.8$
Piperylene	CH_3	CH_3S	CH_2	CH(Cl)	CH	=CH	CH_3	2.10 s	2.78[c] 2.96	4.48 ddd	....5.70 m....		1.71 d	$J_{2,3} = 8.0, 6.0$; $J_{2g} = 13.5$; $J_{3,4} = 8.0$ $J_{5,6} = 5.1$
		CH_2	=CH	CH(Cl)	CH	(SCH_3)	CH_3	5.25 m[e]	5.9 m[e]	~4.5[e]	3.10 dq	2.13 s	1.34 d	$J_{4,6} = 7.0$
	C_6H_5	C_6H_5S	CH_2	CH(Cl)	CH	=CH	CH_3	7.15 m	3.07[c] 3.34	4.38 dt	....5.48 m....		1.54 d	$J_{2,3} = 8.5, 6.0$; $J_{2g} = 13.5$ $J_{3,4} = 8.5$; $J_{5,6} = 5.2$
		CH_2	=CH	CH(Cl)	CH	(SC_6H_5)	CH_3	5.17 m	5.8 m[e]	~4.4	3.40 s	7.15[e]	1.32 d	$J_{4,6} = 6.5$
Chloroprene	CH_3	CH_2S	CH_2	CH(Cl)	C(Cl)	$=CH_2$		2.13 s	2.86[c] 3.13	4.68 dd		5.45 d 5.63 d		$J_{2,3} = 8.0, 6.8$; $J_{2g} = 14.0$ $J_{5g} = 2.0$
		CH_2Cl	CH	(SCH_3)	C(Cl)	$=CH_2$		....3.69[f]....		2.09 s		5.45[e] 5.63		
4-Methyl-1,3-pentadiene	CH_3	CH_3S	CH_2	CH(Cl)	CH	$=C(CH_3)_2$		2.09 s	2.73[c] 3.00	4.77 ddd	5.28 dh	1.75 bs		$J_{2,3} = 8.0, 5.8$; $J_{2g} = 13.6$; $J_{3,4} = 9.9$; $J_{4,5} = 1.3$
Cyclopentadiene	CH_3	CH_3S	CH	CH(Cl)	CH	=CH	CH_2	2.13 s	3.47 dt	4.92 m	....5.85 m....		2.87 m 2.38 m	$J_{2,3tr} = 3.0$; $J_{2,6tr} = 7.5$; $J_{2,6c} = 3.0$

[a] s = singlet; bs = broad singlet; d = doublet; t = triplet; q = quartet; dd = double doublet; dh = double heptet; dt = double triplet; ddd = doublet of double doublet; m = multiplet. [b] c = *cis*; tr = *trans*; g = *gem*. [c] Protons 2 and 3 form an ABX spin system; the chemical shifts of the AB protons are approximated by first-order analysis from the pair of overlapping quartets. [d] The terminal methylene protons form the AB part of an ABX_3 system, and appear as a pair of double quartets. [e] The signal for this group was partially obscured by the major isomer. [f] Protons 1 and 2 are nearly coincident and form an A_2B multiplet.

These previous results and mechanistic considerations stimulated the present investigation of sulfenyl chloride monoadditions to conjugated diolefins. Although a double bond of a conjugated diene may formally be compared with that of styrene, it offers additional interesting possibilities such as the study of 1,2 *vs.* 1,4 addition and the influence of substituents at various positions of the diene on the adduct formation.

It was hoped that the present study would provide information to substantiate further and widen the scope of the mechanistic interpretation of sulfenyl chloride additions to double bonds. Methane- and benzenesulfenyl chloride, the simplest representatives of aliphatic and aromatic sulfenyl chlorides, were chosen as model addends. This selection also assured results comparable to those obtained from terminal olefins.[6] A variety of methyl-substituted 1,3-dienes, cyclopentadiene, and chloroprene were employed as substrates.

Results

A relatively constant set of reaction conditions was maintained during the present study of the addition of sulfenyl chlorides to dienes. To a ~50% solution of 5 equiv[8] of the respective diene in dry methylene chloride, 1 equiv of methane- or benzenesulfenyl chloride was slowly added. A small amount of $CaCO_3$ was suspended in the methylene chloride solution to prevent possible postisomerization of the initial adducts.[5] The reaction temperature was maintained at -20 to $-25°$ during the additions. Upon completion of the spontaneous and exothermic reaction, most of the methylene chloride was removed at *ca.* $-10°$ and reduced pressure. Immediate nmr analysis of the crude products then provided both the structure(s) of the initial products and the isomer distribution. Samples suitable for elemental analysis were obtained by distillation *in vacuo* (Table I, p 2643). These samples frequently were mixtures of the isomeric adducts.

An *in situ* determination of the structure of the initial adducts was important since the tendency of certain β-halomercaptides to isomerize had been recognized in a previous study.[6] Nuclear magnetic resonance spectroscopy proved to be the most useful analytical tool for this purpose.

In general, protons α to chlorine are considerably deshielded relative to those α to sulfur.[9] The relative differences in chemical shift for the signals of such α-methylene- or methine protons have been reported for a variety of compounds to be on the order of 0.7–1.4 ppm.[6] Chemical-shift differences of similar magnitude have also been reported for benzylic or propargylic protons α to chlorine or sulfur, respectively.[10] Thus the abundance of previously compiled nmr data and in particular the earlier published nmr data gleaned from frequency sweep decoupling experiments on a 100-Mc nmr spectrum of the acetylthiosulfenyl chloride–butadiene adduct[11] simplified the structure elucidation of compounds encountered during the present study. Isomer distributions were computed from the relative intensity of nonoverlapping signals. In each case it was possible to assign ~90–95% of the total proton integral of the crude product's spectrum to proton signals of identified compounds. The only exception was the cyclopentadiene adduct where 85% of the integral was assigned. Frequently a small amount of dimethyl disulfide (singlet at 2.40 ppm) was one of the minor impurities. The nmr parameters of the major products are summarized in Table II, p 2643. Characteristic signals for minor products are discussed in the text.

Initial Adducts.—The 1,2-Markovnikov oriented adduct was the exclusive or predominant product in each case investigated (Table III). Methanesulfenyl chloride and benzenesulfenyl chloride gave essentially the same initial product distribution.

TABLE III.—METHANE- AND BENZENESULFENYL CHLORIDE-1,3-DIENE ADDUCTS

Diene	Adducts[b]	Mole %[a] R = CH_3	Mole %[a] R = C_6H_5
CH_2=CHCH=CH_2	$RSCH_2CHClCH$=CH_2	95	98
	$ClCH_2CHSRCH$=CH_2	5	...
CH_2=CHCH=$CHCH_3$	$RSCH_2CHClCH$=$CHCH_3$	86	82
	CH_2=$CHCHClCHSRCH_3$	14	18
CH_2=CHCH=$C(CH_3)_2$	$RSCH_2CHClCH$=$C(CH_3)_2$	88	...
	$RSCH_2CH$=$CHCCl(CH_3)_2$	12	...
CH_2=CCH_3CH=CH_2	$RSCH_2CClCH_2CH$=CH_2	57	60
	CH_2=$CCH_3CHClCH_2SR$	43	40
CH_2=CHCCl=CH_2	$RSCH_2CHClCCl$=CH_2	85	...
	$ClCH_2CHSRCCl$=CH_2	15	...
		85[c]	...

[a] The adduct ratio was calculated from the relative intensity of their characteristic nmr signals. [b] Respective registry numbers: 16728-07-7 (R = CH_3), 16728-08-8 (R = C_6H_5); 16728-09-9 (R = CH_3); 16728-10-2 (R = CH_3), 16728-11-3 (R = C_6H_5); 16728-12-4 (R = CH_3), 16728-13-5 (R = C_6H_5); 16728-14-6 (R = CH_3); 16728-15-7 (R = CH_3); 16728-16-8 (R = CH_3), 16728-17-9 (R = C_6H_5); 16728-19-1 (R = CH_3), 16728-18-0 (R = C_6H_5); 16728-20-4 (R = CH_3); 16728-21-5 (R = CH_3); 16728-22-6 (R = CH_3). [c] Minimum value; minor by-products are formed which remain unidentified.

Butadiene and chloroprene were the only substrates which afforded a detectable amount of the corresponding anti-Markovnikov 1,2 adducts. The presence of ~5% of this minor product from the reaction of methanesulfenyl chloride and butadiene was deduced from the nmr spectrum of the product mixture. A singlet at 2.05 ppm was assigned to the protons of the methylmercapto group. The protons of the $ClCH_2$-CH(SR) group appear as a multiplet at 3.2–3.9 ppm. Its multiplicity is consistent with the overlapping signals of an ABC-type spin system. The chemical shifts observed for this ABC system approximate those found for the anti-Markovnikov adduct from chloroprene (Table II) and similar systems.[10] Formation of the corresponding 1,4 adduct was ruled out by the lack of a signal for allylic CH_2Cl protons (~4.1 ppm) and additional signals at 5.6–5.9 ppm which are characteristic for internal olefinic protons (—CH=CH—).

Substituted butadienes having methyl groups on the 2 or 4 position were chosen to assess the influence of alkyl substituents on the adduct selectivity, *i.e.*, the relative reactivity of the unsubstituted *vs.* the substituted double bond of a conjugated olefin. Isoprene (2-methyl substituent) showed a slight preference for attack on the substituted double bond. With pipery-

(8) This excess of substrate assured essentially exclusive monoaddition.

(9) J. R. Cavanaugh and B. P. Dailey, *J. Chem. Phys.*, **34**, 1099 (1961); B. P. Dailey and J. N. Shoolery, *J. Amer. Chem. Soc.*, **77**, 3977 (1955).

(10) P. E. Butler and W. H. Mueller, *Tetrahedron Lett.*, 3179 (1966).

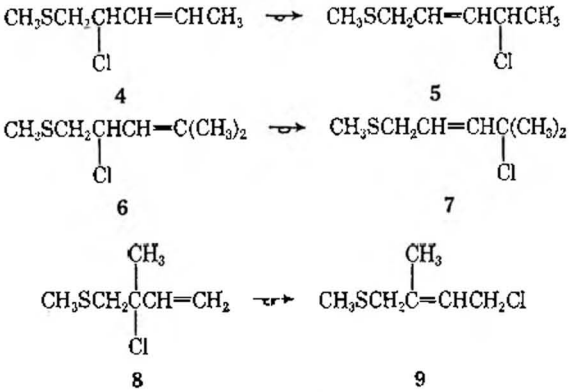
(11) P. E. Butler, W. H. Mueller, and J. J. Reed, *Environ. Sci. Technol.*, **1**, 315 (1967).

lene more than 80% of the addition took place at the 1,2 double bond, and the cumulative effect of two methyl substituents in 4-methyl-1,3-pentadiene caused exclusive attack at the unsubstituted double bond. In the latter case a small amount of 1,4 adduct (Table III) was found to be a by-product. Since this was the only example during the present study where a 1,4 adduct was detected among the initial products its abundance (~8–12%) was substantiated in two consecutive experiments. The propensity for postisomerization of this major 1,2 adduct to the corresponding 1,4 adduct may be in part responsible for the occurrence of the 1,4 adduct among the "initial products" in this particular case.

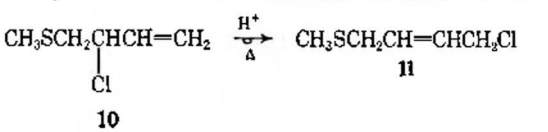
Reaction with chloroprene took place exclusively at the unsubstituted double bond. In this case 15% of anti-Markovnikov adduct also derived from addition to the unsubstituted double bond was observed.

Contrary to the previously assumed 1,4 addition of sulfenyl chlorides to cyclopentadiene[7] the 1,2-Markovnikov oriented adduct was obtained in ~85% selectivity during the present investigation. The ~15% by-product(s) which were also formed with cyclopentadiene remain unidentified.

Postisomerization.—It was found that the major 1,2-Markovnikov oriented adducts initially formed from methanesulfenyl chloride and piperylene (4), 4-methyl-1,3-pentadiene (6), or isoprene (8) rearranged to the corresponding 1,4 products, **5**, **7**, and **9**,



respectively. This isomerization took place at room temperature and could be conveniently followed by nmr analysis. The equilibrium mixtures contained >90% of the 1,4 products. The rate of rearrangement to **7** was the fastest observed, and equilibrium was reached within approximately 70 hr; the analogous isomerizations to **5** or **9** were slower by a factor of 5–10. None of the other adducts, and particularly none of the benzenesulfenyl chloride adducts, showed any tendency to isomerize under these mild conditions. More stringent conditions, however, such as elevated temperature and acid catalysis facilitated isomerization. This has been verified by the partial rearrangement of the 1,2-Markovnikov oriented adduct **10** to its



corresponding 1,4 isomer **11** under acid catalyzed conditions.[12]

The following nmr parameters served to identify the rearranged products. Compound **5** showed a singlet for its methylmercapto group at 2.06 ppm. The methyl, methylene, methine, and olefin protons of the carbon backbone form a complex virtual coupling system.[13] The vinylic methyl group appears as a doublet at 1.58 ppm, the allylic S-methylene group is a multiplet at 3.08 ppm, the allylic methine proton next to chlorine is a multiplet at 4.60 ppm, and the nearly equivalent olefin protons are a multiplet centered near 5.74 ppm.

The structure of compound **7** is characterized by a six-proton singlet at 1.57 ppm for the *gem*-dimethyl group protons β to chlorine. The unsplit (singlet) nature of the peak is good evidence for the $-C(CH_3)_2Cl$ group. The olefin and S-methylene protons form an ABXY virtual coupling system which is not amenable to first-order approximation. The two-proton multiplet for the olefinic protons is centered at about 5.72 ppm, while that of the S-methylene group is at 3.05 ppm (double irradiation of either multiplet collapses the other multiplet to a singlet). In support of the nmr assignment pertinent infrared bands were found at 1670 cm^{-1} (*trans* —CH=CH— stretching), 3040 cm^{-1} (—CH= stretching), and 963 cm^{-1} (—CH= out of plane deformation) which verified the *trans* nature of the double bond.

Compound **9** has characteristic peaks in the proper area ratio for the allylic S-methylene group (3.06 ppm, broad singlet), the vinylic methyl group (1.78 ppm broad singlet), the olefinic methine proton (5.55 ppm, triplet), and the allylic chloromethylene protons (4.10 ppm, doublet) which supports the assigned structure.

Discussion

The most obvious characteristic of the reactions of sulfenyl chlorides with conjugated dienic substrates is the highly selective formation of 1,2-Markovnikov oriented initial adducts and the preference of the addend for the terminally unsubstituted double bond of the diene. This addition reaction is in some cases followed by postisomerization of the 1,2-Markovnikov adduct to its corresponding 1,4 product. These basic observations and their mechanistic interpretation will be discussed in the order of their occurrence.

The first event is the selection of the reaction site on the dienic substrate by the approaching reagent. When methyl substituents are in the 4 position, *e.g.*, piperylene and 4-methyl-1,3-pentadiene, the terminal double bond becomes the strongly preferred point of attack. A methyl substituent in the 2 position (isoprene), however, does not hinder the attack on the substituted double bond. In fact, this position becomes the slightly favored reaction site. It appears, therefore, that steric as well as electronic factors can govern the approach of the two reactants. Strong steric requirements are introduced when methyl groups are in the 4 position of the diene. This steric effect is not observed when this substituent is located in the 2 position. Enhanced nucleophilicity of the double bond from electron release of the methyl substituent may be responsible for the preferred attack on the substituted site of isoprene. The low selectivity encountered in this case, however, indicates the relatively small over-

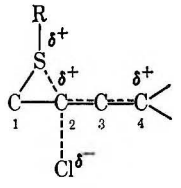
(12) W. A. Thaler, private communication; partial isomerization had been obtained at 60° in the presence of a catalytic amount of concentrated H_2SO_4.

(13) J. I. Musher and E. J. Corey, *Tetrahedron*, **17**, 791 (1962).

all significance of the electronic influence of a methyl substituent on the substrate. Strong electronic factors were recognized with chloroprene. Here the exclusive site of the reaction is the more nucleophilic unsubstituted double bond.

The above discussion of conjugated dienes in terms of isolated (vinyl substituted) double bonds finds justification in the significantly slower rate of addition of methanesulfenyl chloride to butadiene when compared to 1-butene.[14] This finding may be interpreted on the basis of lower nucleophilicity of the conjugated diene, *i.e.*, vinyl-substituted double bond, relative to that of an alkyl-substituted double bond toward the sulfenyl chloride. In that case the vinyl substituent appears to have a significant electron-withdrawing inductive effect.

The kinetically controlled formation of the 1,2-Markovnikov oriented products may involve, without closer inspection of the data on hand, transition state **12** or **13**. Product analysis, *i.e.*, high selectivity



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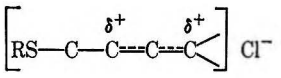

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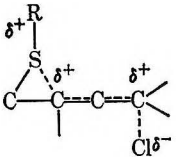
toward the 1,2-Markovnikov adduct, does not allow differentiation between **12** and **13**. Existing data on the polar addition of hydrogen bromide[15] and hydrogen chloride[16] to butadiene show mainly 1,2 addition while the ionic chlorination[17] and the (assumed ionic) bromination[18] of butadiene gave approximately equal amounts of 1,2 and 1,4 products.

In our view a transition state as depicted in **12** satisfactorily accommodates all data available for the kinetically controlled product formation. Markovnikov orientation is the result of stabilization of this transition state due to π-bond overlap of the p orbital of the electron-deficient α carbon with the vinyl substituent's π cloud. This parallels the previously observed Markovnikov orientation of sulfenyl chloride additions to styrene.[6,19] The kinetically favored attack of the chloride on the 2 position rather than on the 4 position of the episulfonium ion intermediate is derived from the relative degree of electron deficiency of the two carbons in question. The partial positive charge residing on the carbon in the 2 position receives its additional stabilization from overlap of the electron-deficient orbital on carbon with the sulfur orbitals. The lower reactivity of dienes *vs.* simple olefins[14] is also in accord with a transition state where relatively little positive charge is developed on carbon (**12**). Higher reactivity of dienes would be expected from the intervention of a resonance-stabilized allylic carbonium ion **13**. Further support for a bridged unsymmetrical episulfonium ion stems from the observed *trans* stereospecific addition of sulfenyl chlorides to acenaphthylene.[6,20] If resonance stabilization of a potential carbonium ion could lead to a deviation from our previous conclusion[4] of a bridged episulfonium ion, it would be expected to become evident here as nonstereospecific addition to acenaphthylene.

The tendency for postisomerization of some of the 1,2-Markovnikov adducts to their corresponding 1,4 products, observed under the mild conditions described in this paper, depends on two factors which could be recognized with the models presently investigated. First, none of the initial benzenesulfenyl chloride adducts rearranged. Second, methyl substituents in the 4 or 2 position of the initial adduct facilitate the rearrangement.

This differing propensity for rearrangement of methane- and benzenesulfenyl chloride adducts finds its explanation in the relative electronegativity of R on sulfur. Increasing electronegativity of R (*i.e.*, $C_6H_5- > CH_3-$) decreases the availability of the unshared electrons on the sulfur atom and diminishes neighboring-group participation, *i.e.*, displacement of the chlorine. The relative propensity for postisomerization previously found with terminal olefin–sulfenyl chloride adducts also parallels this present finding.[6] This is strong evidence that the rearrangement involves the same episulfonium ion intermediate as the initial addition reaction. It also follows that formation of this intermediate is reached through transition state **12**. Isomerization then proceeds through a higher energy transition state **14** to form the thermodynamically favored 1,4 products



14

via SN2′ displacement by the chloride. This step is essentially irreversible, since it would require an unfavorable SN2′ displacement of the chloride in the 4 position by the methylmercapto group.

The role of methyl substituents on the rearrangement can be attributed to the additional stabilization of transition state **12** by electron release of the substituents in the 2 or 4 position. The minor adduct isomers from piperylene, 4-methyl-1,3-pentadiene, and isoprene (Table III) bear methyl substituents in the 1 and 3 position, respectively. No contribution to lowering the transition-state energy would be expected in these positions which is consistent with the failure of such adducts to rearrange. Furthermore, methyl substituents in the 4 position can also contribute to lowering the energy of transition state **14** by stabilizing a partial positive charge on carbon 4. This explains the greater ease of rearrangement observed with the 1,2 adduct **6** from 4-methyl-1,3-pentadiene to its corresponding 1,4 compound **7**.

It is expected that the results obtained in the present study are to some degree subject to reaction conditions, solvent polarity, and the nature of the sulfenyl chloride.

(14) Addition of methanesulfenyl chloride (0.1 mol) to an equimolar mixture of 1-butene (0.4) and butadiene (0.4) resulted in a 7:3 adduct ratio in favor of the butylene adduct.

(15) M. S. Kharasch, E. T. Margolis, and F. R. Mayo, *J. Org. Chem.*, **1**, 393 (1936).

(16) M. S. Kharasch, J. Kritchevsky, and F. R. Mayo, *ibid.*, **2**, 489 (1937).

(17) M. L. Poutsma, *ibid.*, **31**, 4167 (1966).

(18) L. F. Hatch, P. D. Gardner, and R. E. Gilbert, *J. Amer. Chem. Soc.*, **81**, 5943 (1959).

(19) W. L. Orr and N. Kharasch, *ibid.*, **75**, 6030 (1953).

(20) W. H. Mueller and P. E. Butler, *J. Org. Chem.*, **32**, 2925 (1967).

Experimental Section

Nmr Analyses.—Neat samples containing tetramethylsilane as an internal standard were run on a Varian A-60 spectrometer at ambient temperature. Infrared spectra were recorded on a Beckman Model IR-10 infrared spectrophotometer.

Starting Materials.—Isoprene, piperylene, and chloroprene (50% solution in xylene) were obtained from Columbia Organic Chemicals Co. and distilled prior to their use. Butadiene from Matheson Co. and 4-methyl-1,3-pentadiene from Chemical Samples Co. were of ~99% purity and used as such. The cyclopentadiene was freshly prepared by destructive distillation of dicyclopentadiene from Enjay Chemical Co. Methane- and benzenesulfenyl chloride were synthesized *via* chlorination of the corresponding disulfides according to previously described procedures.[6]

General Procedure for the Addition of Methane- or Benzenesulfenyl Chloride to Conjugated Dienes.—To a 50% solution of 5 equiv of the respective diene in dry methylene chloride, 1 equiv of methane- or benzenesulfenyl chloride was slowly added. The solution had a small amount of calcium carbonate (~50 mg in a 0.1 *M* reaction) suspended in it. The reaction was carried out under a nitrogen atmosphere, and reaction temperatures were in general maintained at −20 to −25° during the addition. All reactions were strongly exothermic and took place spontaneously. Decolorization of the orange sulfenyl chloride indicated completion of the reaction. Immediately after completion of the addition the solvent and excess unsaturate were removed under reduced pressure at −5 to −10° and the adducts' isomer ratio (Table III) was determined by nmr spectroscopy. All products were pale yellow oils which were formed in essentially quantitative yield. In general, analytical samples of mixtures of the two isomers were obtained by distillation *in vacuo* (Table I).

Acknowledgment.—The authors gratefully acknowledge Mr. W. C. Whitlock for his excellent technical assistance.

Selenium Dioxide Oxidations. III. The Oxidation of Olefins

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Received December 19, 1967

Details of the oxidation of 1,3-diphenylpropene with selenium dioxide were studied. In acetic acid at 115° an isotope effect (k_H/k_D) of 3.2 was observed for oxidation at the benzylic position; this indicates that an allylic carbon–hydrogen bond is being broken in the rate-determining step. Oxidation is most rapid for electron-rich olefins and is hindered if the double bond is shielded. A mechanism is proposed that involves the formation of an allylic selenium(II) ester (RCH=CHCHROSeOH) that decomposes to products through a solvolysis reaction. Evidence for a second pathway for oxidation is presented. This proceeds through the addition of selenium dioxide and acetic acid to the double bond, followed by pyrolysis of the selenoxide that is produced to the allylic acetate. The intermediate in this reaction was isolated and characterized. Oxidation of the optically active 3- and 4-methylcyclohexenes in acetic acid and in *n*-butanol was investigated, and products that arise from the introduction of oxygen into the 2, 3, and 4 positions were isolated. For the oxidation of the olefins in *n*-butanol, it was found that the product that is formed is in each case the thermodynamically unstable ether. An analysis of the data suggests that oxidation occurs through addition of selenium dioxide and solvent to the double bond, followed by pyrolytic elimination of selenium in a lower oxidation state to produce allylically oxidized product.

Selenium dioxide is often an attractive reagent for oxidizing olefins since it provides a direct entry into the allylic position. Although the reaction frequently proceeds in moderate to poor yields, its simplicity will usually outweigh this disadvantage. Despite the numerous examples of oxidation that are recorded in the literature,[3] few systematic studies concerned with evaluating the stereochemistry of the reaction, the nature of the intermediates, the effect of asymmetry, and electronic influences on the course of reaction have been reported. In an effort to define the characteristics of the reaction more precisely and to correlate the data that are currently available, we have studied certain details of the oxidation of several olefins and have obtained data that clarify some mechanistic aspects of the reaction.

From an examination of the literature, it is apparent that in many cases the oxidation product that is isolated must result from an allylic rearrangement. For example, oxidation of 1-hexene yields hex-2-en-1-yl acetate as the major product.[4] Although in many instances, rearrangement of the double bond may be an artifact arising from subsequent conversion of a kinetically favored product into one that has a greater thermodynamic stability, we felt that it was critical to obtain data on this point since the results would have important implications relating to the reaction intermediates. Accordingly, our initial studies were focused upon the oxidation of 1,3-diphenylpropene (**1**) and its derivatives.

Oxidation of **1** with selenium dioxide in 99% acetic acid at 115° was rapid and produced 1,3-diphenyl-2-propen-1-yl acetate (**2**) in high yields; no significant quantities of other organic products could be characterized. To elaborate the role of the allylic methylene group in the oxidation process, 1,3-diphenylpropene-3-*d* (**1**-*d*) was prepared. The experimental route to this product is shown in Scheme I. Benzoin was deuterated either by a base-catalyzed exchange with deuterium oxide or by neutralization of its disodium salt (from sodium hydride) with deuterium oxide. The product of these reactions was oxidized to benzaldehyde-1-*d* (**3**-*d*) with lead tetraacetate. Condensation of **3**-*d* with acetophenone yielded the deuterated chalcone (**4**-*d*), which subsequently was reduced to 1,3-diphenylpropan-1-ol-3-*d* (**5**-*d*) by lithium aluminum hydride. Dehydration of **5**-*d* by distillation from potassium acid sulfate yielded **1**-*d* containing 0.87 atom of deuterium per molecule. The nmr spectrum indicated the presence of two vinyl protons and therefore precludes any significant hydride shifts during the dehydration process.

(1) For paper II in this series, see J. P. Schaefer, *J. Amer. Chem. Soc.*, **84**, 717 (1962).

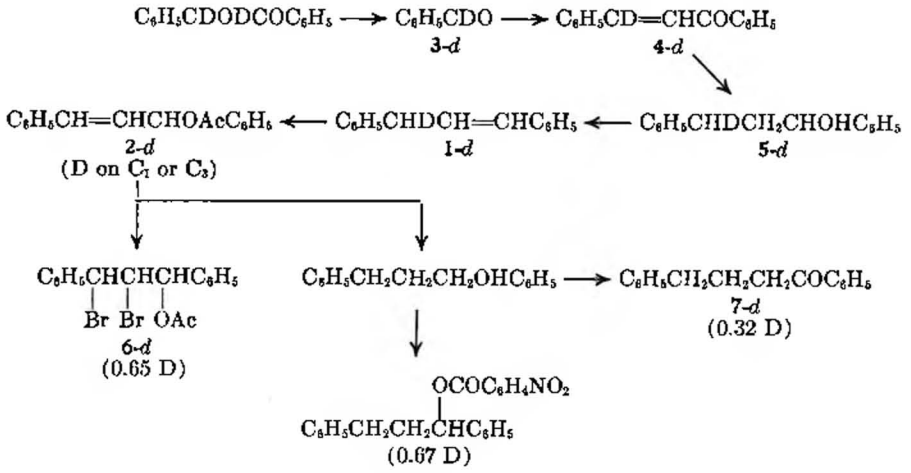
(2) The results of this work are taken in part from the Ph.D. theses of R. Horvath and H. P. Klein as submitted to the Graduate College of the University of Arizona.

(3) N. Rabjohn, *Org. Reactions*, **5**, 331 (1949).

(4) A. Guillemonat, *Ann. Chim.* (Paris), **11**, 143 (1939).

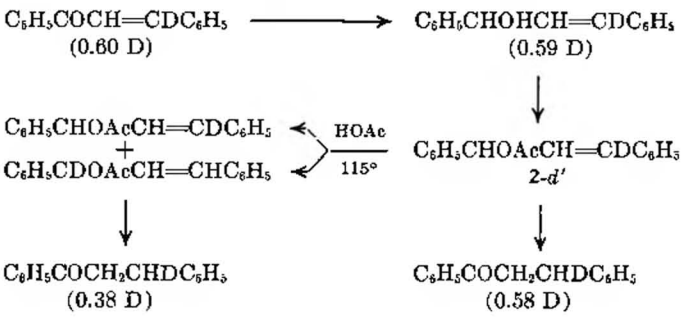
SCHEME I

PREPARATION AND OXIDATION OF 1,3-DIPHENYLPROPENE-3-*d*



SCHEME II

ISOMERIZATION OF 1,3-DIPHENYL-2-PROPEN-1-YL-3-*d* ACETATE



Oxidation of a sample of 1-*d* produced the allylic acetate (2-*d*); a portion of the product was converted into the crystalline dibromide (6-*d*), which was found to contain 0.65 atom of deuterium per molecule. Reduction of 2-*d* with lithium aluminum hydride yielded the saturated alcohol, which gave a *p*-nitrobenzoate containing 0.67 atom of deuterium per molecule. This value is in excellent accord with the results obtained from the dibromide. Since 1-*d* contained 1.13 atom of hydrogen and 0.87 atom of deuterium and was oxidized to product containing 0.34 atom of hydrogen and 0.66 atom of deuterium, it follows that during the course of oxidation of the methylene group 0.79 atom of hydrogen was lost for every 0.21 atom of deuterium. By correcting for the fact that 13% of the starting material contained no deuterium, these values become 0.66 and 0.21, respectively. The ratio of these numbers (3.2) is a measure of the kinetic isotope effect (k_H/k_D) in acetic acid at 115°. This value is sufficiently large to suggest that *the rate-determining step for the oxidation must involve cleavage of an allylic carbon–hydrogen bond.*

Oxidation of the saturated alcohol with chromic acid yielded deuterated 1,3-diphenylpropan-1-one (7-*d*). Analysis of this ketone indicated the presence of 0.32 atom of deuterium per molecule. This observation requires that at some stage of the reaction the two benzylic positions must become equivalent. A decision as to whether this equivalence has its origin in a symmetrical intermediate or is the result of successive allylic rearrangements of the product acetate was reached on the basis of the following experiments.

A sample of 4-*d* containing 0.60 atom of deuterium per molecule (see Scheme II) was reduced to 3-diphenyl-2-propen-1-ol-3-*d* (8-*d*) with sodium borohydride, and the allylic alcohol was converted into 2-*d'* by acetylation. Reduction of 2-*d'* with lithium aluminum hydride followed by oxidation of the saturated alcohol that was produced yielded 7-*d'*, which contained 0.58 atom of deuterium per molecule. This sequence of reactions demonstrates that the degradation scheme used here and in the previous experiments to determine the percentage and position of the deuterium atoms does not involve any rearrangements.

When compound 2-*d'* was refluxed in acetic acid containing phosphoric acid under the reaction conditions used for oxidation of 1 and subsequently converted into 1,3-diphenylpropanone, the latter was found to contain only 0.38 atom of deuterium per molecule. Therefore, although a substantial degree of equilibration of the benzylic positions has taken place, the equilibration is far from complete.

The possibility that partial isomerization of the olefin occurred before oxidation took place was tested by refluxing 1-*d* for an extended period of time in acetic acid containing enough phosphoric acid to simulate the acidity produced by selenous acid. After reisolation of the olefin, the nmr spectrum of this compound was superimposable on that of the starting material. Since neither the starting olefin nor the product acetate isomerizes to a sufficient extent to result in complete equilibration of the benzylic positions, we are forced to conclude that *the oxidation of 1,3-diphenyl-*

propene in acetic acid must involve the formation of a symmetrical intermediate.

In a study of the oxidation of dihydrodicyclopentadiene, Alder and Stern[5] found that the oxidation product was solvent dependent. Oxidation of the olefin in methanol, ethanol, or amyl alcohol produced the allylic methyl, ethyl, or amyl ether whereas oxidation in acetic anhydride yielded the corresponding acetate. When these data are considered in the light of our findings, it appears reasonable to conclude that, in the oxidation of 1, the structure of the symmetrical intermediate is the allylic carbonium ion. Further support for this conclusion was obtained from a study of the oxidation of the methylcyclohexenes (*vide infra*).

To assess the influence of electronic and steric factors on the rate of reaction, five 1,3-diarylpropenes were synthesized. An equimolar mixture of 1 and a 1,3-diarylpropene was allowed to compete for a limited quantity of selenium dioxide, and the percentages of olefins that remained after reaction were estimated by gas chromatographic analysis. The results of these experiments are summarized in Table I.

TABLE I

COMPETITION OF 1,3-DIARYLPROPENES FOR SELENIUM DIOXIDE

Entry	ArCH₂CH=CHAr′ Ar	Ar′	[C₆H₅CH₂CH=CHC₆H₅][a]/[ArCH₂CH=CHAr′]	Oxidation,[b] %
1	*p*-CH₃OC₆H₄	C₆H₅	0.83	59–68
2	C₆H₅	*p*-CH₃OC₆H₄	0.56	42–47
3	*p*-ClC₆H₄	C₆H₅	1.18	64–73
4	C₆H₅	*p*-ClC₆H₄	1.76	65–73
5	C₆H₅	Mesityl	>13.5[c]	82

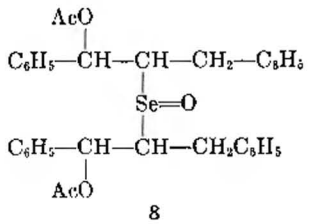
[a] Experiments utilized molar ratios of 1 mol of each olefin and 0.5 mol of selenium dioxide. The ratios reported are the ratios of olefins consumed during reaction. [b] Measured by the weight of selenium precipitated. Reactions were run in duplicate. [c] This represents a minimum value.

The data for entries 2 and 4 are in accord with electrophilic attack of the double bond by selenium dioxide (or its conjugate acid, $HSeO_2^+$). Participation of the double bond in a primary sense, such as through coordination with an attacking electrophile, is further supported by entry 5, which illustrates that shielding the double bond results in a pronounced retardation of the rate of oxidation. Substituent effects observed by varying the environment of the methylene group were small (entries 1 and 3), but they are consistent with the development of an electron-deficient center at that site.

Qualitative observations indicate that the oxidation is acid catalyzed. The rate of formation of selenium was increased markedly by the addition of dichloroacetic acid to the acetic acid solvent. In contrast to these results, oxidation in alcohols at comparable temperatures is much slower than oxidation in acid. The addition of free-radical inhibitors had no detectable effect on the rate or course of the oxidation.

When selenium dioxide (1 mol) and 1 (2 mol) were allowed to stand in acetic acid at room temperature, a white crystalline mass precipitated after several hours. After several days when crystallization was complete, the crystals were collected and purified through repeated recrystallization from hot chloroform and ethanol. An infrared spectrum of this material indicated that it was an acetate ester, and elemental analysis suggested that this compound contains two molecular formulas of 1, two acetate moieties, a selenium atom, and oxygen.

A structure that appears to be consistent with these data is 8.



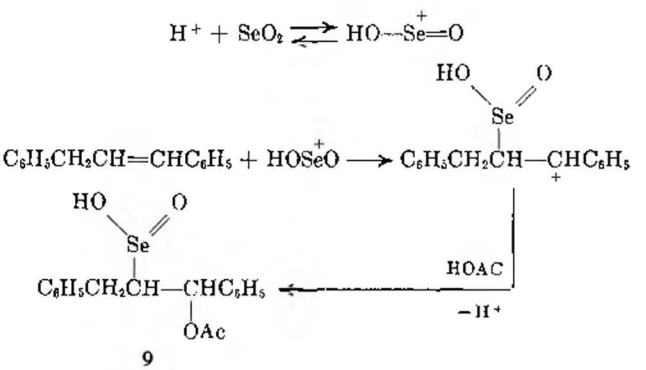
8

When a sample of 8 was dissolved in glacial acetic acid and heated under conditions identical with those used for the oxidations of 1, a total of 7–8% of the theoretical percentage of selenium precipitated. Pyrolysis of the selenium compound in a test tube at 300° for 3–5 min produced a larger percentage of selenium. Parallel experiments employing 1 and selenium dioxide gave consistent yields of selenium of the order of 65%. Analysis of the products of decomposition of 8 using thin layer chromatography indicated that the product of pyrolysis was a mixture of 1 and 2. In view of the discrepancy in yields of selenium obtained by heating the intermediate and by reaction of the olefin directly with selenium dioxide, it is apparent that, although 8 can lead to normal oxidation products, it cannot be the major intermediate formed in the experiments previously described.

Mechanistic Considerations.—From a consideration of the data presented above, it is obvious that there are at least two routes through which allylic oxidation of olefins by selenium dioxide can be achieved. As Wiberg and Nielsen[6] pointed out on the basis of a revealing study of the oxidation of some cyclohexenes, one of these pathways has a pyrolytic aspect to it whereas the other involves a solvolysis step.

For the former reaction, it is reasonable to presume that the first step of reaction involves the addition of a selenium dioxide molecule and a solvent molecule across the double bond in the manner shown in Scheme III.

SCHEME III



9

Reaction of 9 with a second molecule of 1 would yield 8.

Ample precedents for these reactions are to be found in the literature. When selenium oxychloride comes into contact with an olefin, a vigorous reaction that results in a 1,2 addition across the double bond ensues.

(5) K. Alder and G. Stern, *Ann.*, **504**, 205 (1933).

(6) K. Wiberg and S. D. Nielsen, *J. Org. Chem.*, **29**, 3353 (1964).

The β-chloroselenoxide that is produced is subsequently converted into a dichloroselenide.[7] More

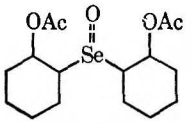
$$2CH_2{=}CH_2 + SeOCl_2 \longrightarrow (ClCH_2CH_2)_2Se{=}O \longrightarrow (ClCH_2CH_2)_2SeCl_2$$

recently, Olson[8] has been able to isolate a stable addition compound (**10**) from the reaction of ethylene with selenium dioxide. Compound **10** presumably arises

$$2CH_2{=}CH_2 + 2CH_3CO_2H + SeO_2 \longrightarrow (CH_3CO_2CH_2CH_2)_2Se{-}O \longrightarrow (CH_3CO_2CH_2CH_2)_2Se$$

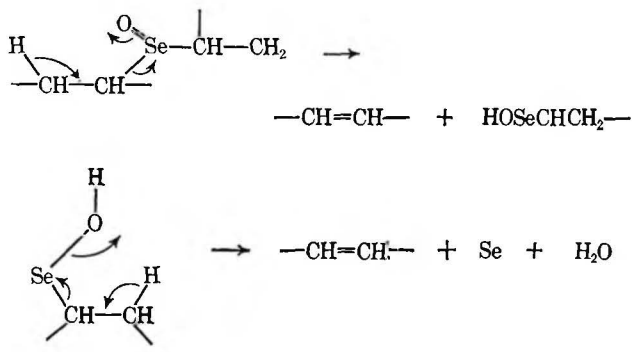
11 **10**

through the preliminary formation of **11** followed by reduction of the latter product by a selenium compound in a similar or lower oxidation state (*e.g.*, Se or SeO). Similarly, Wiberg and Nielsen[6] have isolated an adduct formed from cyclohexene and have found that its properties are consistent wth structure **12**.



12

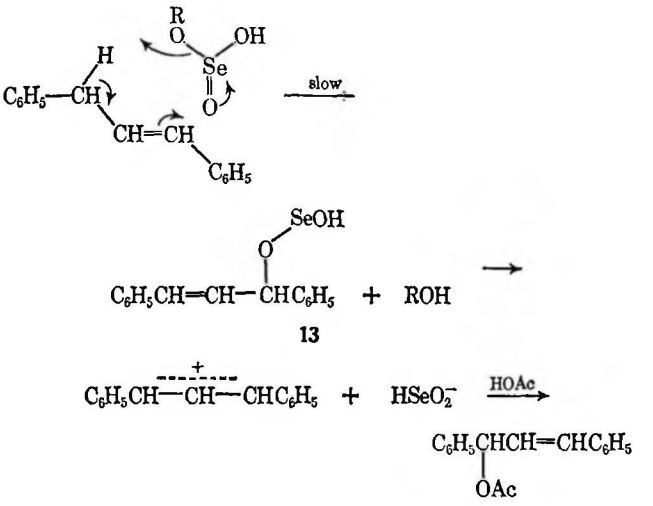
Thermal decomposition of **8** should be facile and probably proceeds through a cyclic transition state. Processes similar to these are commonly encountered in the formation of olefins by the pyrolysis of amine oxides, and a reaction of this kind appears to be reasonable in view of the known thermal instability of



aliphatic selenoxides.[9,10] The isolation of **1** from the pyrolysis mixture suggests that the formation of **8** is reversible to some degree. In accord with this mechanism is the result of Wiberg and Nielsen[6] who have shown that with cyclohexene the acetate group is introduced into one of the original vinyl positions when cyclohexenyl acetate is formed from the pyrolysis reaction.

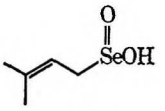
If we consider all of the data presented on the oxidation of **1**, it is clear that the pyrolysis reaction cannot be the major source of product. The reasons for this conclusion follow from the observations that (1) the formation of **2** from **8** is much slower than the formation of **2** from **1** and selenium dioxide, (2) the mechanism provides no route to direct insertion of oxygen at the allylic position, and (3) the substituent effects observed for electrophilic attack at C_2 are too small for this to be a major reaction path.[11,12] A process that appears to be consistent with our results is given in Scheme IV.

SCHEME IV



When selenium is dissolved in water, it is converted into selenous acid. In acetic acid or in an alcoholic solvent, the oxidant will probably exist largely as the mixed anhydride or the half-ester. Attack by the appropriate reagent (R = acetyl, alkyl, or hydrogen) upon the olefin, followed by a molecular reorganization, would lead to a selenium(II) ester (**13**), as we have indicated. The formation of **13** must be rate determining in view of the magnitude of the primary isotope effect that was observed.[13] Solvolysis of **13** would yield an allylic cation that could react with the solvent at either benzylic position. This cationic intermediate provides a satisfactory explanation for the known solvent dependence of the reaction product.[5]

Wiberg and Nielsen[6] have suggested that the structure of the product-producing intermediate should be formulated as a seleninic acid (**14**), which contains a selenium–carbon bond rather than an oxygen–carbon bond. Although there are many examples of inter-



14

(7) C. E. Frick, *J. Amer. Chem. Soc.*, **45**, 1795 (1923).
(8) D. H. Olson, *Tetrahedron Lett.*, 2053 (1966).
(9) M. L. Bird and F. Challenger, *J. Chem. Soc.*, 571 (1942).
(10) H. Rheinboldt and E. Giesbrecht, *J. Amer. Chem. Soc.*, **69**, 645 (1947).

(11) In a kinetic study of the reaction of α-methylstyrene with selenium dioxide, we have found that at 25° the disappearance of oxidant is rapid and first order with respect to oxidant. However, the consumption of selenium dioxide is not directly related to the production of selenium and organic oxidation products; rather, it appears to be leading to an intermediate similar to **8** under these reaction conditions. Trachtenberg and Nelson[12] have studied in greater detail the kinetics of the reaction of a series of substituted α-methylstyrenes and have determined that the ρ value for the reaction is −2.34, which is a reasonable value for a reaction involving electrophilic attack of the double bond with concomitant formation at an electron-deficient center at C_2. Although it is not completely clear to us what facet of the oxidation of the olefin this ρ value represents, it is apparent that the substituent effects that we have observed are too small to be consistent with a process involving attack of an electrophilic species on **1** at C_2 to produce a benzyl cation.

(12) C. H. Nelson, Ph.D. Thesis, Clark University, Worcester, Mass., 1965.

(13) Although the formation of **13** has been formulated for the sake of simplicity as involving a cyclic transition, it is apparent that a two-step process involving addition of the reagent followed by subsequent loss of a proton would accomplish the same result. A two-step process is actually more probable since this would predict the development of a cationic center at one of the vinylic positions, would afford an explanation for the observed[4] selectivity of oxidation sites in unsymmetrical olefins, and also would be in accord with the high ρ value that has been reported.[12]

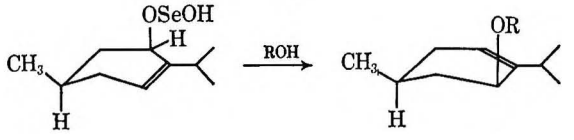
mediates of this type that arise from the reaction of metallic acetates (*e.g.*, mercuric acetate[14]) with olefins and that undergo facile solvolysis reactions, **14** does not appear to have the structural features necessary to produce an allylic cation. Numerous alkyl seleninic acids [RSe(=O)OH] have been described in the literature and they are uniformly stable compounds. In fact, benzylseleninic acid can be crystallized from water or methanol with decomposition.[15-17] On this basis, we regard **13** as being a more plausible intermediate in the oxidation reaction.

From a consideration of the characteristics of the products that are formed during the reactions of other olefins of a more general type than **1**, it is apparent that there must be a spectrum of pathways available for the decomposition of the selenium(II) ester. The oxidation of (+)-*p*-menth-3-ene (**15**), which has been studied in detail by Suga, Sugimoto, and Matsuura,[18] provides an interesting model for illustrating many facets of these conversions.

In analyzing the details of an olefin oxidation, the first point that must be considered is the stereochemistry of formation of the selenium(II) ester. From an application of stereoelectronic principles, it is evident that in the absence of any abnormal steric effects the transition state of minimum energy would be



15



16

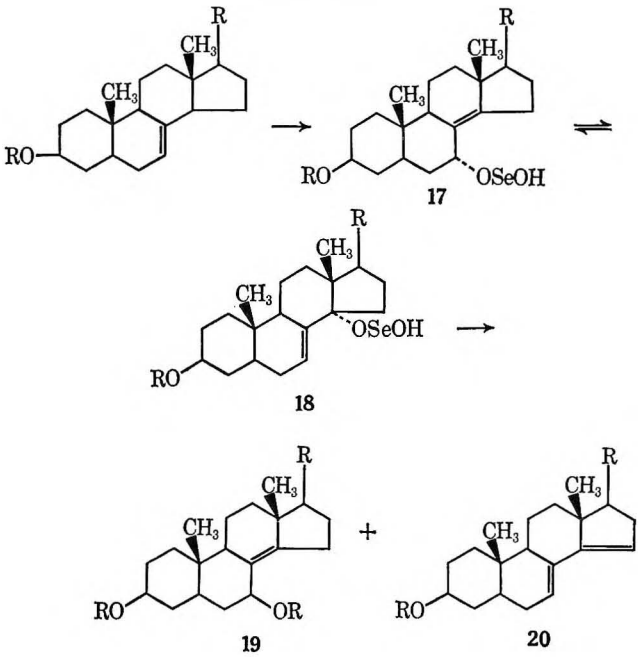
formed by attack of selenium dioxide upon the double bond in a manner such that oxygen will be inserted into an axial position and the allylic proton in the axial position is the one that is abstracted. In solvents of modest ionizing power but of high nucleophilicity, bimolecular displacement of the selenium(II) ester by a neutral solvent molecule in the cyclohexenyl system occurs through an S$_N$2′ path. In accord with the known stereochemistry of the S$_N$2′ reaction is the fact that the isolated product is also axially substituted. Further confirmation for these suggestions is provided by the observation that, in the oxidation of carvomenthene, oxygen is introduced into the allylic position with retention of optical activity.[6]

If the solvent system used for a reaction medium promotes ion pair formation, allylic rearrangements of the selenium(II) ester can occur. In the case of **16** this would result in racemization, and the oxidation of both **15** and carvomenthene in acetic acid led only to racemic products.[6] Similarly, if the allylic cation is particularly stable as in the case of the 1,3-diarylpropenes, ion-pair formation would be expected to be important. The Δ^7 steroids also provide an instructive example for analysis.

(14) Z. Rappaport, P. D. Sleezer, S. Winstein, and W. G. Young, *Tetrahedron Lett.*, 3719 (1965).
(15) C. L. Jackson, *Ber.*, **7**, 1277 (1874).
(16) C. L. Jackson, *Ann.*, 179 (1875).
(17) R. Lesser and R. Weiss, *Ber.*, **57**, 1077 (1924).
(18) T. Suga, M. Sugimoto, and T. Matsuura, *Bull. Chem. Soc. Jap.*, **36**, 1363 (1963).

In the Δ^7 steroids, the C_{18} and C_{19} methyl groups and the stability of the tertiary C_8 cation will promote attachment of selenium dioxide to the axial position at C_7 with generation of a Δ^{8-14} double bond. This selenium(II) ester (**17**) can rapidly equilibrate with its C_{14}-substituted counterpart (**18**), which on reaction with solvent would yield **19** (Scheme V). The relative ease

SCHEME V



of displacement of a secondary *vs.* a tertiary center would result in the isolation of **19** to the exclusion of product that is oxidized at C_{14}. The isolation of considerable amounts of diene **20** suggests that 1,2 or 1,4 eliminations from the selenium(II) ester intermediates provide a favorable alternative route for decomposition.

In systems with less demanding steric requirements for reaction, a transition from an S$_N$2′ to an S$_N$2 reaction may be noted. For example, in the oxidation of 1-hexene, the latter type of reaction would be expected to be dominant and, indeed, the product that is isolated is the primary acetate. A difficulty in interpreting

$$C_3H_7CH_2{-}CH{=}CH_2 \longrightarrow C_3H_7CH{=}CH{-}CH_2OSeOH \longrightarrow C_3H_7CH{=}CHCH_2OAc$$

many of these reactions literally is that the products may represent only thermodynamically stable isomers and not the kinetically formed products.

Further Studies.—In the light of the above findings and of our own data, we were surprised to note that the oxidation of (+)-4-methylcyclohexene (**21**) under conditions similar to those used by other investigators[6,12] has been reported[19] to produce optically active 5-methyl-2-cyclohexen-1-yl acetate (**22**). Although the results of Mousseron and Jacquier[19] could have been a manifestation of the differences in the stabilities of the various allylic cations involved, we felt that these observations had sufficiently important mechanistic implications to merit reinvestigation, especially in view of some experimental ambiguities that existed.

Optically active 3-methylcyclohexanone (**23**) ($\alpha^{25}D$ +13.7°) was reduced with lithium aluminum hydride

(19) M. Mousseron and R. Jacquier, *Bull. Soc. Chim. Fr.*, 467 (1952).

to a mixture of epimeric 3-methylcyclohexanols (**24**), of which about 90% was the *cis* isomer. Using the sulfuric acid dehydration procedure that was previously described,[19] we were unable to obtain olefin that had rotations that were consistently as high as those reported by the French workers. This presumably is due to the partial loss of asymmetry through hydride shifts and should be a sensitive function of the reaction conditions that are employed.

To circumvent this difficulty, the optically active acetate mixture (**25**) was prepared by heating the epimeric alcohols with acetic anhydride in pyridine. Upon pyrolysis of the acetates, an olefin portion ($\alpha^{25}D$ +110°) that corresponded in physical properties to **21** was obtained. Although we were unable to detect the presence of any other olefin by vapor phase chromatography, it seemed highly unlikely on stereoelectronic grounds that the acetate pyrolysis or the acidic dehydration of the alcohols could have produced a single olefin. Accordingly, the following series of experiments was carried out.

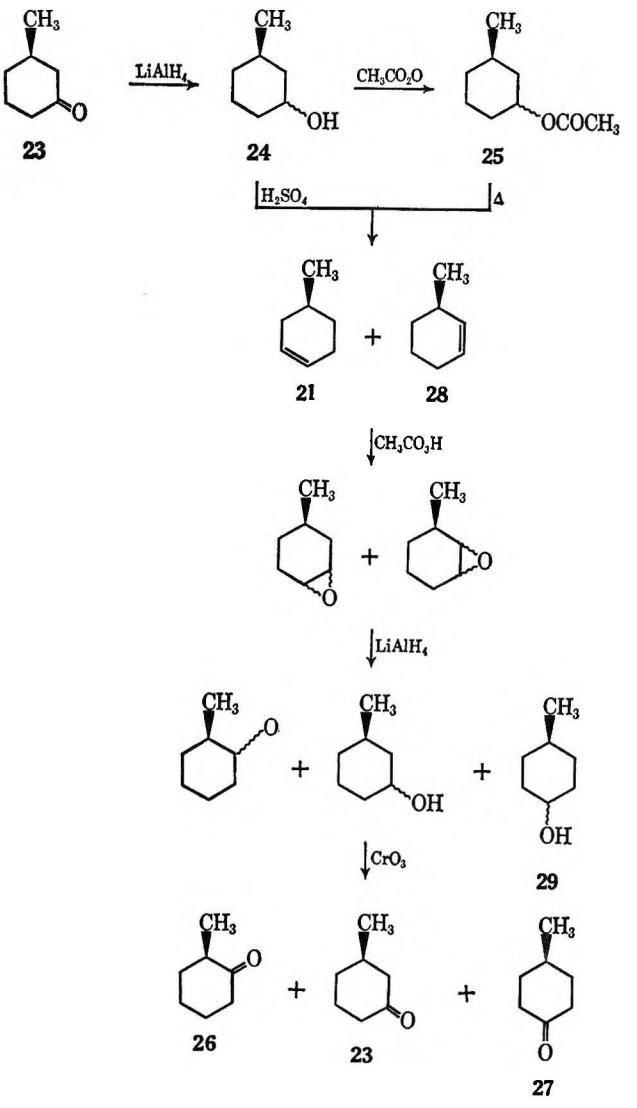
The olefin fraction was allowed to react with peracetic acid, and a mixture of epoxides was obtained in high yield. An examination of the nmr spectrum of this mixture showed two distinct methyl resonances; however, no decision could be reached as to whether these resulted from the presence of a mixture of epimeric epoxides or from isomers that involved formation of an oxide bridge between different carbon atoms. Reduction of the epoxide fraction with lithium aluminum hydride followed by oxidation of the resultant alcohols produced a mixture of 2-methylcyclohexanone (**26**), **23**, and 4-methylcyclohexanone (**27**) in relative yields of 15, 45, and 40%, respectively. The presence of three ketones requires that the olefin starting material must consist of a mixture of 3-methylcyclohexene (**28**) and **21**.

Reduction of **27** with lithium aluminum hydride and acetylation of the epimeric alcohols (**29**) produced a mixture of the epimeric acetates, about 90% of which was the *cis* isomer. Pyrolysis of the acetate mixture yielded an authentic sample of racemic **21**, which was converted into its epoxide by peracetic acid. From a comparison of the nmr spectra of the epoxides produced from the mixture of **21** and **28** with that obtained from pure **21**, it appeared that the ratio of these isomers was about 3:2. Since a separation of these olefins could not be realized, further experiments were carried out on this mixture. A summary of the experiments described above appears in Scheme VI.

Oxidation of the optically active olefins with selenium dioxide in acetic acid containing acetic anhydride[19] produced a mixture of allylic acetates. After hydrogenation of the double bond, the saturated acetates were converted into the corresponding methylcyclohexanols by lithium aluminum hydride. Oxidation of the alcohol mixture with chromic acid yielded a mixture of **26**, **23**, and **27**; these ketones were separated by preparative gas chromatography. The rotation of **26** was $\alpha^{24}D$ −14.6°; this compound was completely racemized after it had been heated in acetic acid for 3 hr.

In contrast, ketone **23** was virtually optically inactive with $\alpha^{25}D$ +0.57°. From these observations it is clear that, for the course of selenium dioxide oxidation of olefins, any interpretations based upon the results reported by Mousseron and Jacquier[19] would be in serious error, since the products of reaction were not correctly identified.[20]

SCHEME VI



A point of further interest was to determine the stereochemistry of the oxygen that is introduced during the course of the oxidation sequence. Details regarding this feature of the reaction were obtained from a study of the reactions of **21** and **28** with selenium dioxide in *n*-butanol.

Oxidation of the olefin in *n*-butanol at reflux produced a mixture of allylic ethers, allylic alcohols, and α,β-unsaturated ketones; the total yield of products was low and varied from 15 to 20%. Analysis of the products after catalytic hydrogenation of the double bond indicated that 75% of the reaction mixture consisted of the isomeric butyl ethers of the methylcyclohexanols, 15% was a mixture of methylcyclohexanols, and the remainder was an aggregate of methylcyclohexanones.

To identify the various butyl ethers that were formed, ketones **23** and **27** were reduced to the alcohols with lithium aluminum hydride. In agreement with the re-

(20) An interesting consequence of these experiments is that the absolute configuration of (−)-2-methylcyclohexanone must be the same as that of (+)-3-methylcyclohexanone, since none of the reactions involved could have changed the configuration of the methyl group relative to the oxygen function.

port by Dauben, Fonken, and Noyce[21] was our finding that about 80% of the products in both cases are the thermodynamically favored epimers, namely, *trans*-4-methylcyclohexanol and *cis*-3-methylcyclohexanol. Each pair of epimers was treated with sodium metal and *n*-butyl bromide to give the corresponding epimeric pairs of butyl ethers. A similar sequence of reactions was carried out on a commercial sample of a mixture of the 2-methylcyclohexanols that contained about 80% of the *trans* isomer; it was found that the three isomeric ethers and their epimers could be separated and distinguished by gas chromatography. From a comparison of the retention times of these authentic samples with the products of oxidation, it was immediately apparent that the ether formed during the oxidation is predominantly (~80%) the thermodynamically unstable isomer.

Experimental Section

Benzaldehyde-1-*d*.—To 106 g (0.50 mol) of benzoin were added 200 ml of dry tetrahydrofuran, 10 g (0.50 mol) of deuterium oxide, and 25 g of anhydrous potassium carbonate. The solution was heated at reflux for 24 hr, and the solvent was removed. This cycle was repeated six times. Then the dry residue was mixed with 1 l. of benzene and the slurry was filtered to remove the potassium carbonate. To the filtrate was added 300 ml of absolute ethanol, and the resultant solution was heated to reflux. Freshly prepared lead tetraacetate (300 g) was added in one portion. The solution was heated at reflux for 1 hr and cooled; the lead salts were removed by filtration through a sintered-glass funnel. The filtrate was washed with 50 ml of dilute hydrochloric acid, refiltered, and washed twice with 300-ml portions of water. The filtrate was then neutralized with sodium bicarbonate, washed with water, and dried over anhydrous magnesium sulfate. Distillation yield 50 g (94%) of benzaldehyde, bp 66–66.5° (14 mm). The product contained 0.88 deuterium atom per molecule.

1,3-Diphenylpropene-3-*d*.—The procedures developed by Rondestvedt[22] for the synthesis of 1,3-diarylpropenes were used. Acetophenone and benzaldehyde-1-*d* were condensed to give deuteriochalcone (0.87 deuterium atom per molecule); the latter was reduced to 1,3-diphenylpropan-1-ol with lithium aluminum hydride. Dehydration by distillation from potassium acid sulfate produced the title compound in over-all yields that varied between 40 and 60%. The olefin contained 0.87 deuterium atom per molecule, bp 161–162° (7.5 mm).

Selenium Dioxide Oxidation of Olefins.—A measured quantity of selenium dioxide was dissolved in a few drops of warm water. To this solution was added 100 ml of glacial acetic acid containing the olefin, and the reaction mixture was heated for about 20 min at reflux. The solution was cooled and filtered to remove selenium, which was formed in yields of 70–80%. The filtrate was poured into 1 l. of water and then extracted with three 100-ml portions of ether. The ether extracts were washed with water, base, and water and then dried over magnesium sulfate. The product was distilled rapidly in a small distillation apparatus at pressures of 0.05–0.10 mm at temperatures below 180°; almost no residue remained in the distillation pot under these conditions.

In the case of 1,3-diphenylpropane, chromatography (gas phase and thin layer on silica gel) indicated that about 80% of the product was 1,3-diphenyl-2-propen-1-yl acetate and that the remainder of the material was the starting olefin along with traces of several organoselenium compounds; small quantities of 1,3-diphenylpropanone could be detected. The structures of the identifiable products were confirmed by a comparison of retention times and infrared spectra with those of authentic samples.

Oxidation of 1,3-Diphenylpropene-3-*d*.—To 1.15 g (0.0104 mol) of selenium dioxide was added 7 drops of water, and the paste that was formed was heated to bring about solution. To this was added 100 ml of glacial acetic acid containing 4.00 g (0.0206 mol) of 1,3-diphenyl-1-propene-3-*d*, and the solution was heated at reflux with an open flame for 20 min. The solution was cooled rapidly in an ice bath and filtered to remove selenium (0.52 g, 63%). The product isolation from this point on was the same as that described under the general procedure.

To 100 ml of anhydrous ether were added 3.0 g of lithium aluminum hydride and 2.70 g of the distillate from the oxidation reaction. After the solution had been heated at reflux for 3 hr, water was added to destroy the excess hydride. Isolation of the product in the usual manner yielded 2.5 g of crude 1,3-diphenylpropan-1-ol. From 0.3 g of the crude alcohol the *p*-nitrobenzoate was prepared, mp 88.5° (lit.[23] mp 88–89°), and analysis indicated that the *p*-nitrobenzoate contained 0.67 atom of deuterium per molecule.

To 0.2 g of the crude oxidate in 10 ml of carbon tetrachloride was added a solution of bromine in carbon tetrachloride until the bromine color persisted. After evaporation of the solvent, the yellow residue was recrystallized from ethanol to give a pure sample of 1,2-dibromo-1,3-diphenylpropan-3-yl acetate, mp 177–179° (lit.[24] mp 176–177°). Analysis indicated that the dibromide contained 0.65 atom of deuterium per molecule.

To 2.0 g of the crude deuterated alcohol was added 15 ml of AR grade acetone, and the solution was cooled to 0–5°. The solution was maintained at this temperature while a solution of 1.0 g of chromic acid, 3.0 ml of water, and 1.0 ml of concentrated sulfuric acid was added over a period of 30 min. After having been stirred for 2 hr at room temperature, the solution was poured into 500 ml of water. The ketone was isolated and purified by crystallization from ethanol. The yield of product was 0.91 g, mp 71–72° (lit.[25] mp 71–72°); it was found to contain 0.32 atom of deuterium per molecule.

Attempted Isomerization of 1,3-Diphenyl-1-propene-3-*d*.—To 50 ml of acetic acid was added 0.60 g of 85% phosphoric acid and 2.0 g of 1,3-diphenylpropene-3-*d*. The solution was heated at reflux for 20 min, and the olefin was then reisolated. The nmr spectrum of this material was identical in every respect with that of the starting material.

1,3-Diphenyl-2-propen-1-ol-3-*d*.—To 20.0 g (0.0957 mol) of 1,3-diphenyl-2-propen-1-one-3-*d* containing 0.60 atom of deuterium per molecule was added 200 ml of absolute ether and 1 ml of absolute ethanol. Then 2.0 g of sodium borohydride was introduced, and the mixture was stirred at room temperature for 48 hr. The solution was poured into an iced solution of 4% sulfuric acid and the ether layer was separated, neutralized, and dried with magnesium sulfate. Evaporation of the ether gave 18.2 g of crude product, which after two crystallizations melted at 55–56° (lit.[26] mp 57–58°). Analysis indicated that the alcohol contained 0.59 atom of deuterium per molecule.

1,3-Diphenyl-2-propen-1-yl-3-*d* Acetate.—To 5.0 g (0.024 mol) of the above alcohol was added 15 ml of acetic anhydride and 15 ml of anhydrous pyridine. This mixture was kept at 35–40° for 4 hr. The solution was poured into 100 ml of water and extracted with three 50-ml portions of ether. The combined ether extracts were washed with acid and with base, dried, and distilled; a total of 3.6 g (70%) of acetate was obtained, bp 211° (11 mm) [lit.[24] bp 211° (11 mm)].

Isomerization of 1,3-Diphenyl-2-propen-1-yl-3-*d* Acetate.—To 2.0 g of the acetate were added 50 ml of acetic acid and 0.60 g of 85% phosphoric acid; the solution was heated at reflux for 20 min. Recovery of the acetate was accomplished in the usual manner, and the nmr spectrum indicated that extensive scrambling of deuterium had occurred. Reduction of the acetate with lithium aluminum hydride and chromic acid oxidation of the product produced 1,3-diphenylpropan-1-one, which contained 0.38 deuterium atom per molecule. The same sequence of reactions with acetate that had not been heated in acetic acid yielded ketone containing 0.58 deuterium atom per molecule.

Isolation and Characterization of the Intermediate.—To 1 ml of water was added 4.29 g (0.0386 mol) of selenium dioxide, and to this solution was added 250 ml of glacial acetic acid containing 15.0 g (0.0773 mol) of 1,3-diphenylpropene. The solution was stirred at room temperature, and after 3 days the white crystals that had formed were removed by filtration (6.2 g, 30%).

The product was recrystallized from a 1:1 mixture of chloroform and ethanol. The product melted with decomposition in

(21) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).

(22) C. S. Rondestvedt, *ibid.*, **73**, 4509 (1951).

(23) T. Kametani and Y. Nomura, *J. Pharm. Soc. Jap.*, **24**, 1037 (1954); *Chem. Abstr.*, **49**, 11593 (1955).

(24) H. Burton and C. K. Ingold, *J. Chem. Soc.*, 905 (1928).

(25) R. Adams, J. W. Kern, and R. L. Shriner, *Org. Syn.*, **1**, 101 (1941).

(26) H. H. Wasserman and N. E. Aubrey, *J. Amer. Chem. Soc.*, **77**, 590 (1955).

the range of 199–201°. An infrared spectrum showed strong bands at 1745 and 1200 cm^{-1} indicating the presence of an acetate ester function in the molecule.

Anal. Found: C, 68.63; H, 5.91; Se, 10.46.

A solution of 1.0 g of the intermediate was dissolved in 50 ml of warm glacial acetic acid, and the solution was heated at reflux for 20 min. At the end of this time, a total of 0.01 g (7%) of selenium had precipitated. (In a parallel experiment starting with dioxide and olefin, the yield of selenium after 20 min was 53% of the theoretical). After isolation of the products, thin layer chromatography showed that the product distribution pattern was the same as that obtained for the olefin oxidation.

The crystals (1 g) were placed in a test tube and heated at 300° for 3–5 min. Thin layer chromatography indicated the presence of some undecomposed intermediate along with 1,3-diphenylpropene and 1,3-diphenyl-2-propen-1-yl acetate.

(+)-3-Methylcyclohexanone.—Oil of pennyroyal (Fritzsche), 97% of which was pulegone having $[\alpha]^{25}D$ +13.7°, was used without further purification. In a 5-l., round-bottomed flask fitted with a reflux condenser were combined 1000 ml of oil of pennyroyal, 650 ml of concentrated hydrochloric acid, and 1950 ml of water. The mixture was heated at reflux for 16 hr, the flask was fitted for distillation, and 327 g of acetone was removed by distillation. The residue was subjected to exhaustive steam distillation. Separation of the organic and aqueous layers of the distillate afforded 620 ml of crude (+)-methylcyclohexanone. From 540 g (4.8 mol) of the crude ketone 895 g (86%) of the sodium bisulfite adduct was prepared. The adduct was stirred for 2 hr with an excess of an aqueous solution of sodium carbonate. The mixture was then extracted several times with diethyl ether. The combined ethereal extracts were dried ($MgSO_4$), concentrated, and distilled to afford 256.4 g (55.3%) of (+)-3-methylcyclohexanone: bp 55–56° (7 mm) [lit.[27] bp 169° (760 mm)]; $[\alpha]^{25}D$ +13.7° (lit.[28] $[\alpha]^{25}D$ +13.38°); semicarbazone, mp 178–179° (lit.[29] mp 171–174° dec).

(−)-3-Methylcyclohexanol.—(+)-3-Methylcyclohexanone (224 g, 2.00 mol) was reduced with lithium aluminum hydride in the usual manner. Distillation of the crude alcohol gave 210 g (92.0%) of (−)-3-methylcyclohexanol: bp 70–71° (7 mm) [lit.[30,31] bp 84° (13 mm), 169–170° (748 mm) for *cis*-3-methylcyclohexanol]; $[\alpha]^{25}D$ −4.63° (lit.[32] $[\alpha]^{25}D$ −4.15°).

(−)-3-Methylcyclohexyl Acetate.—A mixture of 217 g (1.90 mol) of (−)-3-methylcyclohexanol, 230 g (2.25 mol) of acetic anhydride, 74 g (0.90 mol) of sodium acetate, and 630 ml of dry benzene was stirred and refluxed for 6 hr. The reaction mixture was poured into cold water, and the layers were separated. The organic layer was stirred with sodium carbonate solution, washed once with water, dried, concentrated, and distilled to give 283 g (95.5%) of (−)-3-methylcyclohexyl acetate: bp 66–67° (6 mm) [lit.[33] bp 78–79° (20 mm)]; $[\alpha]^{25}D$ −25.59°.

(+)-4-Methylcyclohexene and (+)-3-Methylcyclohexene.—(−)-3-Methylcyclohexyl acetate (139 g, 0.891 mol) was passed dropwise in a dry nitrogen atmosphere through a helix-packed Pyrex tube encased by an oven heated to 450–460°. Nine hours were required for the pyrolysis. The products, which were collected in a receiver cooled in a Dry Ice-acetone bath, were dissolved in ether. The ethereal solution was washed with water and sodium carbonate solution until neutrality was achieved. The ether solution was dried ($MgSO_4$) and concentrated. Distillation of the residue through a Vigreux column afforded 51.3 g (60.0%) of olefin: bp 42° (80 mm); $[\alpha]^{26}D$ +108.9 [lit.[34] bp 102° (760 mm), $[\alpha]^{25}D$ +106.8° for (+)-4-methylcyclohexene]. This product was shown to be a 3:2 mixture of (+)-4-methylcyclohexene and (+)-3-methylcyclohexene by the series of reactions described below.

Epoxidation of the Optically Active Olefin Mixture.—To a cold, stirred solution of 2.4 g (0.025 mol) of a mixture of (+)-4-methylcyclohexene and (+)-3-methylcyclohexene was added dropwise 10 ml of 40% peracetic acid (Becco) to which 0.4 g of sodium acetate had been added. The temperature was maintained at 0° during the addition and while the mixture was stirred for 2 hr after the addition was complete. Stirring was then continued for 4 hr at room temperature. The reaction mixture was washed with water, 10% potassium hydroxide solution, and water again. The chloroform solution was dried and concentrated to give 2.4 g (86%) of the crude epoxide mixture. An nmr spectrum of the product showed two different methyl groups and thus indicated the possible presence of two different epoxides. However, separation of the compounds by vapor phase chromatography could not be achieved. A sample of 4-methylcyclohexene Comparison of the nmr spectrum of this material with that of the epoxide mixture served to identify 4-methylcyclohexene oxide as the major component of the mixture. The following sequence of reactions identified the other component as 3-methylcyclohexene oxide.

Reduction of the Epoxide Mixture.—The crude epoxide mixture (2.0 g, 0.018 mol) was reduced in the usual manner with lithium aluminum hydride in anhydrous ether to afford a mixture of alcohols in quantitative yield.

Oxidation of the Epoxide Reduction Products.—The crude alcohol mixture (1.5 g, 0.013 mol) obtained by reduction of the epoxide mixture was dissolved in 1.5 ml of glacial acetic acid, and the mixture was cooled to 0°. To this solution was added 1.5 g (0.0050 mol) of sodium dichromated in 2.5 ml of glacial acetic acid. The resultant reaction mixture was heated at 40° for 15 min, cooled, poured into water, and subjected to steam distillation. The distillate was extracted with ether, and the combined extracts were washed with an aqueous solution of sodium bicarbonate until neutrality was achieved. The ethereal solution was dried and concentrated to give 1.16 g (80%) of a mixture of ketones. Vapor phase chromatographic analysis on a Carbowax column was carried out; the components of the mixture were shown to be 2-methylcyclohexanone (15%), 3-methylcyclohexanone (45%), and 4-methylcyclohexanone (40%) by comparison of their retention times with those of commercially available authentic samples.

Selenium Dioxide Oxidation of the Olefin Mixture in Acetic Anhydride.—A stirred mixture of 12.0 g (0.108 mol) of selenium dioxide and 40 g of acetic anhydride was heated to 105°. To this mixture was added rapidly 19.3 g (0.201 mol) of the 3:2 mixture of (+)-4-methylcyclohexene and (+)-3-methylcyclohexene in 50 ml of acetic anhydride. The reaction mixture was heated at 105° for 3 hr, cooled, and filtered. The precipitated selenium that was recovered weighed 1.43 g (16.7%). The filtrate was subjected to steam distillation, and the distillate was extracted with ether. The ethereal extract was washed with water, washed with sodium carbonate solution until the wash solution remained basic, dried, concentrated, and distilled to afford 2.91 g (9.27%) of the allylic acetate mixture: bp 64–66° (6 mm). In order to remove organoselenium impurities, the allylic acetate mixture was treated with 1 g of Raney nickel (W-2) in anhydrous ether. The resultant slurry was refluxed overnight. After filtration and concentration, 2.8 g of product, which was free of organoselenium impurites, was recovered.

Catalytic Reduction of the Allylic Acetates.—The mixture of allylic acetates (2.8 g, 0.018 mol) prepared as described above was reduced at 50 psi of hydrogen in glacial acetic acid in the presence of Adams catalyst. Distillation of the product gave 2.6 g (92%) of a mixture of methylcyclohexyl acetates: bp 63–67° (6 mm).

Hydride Reduction of the Methylcyclohexyl Acetates.—The mixture of 2-, 3-, and 4-methylcyclohexyl acetates (2.5 g, 0.016 mol) was reduced in the usual manner with lithium aluminum hydride in anhydrous ether. Distillation of the product gave 1.7 g (94%) of a mixture of 2-, 3-, and 4-methylcyclohexanols: bp 65–68° (6 mm). The products were identified by comparison of the retention times as determined by vapor phase chromatography (Carbowax) with the retention times of commercially available authentic samples.

Oxidation of the Methylcyclohexanols.—The mixture of alcohols (1.5 g, 0.013 mol) obtained by hydride reduction of the acetate mixture was oxidized with potassium dichromate in acetic acid in a manner similar to that described above. Distillation of the product gave 1.3 g (90%) of the product mixture. This mixture was analyzed by vapor phase chromatography on a 5 ft × 0.25 in 20% Carbowax 20M on 80/100 mesh firebrick column at 120°. The chromatogram showed eight peaks, which corresponded to methylcyclohexane, toluene, the 2-, 3-, and 4-methylcyclohexanones, and small amounts of the 2-, 3-, and

(27) E. J. Eisenbraun and S. M. McElvain, *J. Amer. Chem. Soc.*, **77**, 3383 (1955).

(28) R. Adams, C. M. Smith, and S. Loewe, *ibid.*, **64**, 2087 (1942).

(29) D. S. Noyce and D. B. Denney, *ibid.*, **76**, 768 (1954).

(30) A. K. MacBeth and J. A. Mills, *J. Chem. Soc.*, 205 (1947).

(31) A. Skita and W. Faust, *Chem. Ber.*, **64**, 2878 (1931).

(32) W. Huckel and J. Kurz, *ibid.*, **91**, 1290 (1958).

(33) G. A. C. Gough, H. Hunter, and J. Kenyon, *J. Chem. Soc.*, 2052 (1926).

(34) M. Mousseron, R. Richaud, and R. Granger, *Bull. Soc. Chem. Fr.*, 222 (1946).

4-methylcyclohexanols. The hydrocarbons and the ketones were isolated by preparative vapor phase chromatography. Toluene and methylcyclohexane were identified by the nmr spectra. 2-Methylcyclohexanone (35%) had $[\alpha]^{25}D$ −14.6° (lit.[33] $[\alpha]^{25}D$ −15.22°) and gave a semicarbazone, which melted at 193–195° (lit.[29] mp 197°). 3-Methylcyclohexanone (30%) had $[\alpha]^{25}D$ +0.572° (lit.[33] $[\alpha]^{25}D$ +13.06) and gave a semicarbazone melting at 177–178° (lit.[29] mp 179°). 4-Methylcyclohexanone (35%) appeared as a shoulder on the peak corresponding to 3-methylcyclohexanone and was not separated.

Racemization of (−)-2-Methylcyclohexanone.—A small quantity of the (−)-2-methylcyclohexanone collected by vapor phase chromatography was refluxed in glacial acetic acid for 3 hr. The ketone that was recovered had no measurable optical activity.

Selenium Dioxide Oxidation of the Olefin Mixture in *n*-Butanol.—A stirred solution of 19.8 g (0.206 mol) of the 3:2 mixture of (+)-4-methylcyclohexene and (+)-3-methylcyclohexene in 70 ml of *n*-butanol was heated to reflux and 22.2 g (0.200 mol) of selenium dioxide in 100 ml of *n*-butanol was added dropwise. Reflux of the resultant mixture was continued for 30 hr. The reaction mixture was cooled and filtered to yield 6.2 g (39%) of black selenium. Fractional distillation of the filtrate gave 10 ml of a yellow liquid: bp 130–140° (30 mm). This material was treated with Raney nickel as described above to remove organoselenium impurities. Distillation through a spinning-band column gave 5.2 g of product: bp 90–95° (11 mm). Vapor phase chromatography on a Carbowax column showed five peaks. The material corresponding to the first and largest peak was collected and identified by its nmr spectrum as being a mixture of butoxycyclohexenes. The other peaks corresponded to methylcyclohexenones and methylcyclohexenols. The mixture of products was reduced catalytically in the presence of Adams catalyst in acetic acid. Vapor phase chromatography of the reduction product on a 12 ft × 3/8 in. 23% polyamide on Chromosorb W column was carried out. The butyl ethers of commercially available methylcyclohexanols were prepared. By comparison with these and other commercially available authentic samples, the components of the reduction mixture were determined to be *cis*-2-butoxymethylcyclohexane, *trans*-3-butoxymethylcyclohexane, *cis*-4-butoxymethylcyclohexane, *trans*-2-butoxymethylcyclohexane, *cis*-3-butoxymethylcyclohexane, *trans*-4-butoxymethylcyclohexane, a mixture of methylcyclohexanones, and a mixture of methylcyclohexanols.

Registry No.—Selenium dioxide, 7446-08-4; 1,3-diphenylpropene-3-*d*, 16704-20-4; benzaldehyde-1-*d*, 3592-47-0.

Acknowledgment.—The authors would like to express their appreciation to the U. S. Army Research Office (Durham) for generous support of these studies.

Bicyclo[3.3.1]nonanes. IV. Dehydration of the Bicyclo[3.3.1]nonane-2,6-diols

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Received October 24, 1967

Bicyclo[3.3.1]nonane-2,6-dione (**2**), which was prepared from 1,3,5,7-tetracarbomethoxybicyclo[3.3.1]nonane-2,6-dione (**1**), was reduced with sodium borohydride in methanol to a mixture of epimeric bicyclo[3.3.1]nonane-2,6-diols (**3** and **4**). Dehydration of the diol mixture with sulfuric acid gave bicyclo[3.3.1]nona-2,6-diene (**9**), bicyclo[3.3.1]nona-2,7-diene (**8**), bicyclo[3.3.1]nonan-2-one (**5**), *endo*-bicyclo[3.3.1]non-6-en-2-ol (**10**), *endo*-bicyclo[3.3.1]non-7-en-2-ol (**11**), *endo*-bicyclo[3.3.1]non-3-en-2-ol (**12**), and a mixture of tricyclic oxides, which were tentatively identified as oxaadamantane (**6**) and 10-oxatricyclo[3.3.1.$1^{2,7}$]decane (**7**).

The first practical route to simply substituted bicyclo[3.3.1]nonanes was developed by Meerwein and Schürmann.[1] In their approach, dimethyl malonate was caused to react with formaldehyde or methylene iodide to produce 1,3,5,7-tetracarbomethoxybicyclo-[3.3.1]nonane-2,6-dione (**1**) in good yield. Since **1** is so readily accessible, it appeared to be an attractive precursor to a number of derivatives that we were interested in preparing.

Upon reinvestigation of Meerwein's work,[1] we found that the preparation of **1** from formaldehyde could be simplified and expedited significantly by carrying out the initial phases of the condensation under anhydrous conditions and removing the water produced during the reaction by azeotropic distillation. Hydrolysis of the ester and decarboxylation of the resultant acid utilizing a procedure similar to that developed by Stetter and his group[2] afforded bicyclo[3.3.1]nonane-2,6-dione (**2**) in over-all yields as high as 38% based upon dimethyl malonate.

Reduction of **2** with sodium borohydride in methanol produced in high yield a mixture of two diols present in approximately equal percentages. In a previous paper,[3] we demonstrated that reduction of bicyclo-[3.3.1]nonan-2-one (**5**) using similar conditions produces *endo*-bicyclo[3.3.1]nonan-2-ol (**14**) almost exclusively. We have also provided data that show that nucleophilic attack on the bicyclo[3.3.1]nonane system occurs almost exclusively from the *exo* face of the molecule. On these grounds, it is reasonable to presume that the first-formed product of reduction is a boron ester of 6-keto-*endo*-bicyclo[3.3.1]nonan-2-ol (**18**). Two routes for the reduction of the second carbonyl group would now be possible.

Bimolecular reduction of the second carbonyl group, initiated by an attack by borohydride ion on the keto alcohol or its boron ester, would be influenced by the same steric effects that were encountered during the reduction of the first carbonyl group. In this instance, the product would be *endo,endo*-bicyclo[3.3.1]nonane-2,6-diol (**4**). Alternatively, an intramolecular path for reduction is also available, but this route would lead to the formation of *endo,exo*-bicyclo[3.3.1]nonane-2,6-diol (**3**). The details of this process merit further discussion.

To allow the initially formed boron ester of **18** to approach sufficiently close to the second carbonyl group so that an interaction can occur, the rings must assume twist-boat conformations. The expenditure of energy required to bring about this conformational change will be compensated for by two factors, namely, the lower activation energy associated with the reduction of ketones by alkoxyborohydrides[4] and the

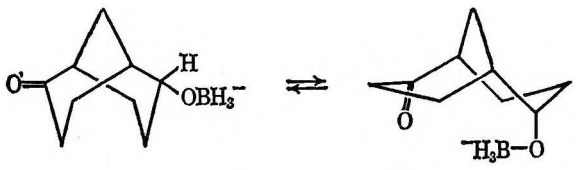
(1) H. Meerwein and W. Schürmann, *Ann.*, **398**, 196 (1913).

(2) H. Stetter, H. Held, and A. Schulte-Oestrich, *Ber.*, **95**, 1687 (1962).

(3) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, **32**, 1372 (1967).

(4) H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, **88**, 2811 (1966).

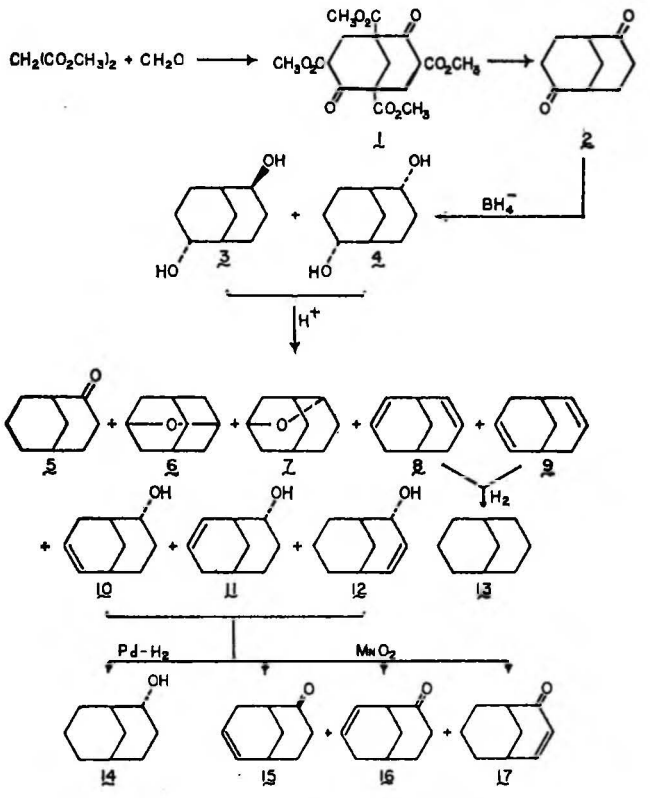
more favorable entropy factors associated with an intramolecular and unimolecular rate process in contrast to a bimolecular reaction. Since almost equal



amounts of **3** and **4** are produced by the reduction of **2**, it is apparent that the factors influencing the opposing reaction paths must nearly counterbalance each other.

By heating the mixture of **3** and **4** in 38% sulfuric acid using the conditions established by Meerwein,[5] eight different products were obtained. These are summarized in Scheme I. To facilitate the interpretation of our data, dione **2** was deuterated in the 3 and 7 positions by an acid-catalyzed exchange with deuterium oxide. It is interesting to note that, although base-catalyzed exchange of bridgehead hydrogens takes place readily for bicyclononanones[6,7] and bicyclo[3.3.1]non-1-ene can be prepared,[8,9] exchange under acidic conditions can be limited to the 3 and 7 positions of dione **2**. The deuterated dione subsequently was reduced to the corresponding 3,3,7,7-tetradeuteriodiol mixture, and the deuterated diol was dehydrated using the same conditions outlined for the nondeuterated mixture.[10-12]

SCHEME I



The lowest boiling fraction, which was a major product of dehydration, consisted of a diene mixture. Catalytic hydrogenation of this fraction produced bicyclo[3.3.1]nonane (**13**). In view of the structure of the diol precursors, it appeared to be reasonable to expect that the dehydration product was bicyclo[3.3.1]-nona-2,6-diene (**9**). However, from an examination of the nmr spectrum and the mass spectral data of the diene fraction, it appeared that some bicyclo[3.3.1]-nona-2,7-diene (**8**) was also present.

The mass spectrum (see Table I) of the diene fraction that resulted from dehydration of the deuterated diol showed that a small but significant percentage of the d_4-diene was present; the only reasonable route to this product would involve the sequence of reactions shown in Scheme II.

TABLE I

RESULTS OF MASS SPECTROMETRY[a]

Compd	Atoms of D/molecule[b]	D_0	D_1	D_2	D_3	D_4
Dienes	1.71 (1.76)	9.2	31.2	37.2	18.7	3.7
En-ols	2.42 (2.08)	12.8	16.5	31.5	28.8	10.4
Ketone	1.52 (1.60)	8.5	38.0	39.4	12.7	1.4
Oxides	1.86 (1.91)	6.4	27.1	40.6	21.2	4.7

[a] The data are given as relative abundances of the parent peaks and are uncorrected for the P + 1 peaks, P + 2 peaks, etc. For the nondeuterated compounds, it was found that the P − 1 peaks were negligible relative to the parent peaks. [b] Determined by Mr. J. Nemeth, Urbana, Ill. The values in parentheses were calculated from mass spectral data.

The detection of **9**-d_4, the isolation of *endo*-bicyclo-[3.3.1]non-7-en-2-ol (**11**), and the detection of **11**-d_4 all clearly demonstrate that 1,2-hydride shifts occur readily in this system. Since **11**-d_4 must be a precursor to **9**-d_4, it therefore is reasonable to expect that it should also produce the 2,7 diene; the occurrence of a large percentage of diene containing three atoms of deuterium provides compelling evidence for the existence of substantial percentages of **8** in the diene fraction.[13]

The second most volatile component, which appeared to be homogeneous by vapor phase chromatography, had an extraordinarily high melting point (215–218°) and analyzed for $C_9H_{14}O$. A comparison of the nmr spectrum of this product with that of an authentic sample[14,15] of oxaadamantane (**6**) showed that our

(5) H. Meerwein, F. Kiel, G. Klösgen, and E. Schoch, *J. Prakt. Chem.* **104**, 161 (1922).

(6) J. P. Schaefer and J. C. Lark, *J. Org. Chem.*, **30**, 1337 (1965).

(7) J. Dale, I. Laszlo, and W. Ruland, *Proc. Chem. Soc.* (London), 190 (1964).

(8) J. A. Marshall and H. Faubl, *J. Amer. Chem. Soc.*, **89**, 5965 (1967).

(9) J. R. Wiseman, *ibid.*, **89**, 5966 (1967).

(10) It should be noted that the composition of the diol mixture is probably significantly different from that used by Meerwein.[5] Meerwein reduced the dione with sodium amalgam in water and obtained a mixture of bicyclic and tricyclic alcohols. It has been shown recently that the reduction of **2** under equilibrating conditions gives a 2:1 mixture of *endo*-bicyclo[3.3.1]-nonan-2-ol and *exo*-bicyclo[3.3.1]nonan-2-ol.[11] Since the steric course of sodium–alcohol reductions closely approximates the product composition that is obtained by equilibration,[12] it seems probable that Meerwein's[5] bicyclic diol mixture was rich in the *exo,exo* epimer.

(11) K. H. Baggaley, J. R. Dixon, J. M. Evans, and S. H. Graham, *Tetrahedron*, **23**, 299 (1967).

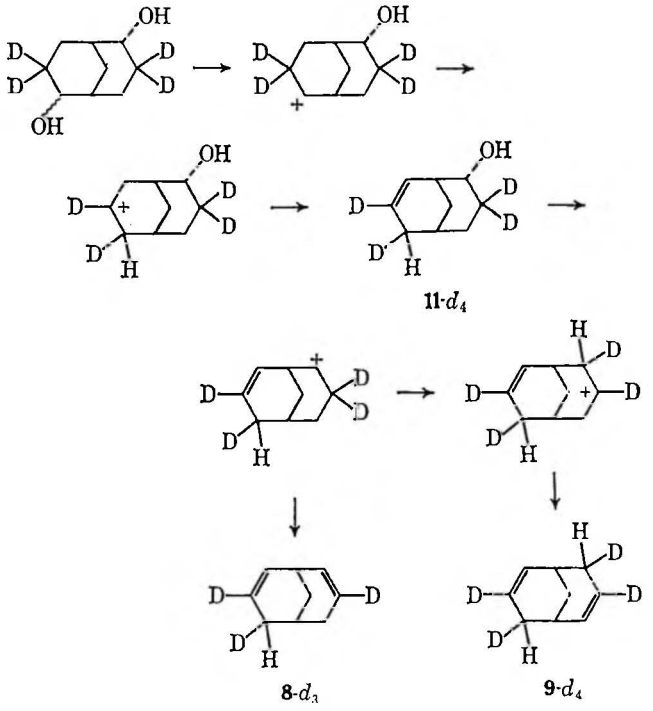
(12) C. P. Rader, G. E. Wicks, Jr., R. L. Young, Jr., and H. S. Aaron, *J. Org. Chem.*, **29**, 2252 (1964).

(13) A danger exists in too literal an interpretation of the percentages of d_4-diene, d_3-diene, etc, as ascertained from the mass spectrum. Since 31% of the diene fraction contained a single deuterium atom, it is apparent that loss of deuterium to solvent through a dynamic protonation–deprotonation equilibrium is occurring. Consequently, it is not possible to determine what percentage of the d_3-diene fraction is a primary reaction product and how much has arisen from loss of deuterium from **8**-d_4.

(14) Kindly provided by Professor H. Stetter.

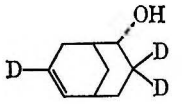
(15) H. Stetter and P. Tacke, *Angew. Chem.*, **74**, 354 (1962).

SCHEME II



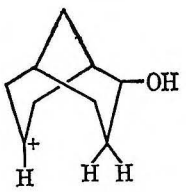
material was predominantly **6** contaminated with at least one other isomer; two reasonable possibilities for the structure of this second acid-stable oxide are 10-oxatricyclo[3.3.1.$1^{2,7}$]decane (**7**) and 10-oxatricyclo-[3.3.1.$1^{2,6}$]decane. The cationic precursors, **19** and **20**, of both oxides have been demonstrated to be reaction intermediates.

The large percentage of d_3-oxide requires that a major precursor of this product be **10**-d_3. Formation of

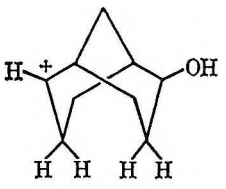


10-d_3

cation **19** by protonation of **10** should be favored over the formation of cation **20**, since the serious eclipsing



19

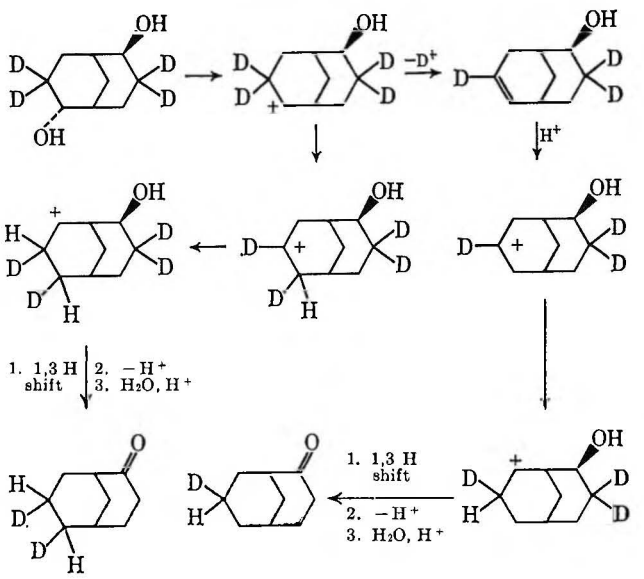


20

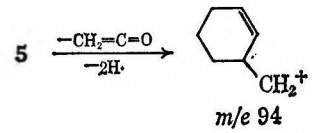
interactions that would exist in **20** would make it the less stable of the two.[16,17] Secondly, the formation of a bridged oxide from **20** would necessitate placing both rings of the cation in the energetically unfavored boat formation. On the other hand, **7** could be formed from **19** with only the ring bearing the hydroxyl group being in the boat formation. For these reasons, we consider the oxide impurity, which constituted about 25% of this fraction of the product mixture, to be **7**.

The third fraction, which constituted 10% of the product mixture, was readily identified as bicyclo[3.3.1]-nonan-2-one (**5**). It is evident that the formation of this compound must involve a transannular hydride shift. Since about 80% of the product was either mono- or dideuterated, the two paths illustrated in Scheme III seem to be the most probable.

SCHEME III



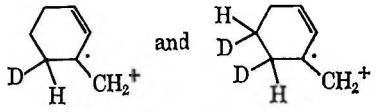
From a consideration of the mass spectra of **5** and of a sample of **5** that had been deuterated only at C_3, it is evident that the major course of degradation after electron impact is as shown in eq 1. The presence of



(1)

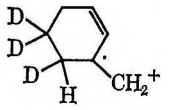
m/e 94

substantial fragments at both *m/e* 95 and 96 for the ketone that is produced from the deuterated diol is readily understood in terms of the species

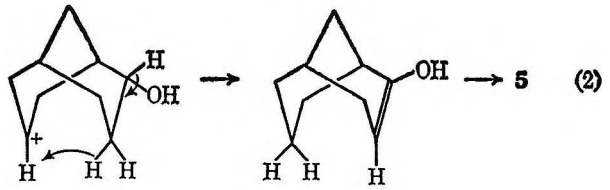


These would be expected to be present if the mechanism for ketone formation outlined above is valid.

A very significant feature of the mass spectrum of the ketone produced from the deuterated diol is the fragment at *m/e* 97 corresponding to



or something equivalent to this species. The presence of this fragment suggests that the sequence in eq 2 may be occurring. Hydride shifts of this type have been



(2)

(16) M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964).
(17) W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965).

observed during the reactions of the 2,3-epoxide,[18] and the sequence outlined above would be stereoelectronically favored.

The last fraction that was produced consisted of a mixture of three en-ols. Oxidation of the mixture produced three unsaturated ketones that were easily identified by their characteristic uv spectra. Catalytic hydrogenation of the en-ol mixture produced a single alcohol, which was identified as *endo*-bicyclo[3.3.1]nonan-2-ol (**14**) by comparison with an authentic sample.[3] Detection of none of the *exo* isomer indicates that dehydration of the 2-*exo* alcohol is significantly faster than dehydration of the 2-*endo* alcohol. This is in accord with our recent observation[19] that the rate constant for solvolysis of the 2-*exo* brosylate is 80 times greater than that of its *endo* counterpart.

The mixture of diols **3** and **4** was dehydrated also under conditions other than those described by Meerwein.[5] When the mixture was heated at 100–105° in a sealed tube in the presence of 5% sulfuric acid, the only products were en-ols **10** and **11**. However, heating the sealed tube and its contents at 150–160° led to the same mixture of products that was obtained using Meerwein's conditions.

From this study it is evident that the dehydration of the diol mixture provides a practical route for the synthesis of bicyclo[3.3.1]nonane and *endo*-bicyclo[3.3.1]nonan-2-ol. In addition, from the results of deuterium-labeling experiments, it appears that 1,2-, 2,8-, and 3,7-hydride shifts occur with ease in the bicyclo[3.3.1]nonane system. Studies attempting to assess the importance of these effects in other reactions are in progress.

Experimental Section

1,3,5,7-Tetracarbomethoxybicyclo[3.3.1]nonane-2,6-dione.—Dimethyl malonate (264 g, 2.00 mol), 48 g (1.5 mol) of 95% paraformaldehyde, 400 ml of benzene, and 4 ml of piperidine were placed in a 2-l. flask fitted with a Dean–Stark trap and reflux condenser. The mixture was stirred with a magnetic bar and heated to reflux by means of a heating mantle. Reflux was continued until water ceased to accumulate in the trap; 26.5 ml (98% of the theoretical volume) was collected. Benzene was removed at reduced pressure, and the residue was dissolved in 150 ml of absolute methanol. The resulting solution was added rapidly to a stirred solution of sodium methoxide prepared from 32.6 g (1.42 g-atoms) of sodium and 400 ml of absolute methanol. More solvent was added as needed to facilitate stirring. This mixture was stirred and refluxed gently for 7 hr. After removal of the solvent at reduced pressure, the residue was dissolved in ice water and the mixture was extracted several times with diethyl ether. Precipitation of the product was achieved by bubbling carbon dioxide through the aqueous layer. The product was recovered by suction filtration, washed with water, dried in air, and combined with 300 ml of benzene. After removal of water by azeotropic distillation, the benzene solution was filtered while hot and then cooled. The product, which crystallized readily, was isolated by suction filtration and dried at room temperature under reduced pressure. The product weighed 108 g (56%) and had mp 145–154° (lit.[1] mp 163–164°).

Bicyclo[3.3.1]nonane-2,6-dione.—Modifications of the method of Stetter[2] were used.

Method A.—To a mixture of 35 g (0.10 mol) of 1,3,5,7-tetracarbomethoxybicyclo[3.3.1]nonane-2,6-dione and 106 ml of glacial acetic acid were added 36 ml of water and 36 ml of concentrated hydrochloric acid. Reflux and stirring were carried out for 11 hr. After removal of all readily volatile materials by distillation at reduced pressure, the residue was sublimed (3 mm, 120°) to afford 9.8 g (65%) of product, mp 119–135° after crystallization from benzene (lit.[1] mp 141°). Analysis by vapor phase chromatography (200° on a 10 ft × 0.25 in. column, 20% GE SE-30 on Chromosorb W) revealed the presence of only negligible amounts of impurity. The product was found to be suitable for use without further purification.

Method B.—The tetraester was refluxed in aqueous acid as described above. After removal of the acids and water, the residue was dissolved in methylene chloride. The methylene chloride solution was washed with several portions of 5% sodium hydroxide solution and with water, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was obtained in 19% yield. Acidification of the basic wash solutions afforded a sizable quantity of a substance that was identified as bicyclo[3.3.1]nonane-2,6-dione-1,5-dicarboxylic acid.

Method C.—The tetraester (10 g, 0.026 mol) was refluxed for 10 hr in aqueous acid as described above. After removal of the acids and water, 70 ml of bromobenzene was added to the residue. The flask was equipped for simple distillation, and 10 ml of material was distilled to ensure complete removal of the acids and water. The remaining solution was refluxed for 70 hr, after which time the evolution of carbon dioxide could no longer be detected. After removal of the bromobenzene by distillation under vacuum, the residue was sublimed (3 mm, 140°) to give 2.8 g (67%) of product.

Bicyclo[3.3.1]nonane-2,6-diol.—To a solution of 35.7 g (0.234 mol) of bicyclo[3.3.1]nonane-2,6-dione in 1 l. of absolute methanol was added 20 g (0.53 mol) of sodium borohydride in small portions. The contents of the flask were cooled by an ice–water bath and stirred with a magnetic bar during the addition. After 24 hr of stirring at room temperature, the solvent was removed at reduced pressure. Ice water was added to the residue, and continuous extraction with methylene chloride was carried out for 6 days. Filtration of the extract afforded 28.7 g of diol, mp 229.5–231.5° after crystallization from acetonitrile; evaporation of the solvent gave additional product. The total yield was 32.5 g (88.6%). An infrared spectrum (Nujol mull) showed absorption at ~3375 cm^{-1}. Vapor phase chromatography (160° on a 10 ft × 0.25 in. column, 5% QF-1 on 60/80 Chromosorb W) revealed the presence of two diols in nearly equal amounts.

Dehydration of Bicyclo[3.3.1]nonane-2,6-diol. Method A.—A modification of the procedure described by Meerwein[5] was employed. In a three-necked flask fitted with an addition funnel and equipped for steam distillation were placed 10 g (0.066 mol) of bicyclo[3.3.1]nonane-2,6-diol and 45 ml of 23% sulfuric acid. This mixture was stirred with a magnetic bar and heated with an oil bath maintained at 143–145°. After sufficient water had distilled from the mixture to bring the acid to a concentration of 38%, water was added from the funnel at a rate equal to the rate of distillation. Thus, the concentration of acid was kept at 38%. A white solid appeared in the distillate shortly after distillation was initiated. Distillation was terminated when organic material no longer appeared in the distillate. After saturation with sodium chloride, the distillate was extracted with several portions of diethyl ether. The ether extract was dried and concentrated to give 7.1 g of crude product.

Vapor phase chromatography (125° on a 5 ft × 0.25 in. column, 20% Carbowax on 80/100 neutral firebrick) of the dehydration product showed five distinct major peaks. The compounds or mixtures of compounds listed below in order of increasing retention time were isolated by preparative vapor phase chromatography (150° on a 6 ft × 0.25 in. column, 20% Carbowax on 50/60 firebrick) and identified.

1. **Bicyclo[3.3.1]nona-2,6-diene and bicyclo[3.3.1]nona-2,7-diene** (35%) were a colorless liquid; an infrared spectrum (film) revealed absorption at 710 and 1640 cm^{-1}; an nmr spectrum displayed a five-line pattern superimposed on a weak complex multiplet (4 H, total) centered at τ 4.4 and a multiplet (8 H) ranging from 7.4 to 8.4.

Anal. Calcd for C_9H_{12}: C, 89.93; H, 10.07. Found: C, 89.84; H, 10.30.

2. **2-Oxaadamantane and 10-oxatricyclo[3.3.1.$1^{2,7}$]decane** (10%) were a white solid with mp 215–218° (sealed capillary); an infrared spectrum (CCl_4) revealed absorption at 1193 cm^{-1}; an nmr spectrum showed a multiplet (2 H) centered at τ 5.8 and a multiplet (12 H) ranging from 7.5 to 8.4.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.16; H, 10.50.

3. **Bicyclo[3.3.1]nonan-2-one** (9%) was identified by comparison with an authentic sample.[3] The mass spectrum of this

(18) R. A. Appleton, J. R. Dixon, J. M. Evans, and S. H. Graham, *Tetrahedron*, **23**, 805 (1967).

(19) J. P. Schaefer and C. A. Flegal, *J. Amer. Chem. Soc.*, **89**, 5729 (1967).

ketone was characterized by the base peak, which occurred at *m/e* 94; the position of this peak was unchanged when the parent ketone was deuterated at the 3 position. An analysis of the mass spectrum of the ketone obtained by dehydration of the deuterated diol indicated the following relative abundances: *m/e* 94 (D_0), 15.7; *m/e* 95 (D_1), 39.7; *m/e* 96 (D_2), 33.3; *m/e* 97 (D_3), 11.3.

4. *endo*-Bicyclo[3.3.1]non-6-en-2-ol and *endo*-bicyclo[3.3.1]non-7-en-2-ol (46%) were a white solid; these compounds were collected together although partial separation was possible; an infrared spectrum displayed absorption at 704, 1650, and 3450 cm^{-1}; an nmr spectrum showed a multiplet (2 H) centered at τ 4.1, a singlet (1 H) centered at 6.2, and a multiplet (10 H) ranging from 7.3 to 8.6; further proof of the identity of these compounds was obtained by the procedures described below. No bicyclo[3.3.1]non-3-en-2-ol was detected in the material that was collected in this manner.

Method B.—A mixture of 2.0 g (0.013 mol) of bicyclo[3.3.1]nonane-2,6-diol and 20 ml of 5% sulfuric acid was heated in a sealed tube at 100–105° for 48 hr. The contents of the tube were extracted with pentane. The pentane solution was washed twice with water, dried, and concentrated to give a residue weighing 0.60 g (34%). The product was identified as a mixture of *endo*-bicyclo[3.3.1]non-6-en-2-ol and *endo*-bicyclo[3.3.1]non-7-en-2-ol by its infrared and nmr spectra and by vapor phase chromatographic analysis. After sublimation, the product had mp 132–134° (sealed capillary) (lit.[5] mp 133° for bicyclo[3.3.1]non-6-en-2-ol). Continuous extraction of the acid solution with methylene chloride led to the recovery of 1 g of starting material.

p-Nitrobenzoate derivatives were prepared by treating the unsaturated alcohols with *p*-nitrobenzoyl chloride in dry pyridine. After crystallization from ethanol–water and from pentane, the mixture of derivatives had mp 112–114°.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96. Found: C, 66.64; H, 5.75.

Method C.—A mixture of 1.0 g (0.006 mol) of bicyclo[3.3.1]nonane-2,6-diol and 20 ml of 5% sulfuric acid was heated in a sealed tube at 150–160° for 24 hr. The product was isolated as described for method B and sublimed to give 0.6 g of material, mp 171–178°. Analysis by vapor phase chromatography showed this material to be a mixture of the same compounds that were obtained by method A.

Manganese Dioxide Oxidation of the Dehydration Products.—A mixture of 0.2 g of the product obtained by dehydration of bicyclo[3.3.1]nonane-2,6-diol by method A, 1.0 of manganese dioxide,[20] and 15 ml of petroleum ether (bp 30–60°) was stirred for 7 days. After removal of the solid reagent by filtration, the solution was concentrated; the residue was sublimed (40 mm, 100°). An ultraviolet spectrum (95% ethanol) showed at 232 mμ, the strong absorption that is characteristic of an α,β-unsaturated ketone. However, oxidation by this method of the material obtained from subsequent dehydrations by method A gave a product that did not show this absorption band. Rather, the ultraviolet spectrum displayed an absorption maximum at 297 mμ. The amount of unsaturated ketone in the oxidation mixture was estimated by vapor phase chromatography, and log ϵ was found to be approximately 2.54. These data, being characteristic of a homoconjugated unsaturated ketone,[21] confirm the presence of bicyclo[3.3.1]non-7-en-2-ol in the starting material.

The unsaturated alcohols obtained by dehydration of the diol by method B were oxidized in the manner described above. An ultraviolet spectrum of the product confirmed the absence of any α,β-unsaturated ketone and revealed the presence of bicyclo[3.3.1]non-7-en-2-one.

Catalytic Reduction of the Dehydration Products.—Catalytic hydrogenation of the unsaturated alcohols obtained by dehydration of bicyclo[3.3.1]nonane-2,6-diol according to method B was carried out on a microhydrogenation apparatus in the presence of 10% palladium on charcoal with 95% ethanol serving as solvent. After collection of the catalyst by filtration and removal of the solvent by distillation, sublimation of the residue afforded a product, identified as *endo*-bicyclo[3.3.1]nonan-2-ol, which had mp 172–176° (sealed capillary) (lit.[3] mp 177–178°). The melting point was depressed when the product was mixed with an authentic sample of *exo*-bicyclo[3.3.1]nonan-2-ol.[3] An infrared spectrum (CCl_4) showed the characteristic absorptions at 1025 and 1060 cm^{-1}.[22] The product gave an nmr spectrum that displayed a singlet (1 H) at τ 5.9, a multiplet (1 H) centered at 6.1, and a multiplet (12 H) ranging from 7.4 to 9.0.

A *p*-nitrobenzoate derivative was prepared by treating the product alcohol with *p*-nitrobenzoyl chloride in dry pyridine. After crystallization from ethanol–water, the derivative had melting point 102–103° (lit.[22] mp 102–103°).

The crude product mixture obtained by dehydration of the diol by method A was hydrogenated in the manner described above. The product mixture was analyzed by vapor phase chromatography. The peak corresponding to bicyclo[3.3.1]nona-2,6-diene had been replaced by a new peak corresponding to a compound that had the same retention time as bicyclo[3.3.1]nonane prepared from an authentic sample of bicyclo[3.3.1]non-2-ene.[3] The unsaturated alcohols had been converted into *endo*-bicyclo[3.3.1]nonan-2-ol, mp 171–174° (lit.[3] mp 177–178°), which was separated from the mixture by preparative vapor phase chromatography. The other two major components of the starting mixture remained unchanged.

Treatment of 2-Oxaadamantane and 10-Oxatricyclo[3.3.1.1^{2,7}]decane with Acid.—A mixture of the oxides (65 mg) and 2 ml of 5% sulfuric acid was heated in a sealed glass tube for 20 hr at 160°. The contents of the tube were poured into pentane, and the layers were separated. The pentane layer was washed with water, dried, and analyzed by vapor phase chromatography. The oxides were found to be intact, and no new products had been formed.

Deuteration of Bicyclo[3.3.1]nonane-2,6-dione.—To 20.0 ml of cold deuterium oxide was added with stirring 0.34 ml of phosphorous oxychloride. This solution was combined with 6.0 g (0.039 mol) of bicyclo[3.3.1]nonane-2,6-dione and 25 ml of ethanol-*d*, which had been prepared by treating triethyl orthoformate with deuterium oxide. Stirring was continued while the mixture was heated at 45 50° for 48 hr. The liquid components of the mixture were removed at reduced pressure (25 mm); care was taken to keep the oil-bath temperature below 50° during the distillation. The residue was treated again in the same manner with ethanol-*d* and deuterium oxide to which a small quantity of phosphorous oxychloride had been added. After 67 hr of stirring at 45–50° and concentration under the conditions described above, the residue was dissolved in 100 ml of methylene chloride. The methylene chloride solution was washed with small portions of cold, saturated sodium bicarbonate solution and with ice water. The organic solution was dried and evaporated to dryness; the amount of dione recovered was 5.6 g. The product had 31.10 atom % excess D or 3.73 atoms of D per molecule.

Bicyclo[3.3.1]nonane-2,6-diol-3,3,7,7-d_4.—Bicyclo[3.3.1]nonane-2,6-dione-3,3,7,7-d_4 was reduced to the corresponding diol in the manner described for the nondeuterated analogs.

Dehydration of Bicyclo[3.3.1]nonane-2,6-diol-3,3,7,7-d_4.—The deuterated diol was dehydrated according to method A described for the nondeuterated analog. The products were separated by preparative vapor phase chromatography under the conditions described above. The results of mass spectral analysis are given in Table I.

Registry No.—**1**, 6966-22-9; **2**, 16473-11-3; **3**, 16710-53-5; **4**, 16710-54-6; **5**, 2568-17-4; **6**, 281-24-3; **7**, 16710-57-9; **8**, 13534-06-0; **9**, 16710-59-1; **10**, 16710-60-4; **10** *p*-nitrobenzoate, 16710-61-5; **11**, 16710-62-6; **11** *p*-nitrobenzoate, 16710-63-7.

Acknowledgment. We wish to thank Dr. David Weinberg of the Phillips Petroleum Co. for determining the mass spectra of most of the compounds studied.

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Reactions of N-Fluoriminonitriles[1]

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Received February 21, 1968

The conversion of N-fluoriminonitriles **1a**, **b**, and **c** into imidates and α-fluorimino esters is reported. Grignard reagents and the fluoriminonitriles give both cleavage and fluorine-substitution reactions. The nitrile function of fluoriminonitriles will participate in 1,3-dipolar cycloaddition with 2,4,6-trimethylbenzonitrile oxide.

The addition of tetrafluorohydrazine to terminal olefins[2] followed by dehydrofluorination[3] of the 1,2-bis(difluoramino)alkanes produced, provides a straightforward route to N-fluoriminonitriles (**1**). In a detailed report on the preparation of fluoriminonitriles,[3] only the chemistry of 1-cyano-N-fluoroformimidoyl fluoride (**1**, R = F) was investigated in detail. Another

$$RCH{=}CH_2 \xrightarrow{N_2F_4} RCH(NF_2)CH_2(NF_2) \longrightarrow RC{\equiv}NF$$

1a, R = C_6H_5
b, R = 4-ClC_6H_4
c, R = *n*-C_4H_9-O-

publication[4] reported briefly on the fragmentation and rearrangement of **1a** and **b** in the presence of alkoxides. This paper reports additional study of the fluorimines **1a–c**.

Because of the tendency of **1a** and **b** to cleave to aromatic nitrile and rearrange to a dialkoxy imidocarbonate in the presence of sodium alkoxides,[4] it was of interest to attempt imidate formation from these α-fluoriminonitriles by the standard base-catalyzed methods.[5] Nucleophilic attack at the nitrile function of **1a** or **b** possibly is responsible for the fragmentation reaction. The interaction of **1a** and **b** with methanol containing a catalytic amount of sodium methoxide, or with potassium cyanide in refluxing methanol, gave the corresponding imidates **2a** and **b**. Some nitrile, the cleavage product, was formed in the preparative runs.

$$RC{\equiv}NF \xrightarrow[NaOR' \text{ or } KCN]{R'OH} RC(=NF)(=NH)COR'$$

2a, R = C_6H_5; R′ = CH_3
b, R = 4-ClC_6H_4; R′ = CH_3
c, R = *n*-C_4H_9-O-; R′ = CH_3

Since the equilibrium between nitrile and imidate was established rapidly, and was overwhelming in favor of the imidate (as evidenced by ^{19}F nmr spectra), the low-temperature, methoxide-catalyzed route to **2a** and **b** was preferable. Characterization of the methyl imidates is summarized in Table I.

Upon exposure to aqueous alcoholic hydrochloric acid, the imidates smoothly hydrolyzed to α-fluorimino esters **3**. The ethyl imidates of **1a** and **b** were prepared and hydrolyzed directly in the ethanolic reaction mixture. Small amounts of α-fluoriminoamides **4** accompanied the esters **3** prepared by this procedure. The amides apparently were a result of the hydrolysis step, since they were not detected (by ^{19}F nmr) prior to this step. Table II summarizes the properties of the α-fluorimino esters **3**.

TABLE I

METHYL α-FLUORIMINOIMIDATES

$RC(=NF)(=NH)COCH_3$

R	^{19}F nmr, ϕ[a]	Anal, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
C_6H_5	−27.3	59.99	5.03	15.55	60.24	4.81	15.22
4-ClC_6H_4	−28.3	50.36	3.76	13.06	49.98	3.35	13.81
n-C_4H_9-O- (*syn*)[b]	+47.7	47.72	7.44	15.90	47.91	7.61	15.52
(*anti*)	+38.2	47.72	7.44	15.90	46.74	7.07	15.40

[a] ϕ values are measured in parts per million (ppm) from internal CCl_3F. [b] F and O *cis*.

$$2 \xrightarrow[HCl]{R'OH} RC(=NF)(=O)COR' \; (\mathbf{3}) + RC(=NF)(=O)CNH_2 \; (\mathbf{4})$$

a, R = C_6H_5; R′ = CH_3
b, R = 4-ClC_6H_4; R′ = CH_3
c, R = *n*′C_4H_9-O-; R = CH_3

TABLE II

α-FLUORIMINO ESTERS

$RC(=NF)(=O)COR'$

R	R′	^{19}F nmr, ϕ[a]	Anal, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
C_6H_5	CH_3	−27.7	59.66	4.45	7.73	59.31	4.48	7.94
C_6H_5	C_2H_5[b]	−28.2	61.53	5.16	7.18	62.01	5.49	7.09
4-ClC_6H_4	CH_3[c]	−30.0	50.13	3.27	6.49	50.10	3.27	6.65
4-ClC_6H_4	C_2H_5[d]	−29.0	52.30	3.95	6.10	52.26	3.93	6.32
C_4H_9-O- (*syn*[e])	CH_3	+48.4	47.45	6.83	7.90	47.48	7.12	8.00
C_4H_9-O- (*anti*)	CH_3	+30.6	47.45	6.83	7.90	47.62	6.72	7.73

[a] ϕ values are measured in parts per million (ppm) from internal CCl_3F. [b] Calcd: F, 9.7. Found: F, 9.8. [c] Mp 34–36°. [d] Mp 35–37°. [e] F and O *cis*.

Fluorimines **1a** and **b** apparently exist mainly in the *anti* form, although some *syn* isomer is present in the usual samples.[3,4] However, imidates **2a** and **b**, and fluorimino esters **3** derived from **1a** and **b**, apparently were isolated in only one configuration; only one sharp ^{19}F nmr resonance peak was observed with each sample. Since the starting configuration is presumed to be *anti* (aromatic ring and fluorine *trans*) and because the *syn* isomers may well be prone to cleavage *via* a *trans* fragmentation process, imidates **2a** and **b** and the corresponding esters **3** are assumed to be the *anti* isomers.

Fluorimine **1c**, a mixture of *syn* and *anti* isomers, did not rearrange or fragment when treated with an equivalent or an excess of sodium methoxide in methanol. Instead, displacement of the cyano function occurred,

(1) This research was carried out under the sponsorship of the U. S. Army Missile Command, Redstone Arsenal, Ala., under Contract DAAH01-67-C-0655.

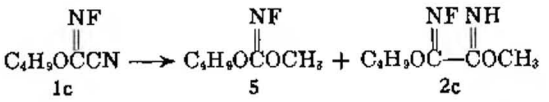
(2) R. C. Petry and J. P. Freeman, *J. Org. Chem.*, **32**, 4034 (1967).

(3) A. L. Logothetis and G. N. Sausen, *ibid.*, **31**, 3689 (1966); A. L Logothetis, U. S. Patent 3,215,709 (Nov 2, 1965).

(4) T. E. Stevens, *J. Org. Chem.*, **32**, 670 (1967).

(5) F. C. Schaeffer and G. A. Peters, *ibid.*, **26**, 412 (1961).

and the fluorimino carbonates **5**, *syn* and *anti*, were produced cleanly. With a catalytic amount of sodium methoxide at −10°, mixtures of **5** and **2c** were produced. A typical reaction mixture, after 15 min or 1 hr at −10°, contained, according to the ^{19}F nmr spectrum, about 7% **1c**, 25% **5**, and 69% the isomers of **2c**. The isomers of **2c** reported in Table I were isolated by vpc from the reaction mixtures.[6] The fluorimino esters **3** (Table II) formed from **2c** were also obtained by vpc of the mixture resulting from acidic hydrolysis of these methanolic solutions. Fluoriminocarbonate **5** hydrolyzed to methyl butyl carbonate under these conditions.

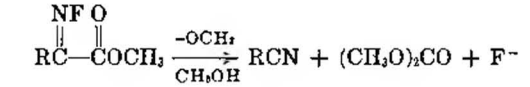


If one makes certain assumptions in assigning structures to the isomers of **1c**, the configuration of imidates **2c** and esters **3c** follows. It seems reasonable to assume that the *anti* isomer, with the F and CN functions adjacent, would have ^{19}F nmr peaks at lower field; this is consistent with earlier assignments in related molecules.[3] Also, the $-CH_2-O-$ protons of the *n*-butoxy group should be most shielded when the fluorine atom is adjacent to it (*syn* isomers); this fluorine, at least, appears to be the most likely part of these molecules to cause a large chemical shift in the protons. Thus, one concludes that **1c**, with a ^{19}F nmr peak at ϕ +23 and the methylene proton resonance at τ 5.83, has the *syn* configuration. The *anti* isomer has ^{19}F resonance at ϕ +8, and the methylene proton peaks are at τ 5.62. Fluoriminoimidate **2c**, with a fluorine peak at ϕ +47.7 and the specific proton peak at τ 6.06, is the *syn* isomer; the *anti* isomer has nmr peaks at ϕ +38.2 and τ 5.72. Along the same line, ester **3c**, characterized by ϕ + 48.4 and τ 5.82 peaks is *syn*, while **3c** with ϕ +30.6 and τ 5.65 is *anti*.

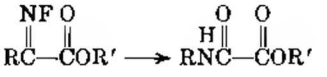
With N-fluoriminocarbonates **5**, there is only a small chemical shift in the ^{19}F nmr spectra. One isomer absorbs at ϕ +89.6, the other at +90. On the basis of the tentative assumptions made for **1c**, the isomer with the +89.6 fluorine peak, and with proton nmr peaks at τ 5.93 for $-O-CH_2-$ and at τ 6.32 for $-O-CH_3$ would have the *anti* $F-C_4H_9-O$ configuration. The *syn* isomer exhibited proton absorption at τ 6.00 for $O-CH_2-$ and 6.22 for CH_3-O-.

The extent to which imidate formation affects the fragmentation and cleavage reactions of **1a** and **b** in alcohols remains unknown. However, both fluoriminonitrile **1b** and fluoriminoimidate **2b** gave the same ratio of nitrile to imidocarbonate when exposed, under identical conditions, to excess sodium methoxide in methanol. By vpc, 4-chlorobenzonitrile[7] (65%) and dimethyl N-(4-chlorophenyl)imidocarbonate (35%) were formed from each. While **1a** and excess sodium methoxide produced benzonitrile (61%) and dimethyl N-(phenyl)imidocarbonate (39%), **2a** gave 48% nitrile and 52% imidocarbonate. There appears to be little doubt, however, that the fragmentation of the fluoriminonitriles arises from attack by base at the nitrile function of the *syn*-fluorimine.[4]

Fluorimino esters **3a** and **b** were readily cleaved by sodium methoxide in methanol. Only the nitrile, and presumably, dimethylcarbonate were produced; there was no sign of any rearrangement product here.



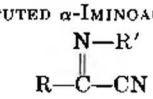
With concentrated sulfuric acid at room temperature, fluorimino esters **3a** and **b**, as well as the related ethyl esters, underwent a clean Beckmann rearrangement to produce esters of oxanilides. Examples are given in the Experimental Section. Fluoriminonitriles **1a** and **b** also undergo a Beckmann rearrangement in warm sulfuric acid.[4]



When treated with Grignard reagents, fluorimines **1a** and **b** were converted into N-substituted α-iminoacetonitriles **6** in low yield. These reactions are summarized in Table III. Fragmentation of the fluoriminonitriles to aromatic nitrile accounted for much of **1a** and **b** in each reaction, although some fluoriminonitrile was usually recovered even with an excess of Grignard reagent. Fluorimine **1c** and the Grignard reagents (*n*-butyl, phenyl) used did not interact.

TABLE III

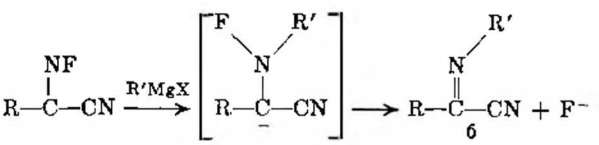
N-SUBSTITUTED α-IMINOACETONITRILES



			Anal, %					
		Yield,	Calcd			Found		
R	R′	%	C	H	N	C	H	N
C_6H_5	*n*-C_4H_9	18	77.38	7.58	15.0	77.35	7.86	14.8
C_6H_5	C_6H_5[a]	19	81.53	4.89	13.6	81.30	4.77	13.5
4-ClC_6H_4	*n*-C_4H_9	13	64.30	5.94	12.7	65.42	6.22	12.8
4-ClC_6H_4	C_6H_5[b]	18	69.86	3.77	11.6	69.63	3.75	11.8

[a] Mp 70°; F. Barrow and F. J. Thorneycroft [*J. Chem. Soc.*, 769 (1939)] reported 71°. [b] Mp 105°; U. Bellavita [*Gazz. Chim. Ital.* 65, 899 (1937); *Chem. Abstr.*, 30, 3420 (1936)] reported 108°.

Although a radical process could account for the low yield of the iminonitriles **6**, ionic addition of the anion



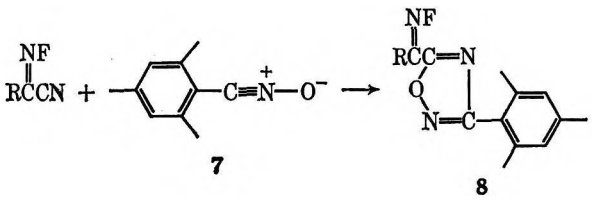
from the Grignard reagent to the >C=N— bond, as sketched, also appears to be a reasonable process. Cleavage probably results from attack of organometallic at the nitrile function. No definitive sign of valeronitrile could be found in the reaction with the *n*-butyl Grignard reagents, but small amounts of benzonitrile were detected (vpc) from reaction of **1b** and the phenyl Grignard reagent.

Using 2,4,6-trimethylbenzonitrile oxide (**7**) as the 1,3-dipole, 1,3-cycloadditions with the N-fluorimino-

(6) A detailed, kinetic study of the reactions of **1c** will be reported by Dr. F. A. Johnson of these laboratories. In this report, the configurations and interconversions of **1c**, **2c**, and **5** will be reported in detail. However, it was established that the same mixtures of isomers of **5** resulted from either isomer of **1c**; the ratio of **2c** to **5** did depend upon the configuration of **1c**.

(7) Some of which was present as the methyl imidate.[5]

nitriles was explored briefly.[8] The progress of the addition could be monitored easily by ^{19}F nmr, and, in ether solution, formation of the 1,2,4-oxadiazole **8** was



7 **8**

complete after 3 days with fluorimines **1a**, **b** and with the *n*-butyl fluorimine **1**, R = C_4H_9. Formation of the oxadiazole from **1c** and **7** was complete after 2 days. Properties of the adducts **8** are summarized in Table IV.

TABLE IV

3-MESITYL-5-(α-FLUORIMINO)-1,2,4-OXADIAZOLES (**8**)

		Anal, %					
		Calcd			Found		
R	^{19}F,[a] φ	C	H	N	C	H	N
C_6H_5[b]	−42.6	69.89	5.21	13.58	70.05	5.20	13.58
4-ClC_6H_4[c]	−43.2	62.70	4.68	12.19	63.27	4.43	12.26
n-C_4H_9-O-[d]	+24.4, +35.6	62.93	6.60	13.76	63.05	6.67	14.08
n-C_4H_9	−42.0	66.41	6.97	14.52	66.57	7.06	14.57

[a] φ values are measured in parts per million (ppm) from internal CCl_3F. [b] Mp 52–53°. [c] Mp 112–114°. [d] Mixture of *syn* and *anti* isomers.

Since the nitrile band was absent in the infrared spectra of adduct **8**, and the ^{19}F nmr spectra of the adduct exhibited peaks characteristic of the fluorimine function (see Table IV), there is little doubt that the cycloaddition process involved the C≡N rather than the C=N—F function. Only with **1c** were *syn* and *anti* isomers detected.[9]

Experimental Section

Melting points and boiling points are not corrected. ^{19}F spectra were run in carbon tetrachloride solution on a Varian 4300B spectrometer operating at 40 MHz; φ values are measured in parts per million from internal CCl_3F standard. Proton nmr spectra were recorded on a Varian A-60 spectrometer. The N-fluoriminonitriles **1a** and **b** were prepared as described earlier.[4]

Preparation of *n*-Butoxyfluoriminonitrile (1c).—The crude adduct,[2] prepared from 45 mmol of butyl vinyl ether and tetrafluorohydrazine in 100 ml of methylene chloride, was cooled in an ice bath while 18 ml of triethylamine in 50 ml of methylene chloride was added dropwise. The mixture was stirred at 20° for 1 hr and then poured into water. The organic phase was washed with 5% aqueous hydrochloric acid and water. The methylene chloride was removed in the Holzmann column and the residue was distilled in the same column to give 5.0 g (77%) of the *n*-butoxyfluoriminonitrile, a mixture of *syn* and *anti* isomers, bp 40° (4 mm).

Anal. Calcd for $C_6H_9N_2OF$: C, 49.99; H, 6.29; N, 19.44. Found: C, 50.05; H, 6.49; N, 19.57.

The isomers could be separated on a 5-ft silicon (G.E. SF-96) on Chromosorb vpc column at 80°. The major isomer was eluted first; on the basis of the ^{19}F nmr peak at φ +23 it was assigned the *syn* configuration. The minor (*anti*) isomer had ^{19}F resonance at φ +8.

Preparation of *n*-Butylfluoriminonitrile.—The tetrafluorohydrazine adduct of 1-hexene (4 g of olefin) in 150 ml of methylene chloride was maintained at 15° while 22 ml of triethylamine in 100 ml of methylene chloride was added dropwise. After 1 hr at 25° the solution was washed with water and 10% aqueous hydrochloric acid. The residue was distilled to give *n*-butylfluoriminonitrile: bp 46° (15 mm); ^{19}F nmr, single peak at φ −64.2.

Anal. Calcd for $C_6H_9N_2F$: C, 56.23; H, 7.08; N, 21.87. Found: C, 56.21; H, 7.29; N, 21.88.

Reaction of Phenylfluoriminonitrile (1a) and Potassium Cyanide in Methanol.—A mixture of 2.96 g of **1a**, 0.40 g of potassium cyanide, and 40 ml of methanol was heated at reflux for 2 hr. The mixture was poured into water and the organic products were extracted into methylene chloride. The residue obtained upon evaporation of the methylene chloride was chromatographed on silica gel. Elution of the column with pentane–methylene chloride elected 0.34 g of starting material and 0.20 g of benzonitrile. Methylene chloride eluted 2.06 g of the methyl imidate of phenylfluoriminonitrile (**2a**), a yellow oil.

Reaction of 4-chlorophenylfluoriminonitrile (1b) and Potassium Cyanide in Methanol.—A mixture of 3.62 g of **2a**, 0.40 g of potassium cyanide and 40 ml of methanol was refluxed for 2 hr. When the mixture was worked up as described for **1a** and the residue chromatographed on silica gel, 0.24 g of recovered **1b**, 0.59 g of 4-chlorobenzonitrile, and 2.08 g of the methyl imidate of 4-chlorophenylfluoriminonitrile (**2b**) was obtained.

Reaction of *n*-Butoxyfluoriminonitrile (1c) and Sodium Methoxide in Methanol. A. With Excess Sodium Methoxide.—To 0.72 g (5 mmol) of **1c** in 10 ml of methanol was added 4 ml of 1.38 *N* sodium methoxide in methanol. After 2 hr at ambient temperature, methylene chloride was added. The organic phase was washed with water. The ^{19}F nmr spectrum indicated fluorine resonance only at φ +89.6 and +90.0. Chromatography (vpc) on the SF-96 column (80°) indicated only two materials, not the starting **1c** isomers, to be present. A sample of these isomers of butyl methyl fluoriminocarbonate (**5**) was distilled, bp 60° (2 mm).

Anal. Calcd for $C_6H_{12}FNO_2$: C, 48.31; H, 8.11; N, 9.39; F, 12.74. Found: C, 48.28; H, 8.51; N, 10.51; F, 12.22.

The isomers were separated on the SF-96 column at 80°; the first material eluted was the minor isomer (ratio *ca.* 1:2). It had an nmr peak at φ +89.6 ^{19}F.

Anal. Found: C, 47.87; H, 8.16.

The second material eluted, the major isomer, had an ^{19}F nmr spectrum peak at +90.0.

Anal. Found: C, 48.21; H, 8.27.

B. With Catalytic Sodium Methoxide.—To 0.72 g (5 mmol) of **1c** in 3 ml of methanol at −15° was added 0.3 ml of 1.3 *N* sodium methoxide in methanol. After 1 hr at −10°, the reaction mixture was partitioned between methylene chloride and water. The methylene chloride solution contained, by integration of peak areas in the ^{19}F nmr spectrum, 7% **1c** (φ +8 and +23), 60% **2c** (φ +38 and +48), and 24% **5** (φ +89–90). The isomers of **2c**, reported in Table I, were separated on the SF-96 vpc column at 100°. The *syn* isomer (^{19}F nmr spectrum had φ +48) was eluted first; it predominated by a 3:2 ratio.

Reaction of 4-Chlorophenylfluoriminonitrile (1b) and Methanol with Sodium Methoxide.—A solution of 0.91 g of **1b** (5 mmol) in 2 ml of methanol was stirred at −10° while 0.20 ml of 1.3 *N* sodium methoxide in methanol was added. After 1 hr at −10°, the reaction mixture was partitioned between methylene chloride and water. The residue obtained from the organic layer was chromatographed on silica gel. Elution of the column with pentane–methylene chloride (1:1) gave 4-chlorobenzonitrile, 0.03 g, identified by infrared spectrum. Continued elution of the column with methylene chloride and ethyl acetate–methylene chloride (1:9) gave **2b**, 0.88 g (83%).

Hydrolysis of Butyl Methyl Fluoriminocarbonate (5).—A mixture of 0.25 g of **5**, 2 ml of methanol, 1 ml of water, and 0.2 ml of aqueous hydrochloric acid was stirred at 40° for 1 hr. The mixture was then partitioned between methylene chloride and water. The methylene chloride solution contained only butyl methyl carbonate by infrared and proton nmr spectra and by retention time on an SF-96 column at 80°. The authentic sample of butyl methyl carbonate was prepared from butanol and methyl chlorocarbonate.

Preparation of *n*-Butoxyfluorimino Esters (3c).—A 3-g portion of a mixture of **2c** and **5**, prepared by the catalyzed addition of methanol to **1c**, was stirred for 1 hr with 40 ml of methanol, 8 ml of water, and 0.25 ml of concentrated hydrochloric acid. The reaction mixture was partitioned beween methylene chloride and water. The methylene chloride extract, by vpc on a Carbowax 20M column at 105°, contained unhydrolyzed **5** and two new peaks, the isomers of *n*-butoxyfluorimino ester **3c**. Since **5** and the *syn* isomer of **3c** overlapped on this column, the reaction

(8) C. Grundmann and J. M. Dean, *J. Org. Chem.*, **30**, 2809 (1965).

(9) The predominant isomer here was presumably the *syn* isomer with a φ +35.6 ^{19}F nmr spectrum; proton absorption due to CH_2O– was at τ 5.62. The isomer with ^{19}F nmr peak at φ 24.4 had the methylene proton at τ 5.38.

mixture was chromatographed on silica gel. Elution of the column with pentane–methylene chloride (2:1) gave the *syn* isomer of **3c**; its purity was established by vpc. Elution of the column with pentane–methylene chloride (1:1) gave a mixture of **5** and *anti* **3c**. The pure sampe of *anti* **3c** (Table II) was trapped from the Carbowax vpc column.

Preparation of Methyl α-Fluoriminophenylacetate (3c).—A mixture of 1.61 g of the methyl imidate of α-fluoriminoacetonitrile, 20 ml of methanol, 4 ml of water, and 1 ml of concentrated hydrochloric acid was stirred at 40° for 1 hr. The mixture was diluted with water and the organic product then was extracted into methylene chloride. Chromatography of the residue over silica gel gave methyl α-fluoriminophenyl acetate (**3a**), 1.05 g, a clear liquid.

The ester **3a** was prepared directly from **1a** as follows. To 0.74 g (5 mmol) of phenylfluoriminonitrile (**1a**) in 5 ml of methanol at −10° was added 0.3 ml of 1.3 *N* sodium methoxide in methanol. The mixture was stirred at −10° for 30 min; then 2 ml of 6 *N* aqueous hydrochloric acid was added. The mixture was warmed to 40°, then set aside 1 hr; it was then partitioned between methylene chloride and water. The residue obtained upon evaporation of the methylene chloride was taken up in pentane and filtered to remove a solid (0.08 g). The solid, from chloroform–hexane, was α-fluoriminophenylacetamide: mp 116–118°; ^{19}F nmr, single peak at ϕ −23.2 in dimethylformamide solution.

Anal. Calcd for $C_8H_7FN_2O$: C, 57.8; H, 4.25; N, 16.9; F, 11.4. Found: C, 57.4; H, 4.31; N, 16.7; F, 11.4.

The filtrate from the pentane extracted yielded 0.54 g of methyl α-fluoriminophenylacetate (**3a**).

Preparation of Ethyl α-Fluoriminophenylacetate.—To 0.37 g of **1a** in 5 ml of absolute ethanol at −10° was added 2 drops of 4.3 *N* aqueous sodium hydroxide. After 1 hr at −10°, the aqueous hydrochloric acid (1.5 ml, 4 *N*) was added and the mixture was handled as described above. Work-up gave 0.03 g of α-fluoriminoacetamide and about 0.25 g of ethyl α-fluoriminophenylacetate, purified by chromatography on silica gel.

Preparation of Methyl α-Fluorimino-4-chlorophenylacetate (3b) and α-Fluorimino-4-chlorophenylacetamide.—To 0.91 g of 4-chlorophenylfluoriminonitrile (**1b**) in 5 ml of methanol at −10° was added 0.30 ml of 1.3 *N* sodium methoxide in methanol. The mixture was stirred at −10° for 30 min, then 2 ml of 6 *N* aqueous hydrochloric acid was added, and the mixture was warmed at 40° for 15 min. After cooling, the reaction mixture was partitioned between methylene chloride and water. The residue, 1.0 g, was recrystallized from chloroform–hexane, and gave α-fluorimino-4-chlorophenylacetamide, 0.10 g: mp 118–120; ^{19}F nmr, ϕ −24.4 in dimethylformamide solution.

Anal. Calcd for $C_8H_6ClFN_2O$: C, 47.9; H, 3.02; N, 13.96; F, 9.5. Found: C, 47.7; H, 3.15; N, 14.60; F, 10.1.

The filtrates were concentrated and crystallized from hexane to 0.82 g give methyl 4-chlorophenylacetate, mp 34–36°.

Preparation of Ethyl α-Fluorimino-4-chlorophenylacetate.—From 0.46 g of **1b** in 5 ml of ethanol, treated first with 2 drops of 4.3 *N* aqueous sodium hydroxide solution at −10°, followed by the usual acid hydrolysis, was obtained 0.03 g of α-fluorimino-4-chlorophenylacetamide, and 0.40 g of ethyl α-fluorimino-4-chlorophenylacetate, mp 35–37°.

Reaction of Methyl α-Fluoriminophenylacetate (3c) and Sodium Methoxide.—To 0.090 g of **3a** in 3 ml of methanol was added 0.60 ml of 1.30 *N* sodium methoxide in methanol. The mixture was heated at reflux for 1 hr, then cooled, and partitioned between methylene chloride and water. The methylene chloride solution was evaporated at reduced pressure; only benzonitrile (infrared spectrum and vpc) remained.

Beckmann Rearrangement of α-Fluorimino Esters.—The general procedure, used for the three esters cited below, is as follows. To 2.5 ml of sulfuric acid at 20° was added 0.40 g of the fluorimino ester. After 15 min at ambient temperature, the mixture was poured over ice, and the organic product was extracted into methylene chloride. The residue obtained upon evaporation of the methylene chloride was recrystallized from hexane–chloroform.

In this way methyl α-fluoriminophenyl acetate gave methyl oxanilide, mp 111–112.5° (lit.[10] mp 111°), the corresponding ethyl ester gave ethyl oxanilide, mp 64–65.5° (lit.[11] mp 66–67°), and ethyl α-fluorimino-4-chlorophenylacetate gave ethyl 4-chlorooxanilide, mp 159–160° (lit.[12] mp 155°). All three oxanilides gave acceptable elemental analyses.

Reaction of 4-Chlorophenylfluoriminonitrile (1b) and the Phenyl Grignard Reagent.—The procedure used to obtain the results reported in Table III are illustrated by the following. To a solution of 1.82 g (10 mmol) of **1b** in 20 ml of tetrahydrofuran at ice bath temperature was added 7.0 ml of 3M Arapahoe phenyl magnesium bromide. The mixture was allowed to warm to 25° over 1 hr, then stirred at 35° for another hour. The mixture was poured over ice–hydrochloric acid, and the organic product was extracted into methylene chloride. A small amount of benzonitrile was detected in the residue obtained upon evaporation of the methylene chloride; on an SF-96 column at 140°, a small peak (10% of the peak area of 4-chlorobenzonitrile–**1b** combined peak) due to benzonitrile was observed. Chromatography on silica gel gave, following the biphenyl fraction, 0.42 g of a mixture of 4-chlorobenzonitrile and **1b**, and then N-phenylimino-4-chlorophenylacetonitrile, 0.43 g, a bright yellow solid, mp 103–105°; further characterization is reported in Table III.

Reaction of Phenylfluoriminonitrile (1a) and 2,4,6-Trimethylbenzonitrile Oxide (7).—A mixture of 2.40 g of **7** and 2.25 g of **1a** in 50 ml of ether was allowed to stand for 3 days. At the end of this time, only a very weak ϕ −53 peak due to **1a** could be detected in the ^{19}F nmr spectrum; the major ^{19}F resonance was at ϕ −42.6. The ether was removed at reduced pressure, and the solid residue was recrystallized from hexane to give 3-mesityl-5-(α-fluoriminotolyl)-1,2,4-oxadiazole, mp 52–53°.

Registry No.—**1c** (*syn*), 16717-37-6; **1c** (*anti*), 16717-38-7; **2a**, 16753-57-4; **2b**, 16753-58-5; **2c** (*syn*), 16753-59-6; **2c** (*anti*), 16753-60-9; **3a**, 16717-39-8; **3b**, 16717-40-1; **3c** (*syn*), 16717-41-2; **3c** (*anti*), 16717-42-3; **3** (R = C_6H_5, R′ = C_2H_5), 16717-43-4; **3** (R = 4-ClC_6H_4, R′ = C_2H_5), 16717-44-5; **5** (*syn*), 16717-45-6; **5** (*anti*), 16717-46-7; **8** (R = C_6H_5), 16717-47-8; **8** (R = 4-ClC_6H_4), 16753-61-0; **8** (R = *n*-C_4H_9O, *syn*), 16717-48-9; **8** (R = *n*-C_4H_9O, *anti*), 16717-49-0; **8** (R = *n*-C_4H_9), 16749-02-3; α-fluoriminophenylacetamide, 16717-50-3; α-fluorimino-4-chlorophenylacetamide, 16717-51-4; *n*-butylfluoriminonitrile, 16717-52-5.

(10) G. D. Landers, *J. Chem. Soc.*, **85**, 984 (1904).
(11) H. Klinger, *Ann.*, **184**, 261 (1877).
(12) F. D. Chattaway and W. H. Lewis, *J. Chem. Soc.*, **89**, 155 (1906).

Rearrangements of Organic Fluoramines. Aromatic Nucleophilic Rearrangements in Fluorosulfonic Acid

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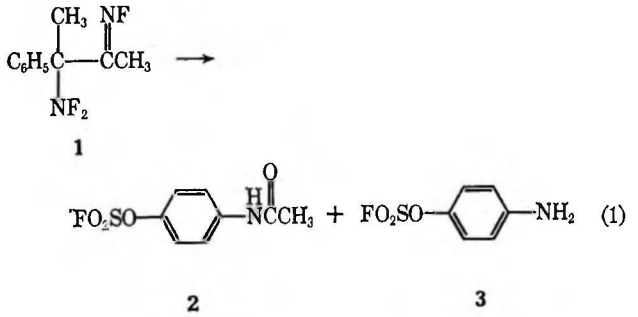
Received February 26, 1968

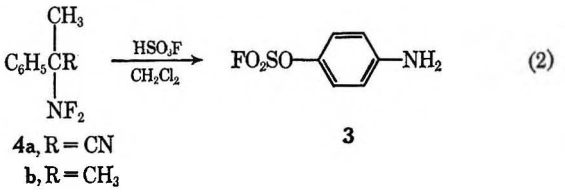
The rearrangement of the α-(difluoramino)toluene derivatives **1**, **4a**, and **4b** in fluorosulfonic acid produces 4-(fluorosulfato)anilines. This rearrangement probably proceeds by way of an N-phenyl-N-fluorimmonium salt, and is similar to the acid-promoted rearrangements of other oxidized nitrogen compounds, such as aromatic hydroxylamines, nitrones, azoxybenzenes, and aniline N-oxides.

During a study of acid-catalyzed reactions of α-difluoramino fluorimines, certain reactions conducted in fluorosulfonic acid led to products reminiscent of rearrangements of oxidized nitrogen compounds. Specifically, it was observed that fluorimine **1**, under conditions intended to lead to Beckmann rearrangement or fragmentation,[1] was converted into 4-(fluorosulfato)acetanilide (**2**), mp 146–148° (up to 44% yield),[2] along with lesser amounts of 4-(fluorosulfato)aniline (**3**), 4-aminophenol, and acetophenone (eq 1). α-(Difluoramino)toluenes **4a** and **b** were converted into 4-(fluorosulfato)aniline (**3**) under the same reaction conditions (eq 2). This paper reports a study of these reactions and of other apparently analogous rearrangements.



1

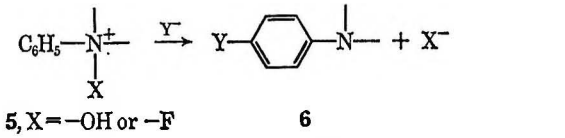
2 **3** (1)



4a, R = CN
b, R = CH_3

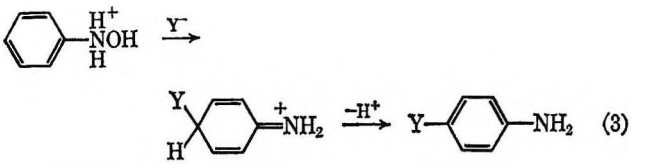
3 (2)

The incorporation of a nucleophile into the *para* position of an aromatic ring attached to an oxidized nitrogen atom is, of course, characteristic of aromatic rearrangements and substitutions called "aromatic nucleophilic rearrangements."[3] It does not appear to be generally recognized, however, that nucleophilic substitution may take place whenever an aromatic ring is attached to a tetravalent, positively charged nitrogen atom bearing a leaving group (**5** → **6**). Thus, the examples that at least formally[4] appear to fall in this category include the aromatic hydroxylamine–aminophenol case cited,[2] the Wallach rearrangement,[5–8] the acid-promoted cleavage of aromatic nitrones to *para*-substituted phenols,[9] the rearrangement of N,N-dimethylaniline oxide to *p*-dimethylaminophenol,[10] and the organodifluoramine rearrangements reported here.

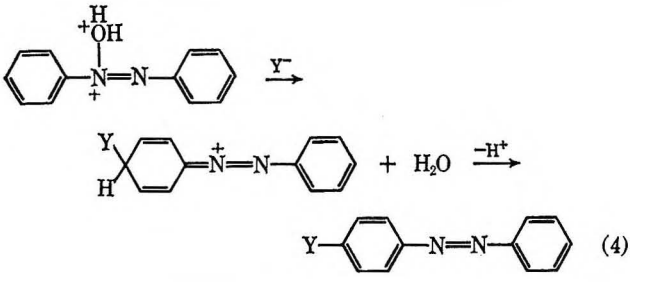


5, X = −OH or −F **6**

In the context of structure **5**, the hydroxylamine rearrangement can be formulated as shown[3] in eq 3 and the Wallach rearrangement[4,7] as shown in eq 4. The possibility of S_N2' mechanism for the hydroxylamine reaction[2] and the kinetic evidence for the intermediacy of a dicarbonium ion in the Wallach rearrangement[4,6] must be noted.



(3)



(4)

Now, if the first step in the conversion of difluoramine **1** into fluorosulfate **2** (Scheme I) is the migration of the phenyl group to nitrogen to produce N-phenyl-N-fluorimmonium salt **7**,[11] this reaction falls into the aromatic

(1) T. E. Stevens, *Tetrahedron Lett.*, 3017 (1967).

(2) A preliminary account of this work has appeared: T. E. Stevens, *Chem. Commun.*, 1181 (1967).

(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1950, pp 621–624.

(4) The formal comparisons should be emphasized here; the timing and details of the processes involved may be very different; and, in the Wallach rearrangement, nucleophilic attack may occur in the ring attached to oxidized nitrogen or in the far ring (as often postulated). For pertinent comments, see P. H. Gore, *Chem. Ind.* (London), 191 (1959).

(5) (a) E. C. Buncel and B. T. Lawton, *Can. J. Chem.*, **43**, 862 (1965); (b) M. M. Shemyakin, V. I. Maimind, and T. E. Agadzhanyan, *Chem. Ind.* (London), 1223 (1961).

(6) C. S. Hahn and H. H. Jaffé, *J. Amer. Chem. Soc.*, **84**, 946 (1962); C. S. Hahn, K. W. Lee, and H. H. Jaffé, *ibid.*, **89**, 4975 (1967).

(7) S. Oae, T. Fukumoto, and M. Yamagami, *Bull. Chem. Soc. Jap.*, **36**, 601 (1963).

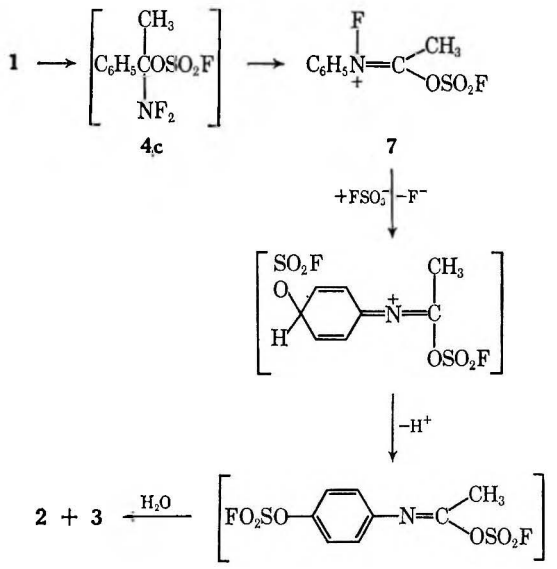
(8) For a recent review, see P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 313–315.

(9) E. Bamberger, *Ber.*, **27**, 1556 (1894).

(10) E. Bamberger and P. Seyden, *ibid.*, **34**, 12 (1901); A. F. Douglas, P. H. Gore, and J. W. Hooper [*J. Chem. Soc., Sect. C*, 674 (1967)] report related reactions.

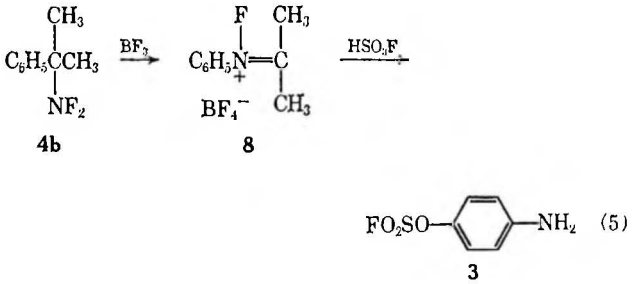
(11) Beckmann fragmentation of the fluorimine probably occurs first,[1] and fluorosulfonic acid may then trap the α-difluoramino carbonium ion to give **4c**. In certain cases, such fluorosulfates have been isolated (unpublished studies). The formation of structures such as **4c** and **7** explains the formation of the acetanilide **2** along with free amine **3**. Also, acetophenone, from hydrolysis of **4c** or the carbonium ion, was the major by-product here.

SCHEME I



nucleophilic substitution class also. In view of the tendency of organic compounds to rearrange with loss of fluoride ion from nitrogen,[12] such a process appears likely.

Strong support for the reaction scheme outlined was obtained from experiments with the organic difluoramine **4b**. This difluoramine, prepared by the acid-catalyzed addition of difluoramine to α-methylstyrene,[13] was converted into N-phenyl-N-fluoroisopropylidenimmonium fluoroborate (**8**) by boron trifluoride in pentane or methylene chloride solution (eq 5). The salt **8** was characterized only by its nmr spec-



(5)

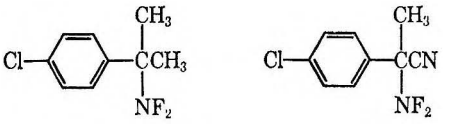
tra; its ^{19}F spectrum exhibited peaks at ϕ −90.7 (NF) and at +150.4 (BF_4^-), and the proton spectrum had nonequivalent methyl groups at δ 2.92 and 2.61 (doublets, J_{HF} = 5 and 3 Hz, respectively). When fluorosulfonic acid was added to **8** in methylene chloride solution, aniline **3** (68%) could be isolated after hydrolysis.

Aniline **3** (21% yield) also was prepared directly from α-methylstyrene, difluoramine, and fluorosulfonic acid. Under these conditions, ionic addition of difluoramine to the olefin should be followed by rearrangement and then nucleophilic substitution.

It was not possible to prepare an N-fluorimmonium salt from **4a** and boron trifluoride; the nitrile function apparently complexed the BF_3. However, with an excess of boron trifluoride and an extended reaction time, 4-fluoroaniline (22%) formed from **4a**. And, fluorosulfonic acid converted **4a** into **3** (45% yield) readily.

(12) K. Baum and H. M. Nelson, *J. Amer. Chem. Soc.*, **88**, 4457 (1966).
(13) W. H. Graham and J. P. Freeman, *ibid.*, **89**, 716 (1967).

No definitive products could be obtained from related difluoramines (**9** and **10**) in which the 4 position was

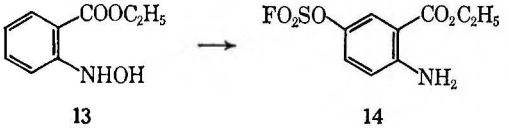


blocked. Although **9** rearranged readily in the presence of boron trifluoride to give N-(4-chlorophenyl)-N-fluoroisopropylidenimmonium fluoroborate,[14] only intractable products resulted from treatment of this salt with fluorosulfonic acid. Excess boron trifluoride and **10** also gave dark, intractable materials.

Although there appears to be little doubt that the rearrangements reported here proceed by mechanisms analogous to those discussed above, a detailed description of the process leading from N-fluorimmonium salt to the 4-fluorosulfato aniline cannot be made on the basis of the information at hand. Suffice it to say that it probably involves intermediates between the extremes of dication **11** and an SN2′ process sketched as **12**.



It was also of interest to observe the rearrangements of some of the oxidized nitrogen compounds in the presence of fluorosulfonic acid.[15] Aromatic hydroxylamines with the *para* position open were readily converted into 4-(fluorosulfato)anilines by fluorosulfonic acid at ice-bath temperatures. Aniline **3** was obtained in 54% yield from N-phenylhydroxylamine; acetylation of **3** produced in this way gave samples of **2** identical with those isolated from fluorimine **1**; and N-(3-chlorophenyl)hydroxylamine gave 3-chloro-4-(fluorosulfato)aniline in 56% yield.[16] Hydroxylamine **13** gave the ester **14** (53%).[16]



(6)

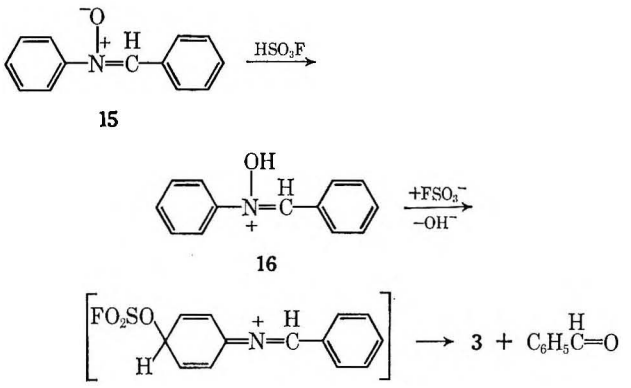
p-Tolylhydroxylamine was reduced to *p*-toluidine (42%) by fluorosulfonic acid. The fate of the oxygen atom, or the nature of the oxidizing species resulting from the reduction, is unknown. No oxygen was produced in the experiments, no active oxygen material could be detected in the reaction mixtures, and azobenzene introduced into the reaction mixture was not oxidized.[15] Of course, either starting material or *p*-toluidine could have been oxidized during the course of the reaction.

As expected,[9] the nitrone N-phenylbenzaldoxime (**15**) gave benzaldehyde (52%) and aniline **3** (38%) when exposed to fluorosulfonic acid; however, steam-bath

(14) Characterized by ^{19}F nmr spectrum peaks at ϕ −91.5 (NF) and +150.9 (BF_4^-), and proton nmr spectrum methyl peaks at δ 2.88 (doublet, J_{HF} = 5 Hz) and 2.67 (doublet, J_{HF} = 3 Hz).
(15) The Wallach rearrangement in fluorosulfonic acid and in fluorosulfonic acid–difluoramine is discussed in another paper: T. E. Stevens, *J. Org. Chem.*, **33**, 2667 (1968).
(16) In these experiments no attempt was made to isolate any phenolic amine produced by hydrolysis of the fluorosulfate.

temperatures were required for this transformation. The probable course of this reaction is outlined in Scheme II. Again, either a dication from ionization of **16** or an S_N2' process involving **16** can be visualized.

SCHEME II



Certain spectral properties of the aromatic fluorosulfates prepared here allow them to be recognized easily. The ^{19}F nmr spectra of the fluorosulfates exhibit a peak in the ϕ −40 to −35 region, somewhat higher field than aliphatic perfluorofluorosulfates.[17] Specific values for the fluorosulfates prepared here are reported in the Experimental Section. The most characteristic peak in the infrared spectra of the fluorosulfates was the symmetric S=O stretch at 8.1 μ.[17] The asymmetric S=O stretching band at 6.70–6.75 μ[17] was also observed. Strong infrared absorption (unassigned) was also noted in the 10.8–11.2-μ region.

Finally, attempts to prepare aromatic difluoramines[18] by using difluoramine as the nucleophile in these rearrangements were completely unsuccessful. There was no sign of aromatic NF materials when salt **8** was exposed to difluoramine in the presence of BF_3 or HSO_3F; the same was true when N-phenylhydroxylamine, HNF_2, and HSO_3F were allowed to interact. Some 4-(fluorosulfato)aniline, or 4-fluoroaniline when BF_3 was used, could be obtained along with intractable material. It is possible that the 4-(difluoramino)anilines, if they form at all, are unstable to the reaction conditions.[18]

Experimental Section

The ^{19}F nmr spectra (40 MHz) were run in CCl_4 or $CDCl_3$ solutions; ϕ values are measured in parts per million (ppm) from internal CCl_3F. Melting points are uncorrected. Proton nmr spectra were run on a Varian A-60 spectrometer. Fluorosulfonic acid was Baker and Adamson technical grade. Methylene chloride was dried by passage through a silica gel column. Chromatogaphy on Brinkmann or G. F. Smith silica gel was conducted by packing the column in pentane; elution with pentane containing increasing amounts of methylene chloride followed. Finally, methylene chloride–ethyl acetate (9:1) and methylene chloride–methanol (9:1) completed the elution.

Previous warnings[13,19] concerning the explosive nature of difluoramine and of organic difluoramino compounds must be heeded.

2-Difluoramino-2-phenyl-3-fluoriminobutane (**1**), a colorless liquid, was prepared by dehydrofluorination of the α,β-dimethylstyrene–tetrafluorohydrazine adduct with sodium methoxide in methanol,[19] bp 64° (0.3 mm). Purification was best effected by passage through a silica gel column. Elution with pentane–methylene chloride (10:1) gave pure **1**: ^{19}F nmr, $-NF_2$, AB quartet; F_A, ϕ −30.0; F_B, −25.0 (J_{FF}, 582 Hz); C=NF, single peak at −28.6.

Anal. Calcd for $C_{10}H_{11}F_3N_2$: C, 55.55; H, 5.13; N, 12.96. Found: C, 55.35; H, 5.27; N, 13.45.

2-Difluoramino-2-phenylpropane (**4b**) was prepared by the addition of difluoramine to α-methylstyrene.[13] From 0.47 g of α-methylstyrene, 110 cc (STP) of difluoramine, 2 ml of methylene chloride, and 0.1 g of Amberlyst 15, stirred 4 hr at ambient temperature and pressure, was obtained 0.36 g of **4b**, isolated by distillation *in vacuo* into a −10° trap. The ^{19}F nmr spectrum exhibited a single peak at ϕ −29.2.

Anal. Calcd for $C_9H_{11}F_2N$: C, 63.1; H, 6.48; N, 8.18. Found: C, 62.7; H, 6.61; N, 7.94.

2-Difluoramino-2-(4-chlorophenyl)propane (**9**) was prepared in the same way; 0.62 g of 4-chloro-α-methylstyrene gave 0.48 g of **9**.

Anal. Calcd for $C_9H_{10}ClF_2N$: C, 52.6; H, 4.90; N, 6.81; F, 18.5. Found: C, 53.0; H, 5.39; N, 6.59; F, 18.7.

Fluoramines **4a** and **10** were prepared as reported.[19]

Reaction of Fluorosulfonic Acid and 2-Difluoramino-2-phenyl-3-fluoriminobutane (**1**).—To a mixture of 4 ml of methylene chloride and 4 ml of fluorosulfonic acid cooled to 0° was added 0.86 g (4 mmol) of **1** in 2 ml of methylene chloride. The mixture was stirred at 0° for 1 hr and at ambient temperature for 3 hr. The mixture was poured into ice water and the organic product was extracted into methylene chloride. The residue obtained upon evaporation of the methylene chloride was pumped *in vacuo;* a −10° trap collected 0.05 g (10%) of acetophenone, identified by infrared and nmr spectra. The solid residue, mp 132–137°, 0.24 g (27%), was crude 4-(fluorosulfato)acetanilide. After further recrystallization from chloroform–hexane, **2** had mp 146–148°. The ^{19}F nmr of **2** had a peak at ϕ −36.9; the proton nmr had peaks at τ 7.83 (CH_3–CO) and 2.2–2.8 (aromatic protons).

Anal. Calcd for $C_8H_8NFO_4S$: C, 41.20; H, 3.46; N, 6.01. Found: C, 41.35; H, 3.84; N, 6.06.

To 0.15 g of **2** in 10 ml of 90% methanol was added 2 ml of 1.3 *N* sodium methoxide in methanol. The mixture was refluxed for 30 min, cooled, acidified, and stripped to dryness. To the residue was added 10 ml of acetic anhydride and 1 drop of concentrated sulfuric acid. After stirring overnight, the mixture was poured into water and stirred 2 hr. The organic product, isolated by extraction into methylene chloride, melted at 147–148° after recrystallization from chloroform–pentane; 4-acetoxyacetanilide has reported mp 152°.[20] The 4-acetoxyacetanilide prepared from **2** was identical, by infrared and proton nmr spectra and mixture melting point (146–147°), with a sample prepared (mp 146–147°) by acetylation of 4-hydroxyacetanilide (Eastman).

The acid aqueous phase was basified and again extracted with methylene chloride. Evaporation of the methylene chloride gave 0.19 g (25%) of 4-(fluorosulfato)aniline (**3**), mp 41–42.5° (chloroform–hexane). The ^{19}F nmr spectrum had a peak at ϕ −35.5.

Anal. Calcd for $C_6H_6FNO_3S$: C, 37.7; H, 3.16; N, 7.33; F, 9.94. Found: C, 37.5; H, 3.04; N, 7.24; F, 10.2.

The aqueous layer was made acidic stripped to dryness, and treated with acetic anhydride (10 ml) as described above. After work-up of the reaction mixture, 0.16 g (21%) of 4-acetoxyacetanilide was obtained from the soluble 4-aminophenol.

Up to 44% of **2** was obtained in other runs, along with lesser quantities of **3**.

Reaction of 2-Difluoramino-2-phenylpropanenitrile (**4a**) **and Fluorosulfonic Acid.**—To 5 ml of fluorosulfonic acid cooled in an ice bath was added 0.90 g (5 mmol) of **4a** in 5 ml of methylene chloride. The mixtue was stirred at 30° for 4 hr, then poured on ice–dilute aqueous hydrochloric acid. Extraction with methylene chloride gave less than 0.2 g of material; this was discarded. The aqueous layer was made basic and again extracted with methylene chloride. This yielded 0.43 g of 4-(fluorosulfato)-aniline (**3**), mp 41–42.5°.

Reaction of N-Phenyl-N-fluoroisopropylidenimmonium Fluoroborate (**8**) **and Fluorosulfonic Acid.**—A mixture of 0.17 g (1 mmol) of 2-difluoramino-2-phenylpropane (**4b**), 25 cc (STP) of boron trifluoride, and 5 ml of methylene chloride in the pressure tube[21]

(17) M. Lustig and J. K. Ruff, *Inorg. Chem.*, **3**, 287 (1964); M. Lustig, *ibid.*, **4**, 1828 (1965).

(18) C. L. Coon, M. E. Hill, and D. L. Ross, Abstracts, 154th National Meeting of the American Chemistry Society, Chicago, Ill., Sept 1967, p S123.

(19) R. C. Petry and J. P. Freeman, *J. Org. Chem.*, **32**, 4034 (1967).

(20) L. Galatis, *Ber.*, **59**, 846 (1926).

(21) Described by R. P. Rhodes, *J. Chem. Educ.*, **40**, 423 (1963).

was stirred at ice-bath temperature for 1 hr, warmed briefly to 20°, and cooled to 0°, and excess boron trifluoride was vented (the ^{19}F and proton nmr spectra of **8** prepared in this way, or in pentane solution, had the properties described in the discussion section). To the stirred mixture at 0° was added 0.5 ml of fluorosulfonic acid. The contents of the tube were stirred for 1 hr at 0°, and then poured over ice–dilute aqueous hydrochloric acid. A methylene chloride extract was discarded; the aqueous layer was basified and again extracted. From this methylene chloride extract was obtained 0.13 g (68%) of **3**, mp 40–41°.

Reaction of α-Methylstyrene, Difluoramine, and Fluorosulfonic Acid.—A mixture of α-methylstyrene (0.39 ml, 3 mmol), 70 cc (STP) of difluoramine, 1 ml of fluorosulfonic acid, and 5 ml of methylene chloride was stirred 90 min at 0° in a 25-ml pressure tube.[21] The tube was vented *in vacuo*, and the residue was worked up as usual. Extraction of the basified aqueous layer gave **3**: yield, 0.12 g (21%); mp 38.5–40.5°.

Reaction of 2-Difluoramino-2-phenylpropanenitrile (4a) and Boron Trifluoride.—A mixture of 0.55 g of **4a** (3 mmol), 70 cc (STP) of boron trifluoride, and 5 ml of methylene chloride was stirred 5 hr at ambient temperature in a pressure tube. The tube was the vented and the reaction mixture poured on ice–hydrochloric acid. The extract from the basified aqueous layer was chromatographed on silica gel and gave 4-fluoroaniline 0.074 g (22%), identified by comparison of its infrared spectrum, and its ^{19}F and proton nmr spectra with those of a authentic sample. The ^{19}F nmr peak of 4-fluoroaniline was observed at ϕ +126.1.

Reaction of N-Phenylhydroxylamine and Fluorosulfonic Acid.—To 3 ml of fluorosulfonic acid stirred at ice bath temperature was added 1 g of N-phenylhydroxylamine in 4 ml of methylene chloride. After 2 hr at ice bath temperature, the mixture was poured on ice. Only a trace of material could be extracted from the acidic aqueous layer; on the basic side, 0.95 g (54%) of **3** was extracted. A 0.65-g portion of **3** prepared in this way was acetylated with 10 ml of acetic anhydride and 1 drop of concentrated sulfuric acid. After hydrolysis of excess acetic anhydride, 0.60 g of **2**, mp 145–147°, infrared and nmr spectra identical with that of **2** prepared from **1**, was obtained.

The aqueous phase from the fluorosulfonic acid reaction was acidified, stripped to dryness, and acetylated with acetic anhydride. In this way, 0.13 g of 4-acetoxyacetanilide (7%) was obtained.

Reaction of N-(3-Chlorophenyl)hydroxylamine and Fluorosulfonic Acid.—The procedure used with N-phenylhydroxylamine was followed. From 2 g of the hydroxylamine was obtained 1.76 g of 3-chloro-4-(fluorosulfato)aniline, a clear liquid that darkened on standing. The ^{19}F nmr spectrum peak was at ϕ −39.3. A sample chromatographed on silica gel gave the following analysis.

Anal. Calcd for $C_6H_5ClFNO_3S$: C, 31.94; H, 2.23; N, 6.21. Found: C, 32.59; H, 2.20; N, 6.22.

The *p*-toluenesulfonyl derivative of 3-chloro-4-(fluorosulfato)-aniline had mp 121–123°. The ^{19}F nmr spectrum had a peak at ϕ −41.1.

Anal. Calcd for $C_{13}H_{11}ClFNO_5S_2$: C, 41.1; H, 2.92; N, 3.69. Found: C, 41.5; H, 3.34; N, 3.64.

Reaction of Fluorosulfonic Acid and Ethyl 2-(Hydroxylamino)-benzoate (13).—The reaction was carried out at ice-bath temperature using 1.71 g (10 mmol) of **13**, 3 ml of fluorosulfonic acid, and 5 ml of methylene chloride. After the usual hydrolysis, a total of 1.4 g of ethyl 2-amino-4-(fluorosulfato)benzoate (**14**), a liquid, was recovered from both the acidic aqueous phase (1.1 g) and the basic aqueous phase (0.3 g). A satisfactory elemental analysis on **14** could not be obtained. The ^{19}F nmr spectrum had a peak at ϕ −35.6. The *p*-toluenesulfonyl derivative of **14** melted at 105–107°.

Anal. Calcd for $C_{16}H_{16}FNO_7S_2$: C, 46.04; H, 3.86; N, 3.35. Found: C, 46.05; H, 3.91; N, 3.43.

Reaction of N-Phenylbenzaldoxime (15) and Fluorosulfonic Acid.—A mixture of 0.78 g (3.96 mmol) of **15** and 3 ml of fluorosulfonic acid was heated on the steam bath for 30 min. The mixture was cooled, hydrolyzed, and extracted as usual. From the aqueous acid layer came 0.37 g of a mixture of benzaldehyde (0.22 g, 52%) and **3**, 0.15 g (by infrared and proton nmr spectra). The basic layer gave an additional 0.14 g of **3**, mp 39–40°.

Registry No.—Fluorosulfonic acid, 7789-21-1; **1**, 16704-36-2; **2**, 16704-37-3; **3**, 16704-38-4; **4b**, 16704-39-5; **9**, 16704-40-8; 3-chloro-4-(fluorosulfato)aniline, 16704-41-9; *p*-toluenesulfonyl derivative of 3-chloro-4-(fluorosulfato)aniline, 16704-42-0; *p*-toluenesulfonyl derivative of **14**, 16704-43-1.

Acknowledgment.—This research was carried out under the sponsorship of the U. S. Army Missile Command Redstone Arsenal, Ala., under Contract DAAH01-67-C-0655.

Reaction of Azoxy Compounds with Fluorosulfonic Acid and Fluorosulfonic Acid–Difluoramine[1]

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Received February 26, 1968

Azoxybenzenes unsubstituted in the 4 or 4′ position are converted into 4-fluorosulfatoazobenzenes by the Wallach transformation in fluorosulfonic acid. With added difluoramine, azoxybenzenes with both 4 positions open produce 4,4′-diaminoazobenzenes. Evidence for intermolecular transfer of oxygen between azoxybenzenes is reported. Some rearrangements apparently related to the Wallach rearrangement are discussed.

Our interest in the Wallach rearrangement, the conversion of azoxybenzene and its derivatives into 4-substituted azobenzenes, in the presence of fluorosulfonic acid was prompted by our interest in related aromatic nucleophilic substitutions in this medium,[2] and by the possibility that difluoramine (HNF_2), a reagent known to be alkylated by carbonium ions in acid solutions,[3] might be incorporated into the Wallach product and lead to a difluoraminoazobenzene. It should be noted that attempts to utilize difluoramine in the same manner in the apparently related rearrangements of N-phenyl-N-fluoroimmonium salts and of N-phenylhydroxylamine failed.[2]

Among the studies of the Wallach rearrangement[4] in strong acids is the report that azoxybenzene and azoxybenzenes with an open 4 or 4′ position are converted into 4-chlorosulfatoazobenzenes by chlorosulfonic acid.[5] Kinetic studies which support a dication inter-

(1) This research was carried out under the sponsorship of the U. S. Army Missile Command, Redstone Arsenal, Ala., under Contract DA-01-021 AMC-11536(Z).

(2) T. E. Stevens, *J. Org. Chem.*, **33**, 2664 (1968); T. E. Stevens, *Chem. Commun.*, 1181 (1967).

(3) W. H. Graham and J. P. Freeman, *J. Amer. Chem. Soc.*, **89**, 716 (1967).

(4) For a recent review, see P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 313–315.

(5) V. O. Lukashevich and T. N. Sokolova, *Compt. Rend. Acad. Sci. URSS*, **54**, 693 (1946); *Chem. Abstr.*, **41**, 5472 (1947).

SCHEME I

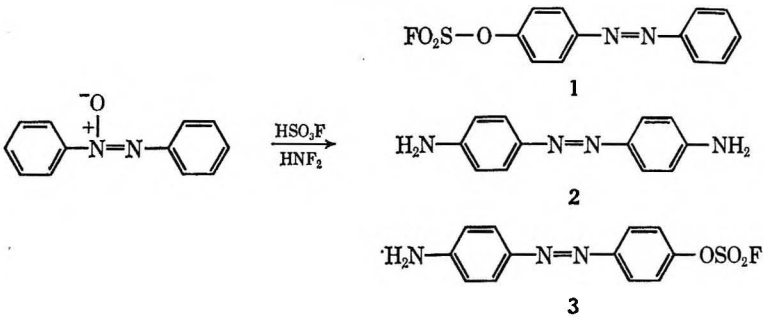
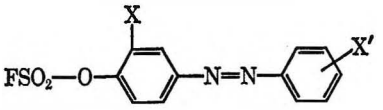


TABLE I

4-FLUOROSULFATOAZOBENZENES



X	X′	Mp, °C	Yield, %	Anal, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	^{19}F nmr, ϕ^a
H	H	98–100	71	51.42	3.24	10.00	51.21	3.32	9.99	−37.4
H	4-Cl[b]	99–101	80	45.79	2.56	8.90	45.50	2.60	8.80	−37.4
H	4-Br[c]	88–90	61	40.12	2.24	7.80	40.12	1.80	7.48	−37.5
Cl	3-Cl[d]	77–79	48	41.28	2.02	8.20	41.48	2.35	8.22	−41.0
H	4-CH_3[e]	79–81	10	53.05	3.77	9.52	53.40	3.82	9.70	−37.5

[a] ϕ values in parts per million (ppm) from internal CCl_3F in dilute $CDCl_3$ solution. [b] Registry no.: 16704-28-2; [c] 16704-29-3; [d] 16704-30-6; [e] 16704-31-7.

mediate[6] and labeling investigations[7] have also been published recently.[8]

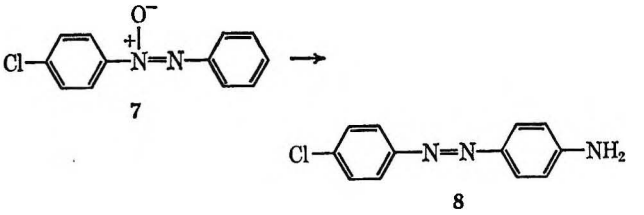
It was, therefore, not surprising to find that azoxybenzene was converted cleanly into 4-(fluorosulfato)-azobenzene by fluorosulfonic acid in methylene chloride under mild (0–25°) reaction conditions. Both 4- and 4′-chloroazoxybenzene gave the same product, 4-chloro-4′-(fluorosulfato)azobenzene, upon exposure to fluorosulfonic acid. The fluorosulfates prepared are listed in Table I; only with azoxybenzene was an attempt made to optimize the yield of fluorosulfate.

Three minor products accompanied the 4-(fluorosulfato)azobenzene produced from azoxybenzene; these were azobenzene (3%), a material (3%), mp 102–104°, that appeared to be 4-fluorosulfato-4′-hydroxyazobenzene, and a small amount of 4-hydroxyazobenzene. Formation of these materials will be discussed later. Both 4- and 4′-methylazoxybenzenes and fluorosulfonic acid gave considerable intractable material and only a low yield of fluorosulfate (Table I). On the basis of the normal position of the ^{19}F nmr peak and the indication of the only *para* substitution in the infrared spectrum, this product is assigned the 4-fluorosulfato-4′-methylazobenzene structure despite claims[6b] (disputed, however[8b]) that sulfuric acid and the 4-methylazoxybenzenes give 2′-hydroxy-4-methylazobenzene.

It was somewhat surprising to find that the products of the reaction of azoxybenzene, fluorosulfonic acid, and difluoramine (Scheme I) included, in addition to the usual Wallach fluorosulfate **1**, two 4,4′-disubstituted azobenzenes. These were 4,4′-diaminoazobenzene (**2**) and 4-amino-4′-(fluorosulfato)azobenzene (**3**). Under the experimental conditions outlined in the Experimental Section, yields of **1** ranged from 17 to 37%, yields of **2** ranged from 16 to 45%, and **3** was formed in yields of 5–20%. Excess difluoramine was present in these reactions, and a considerable portion of it was oxidized to tetrafluorohydrazine (N_2F_4) during the reaction. Thus, it appears likely that reduction of a fluoramino intermediate leads to the aminoazobenzenes.

With 3,3′-dichloroazoxybenzene, very analogous results were obtained (Scheme II). Fluorosulfate **4** (27–48.5%), the diaminoazo compound **5** (22–40%), and aminoazo fluorosulfate **6** (13–19%) could be isolated here.[9]

Small amounts of 4-amino-4′-chloroazobenzene (**8**) (10–18%) could be obtained from either 4- or 4′-chloroazobenzene (**7**), fluorosulfonic acid, and difluoramine. The formation of some fluorosulfate, as well as some reduction of **7** to 4-chloroazobenzene, also occurred in this reaction.



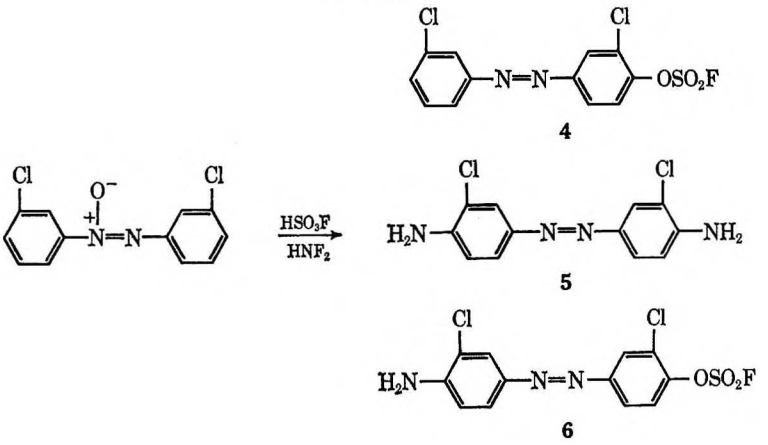
(6) (a) E. C. Buncel and B. T. Lawton, *Can. J. Chem.*, **43**, 862 (1965); (b) C. S. Hahn, K. W. Lee, and H. H. Jaffe, *J. Amer. Chem. Soc.*, **89**, 4975 (1967).

(7) (a) L. C. Behr and E. C. Hendley, *J. Org. Chem.*, **31**, 2715 (1966); (b) M. M. Shemyakin, V. I. Maimind, and T. E. Agadzhanyan, *Chem. Ind.* (London), 1223 (1961).

(8) For other pertinent discussions, see (a) P. H. Gore, *ibid.*, 191 (1959); (b) S. Oae, T. Fukumoto, and M. Yamagami, *Bull. Chem. Soc., Jap.*, **36**, 601 (1963).

(9) A small amount of amination of toluene, biphenyl, and *m*-xylene by HNF_2–BF_3–CH_2Cl_2 mixtures was observed. The nature of the amines produced, however, could not be determined easily; the products were complex mixtures and did not correspond to those produced in aminations with trichloroamine–aluminum chloride. See P. Kovacic and coworkers, *J. Org. Chem.*, **32**, 585 (1967), and earlier papers.

SCHEME II

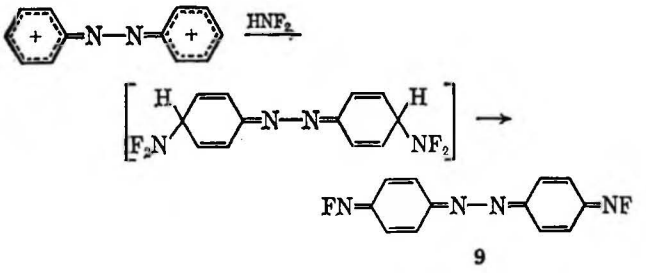


Both 4,4′-dichloro- and 4,4′-dibromoazoxybenzenes were reduced to the corresponding 4,4′-dihaloazobenzene by fluorosulfonic acid. Similar reductions were observed earlier with sulfuric acid[10] and chlorosulfonic acid.[5]

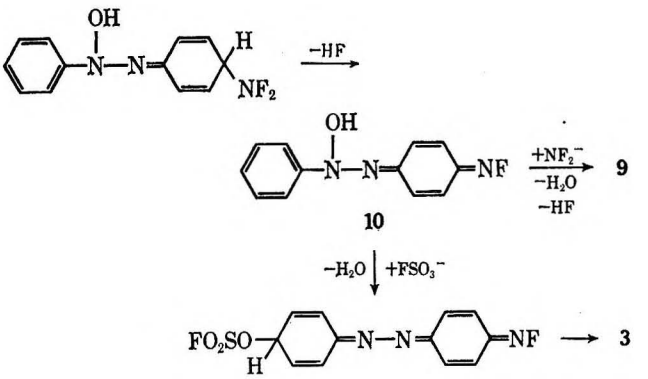
Since neither fluorosulfate **1** nor 4-aminoazobenzene is aminated by difluoramine–fluorosulfonic acid mixtures,[11] the unusual disubstitution products found here do not appear to arise by such an amination process.

It also is unlikely that the azoxybenzene present in the reaction mixture oxidizes fluorosulfate **1** or 4-aminoazobenzene (intermolecular exchange of oxygen can apparently occur between azoxy- and azobenzenes as discussed below) to a 4-substituted azoxybenzene, which then undergoes a second Wallach reaction. Little azobenzene, the reduction product in this scheme, is isolated from these experiments, and fluorosulfate **1** and 4-aminoazobenzene were neither fluorosulfated by azoxybenzene–fluorosulfonic acid nor aminated by azoxybenzene (or 4,4′-dichloroazoxybenzene)–fluorosulfonic acid–difluoramine.

It is, of course, possible that difluoramine traps the dicarbonium ion postulated as an intermediate in the Wallach rearrangement,[6] and that loss of HF from the initial adduct gives **9**.[12] Fluorimine **9**, then, would be the material reduced to 4,4′-diaminoazobenzene.



Since disubstitution does not normally occur in the Wallach reaction, the unique nature of the difluoramino function—the potential leaving group present—may actually lead to the disubstitution products. Thus, azoxybenzene and HNF_2 may give an adduct that loses HF instead of H_2O; an intermediate (**10**) remains that may again undergo nucleophilic substitution to give either **9** (and eventually **2**) or the precursor to **3**.



At this time, the mechanism of these aminations must be considered obscure.

Although the intermolecular transfer of oxygen between azoxy- and azobenzenes does not explain the results of the amination with difluoramine, it appears to be the most likely cause of the small amount of 4,4′ disubstitution observed in the azoxybenzene–fluorosulfonic acid reaction. Here the azobenzene produced corresponded to the amount of disubstitution observed; so it is reasonable that azoxybenzene + **1** → azobenzene + 4-(fluorosulfato)azoxybenzene[13] → 4,4′ disubstituted azobenzene.

Strong support for this hypothesis was obtained when a mixture of 4,4′-dichloroazoxybenzene and azobenzene was heated with fluorosulfonic acid; a 28% yield of **1** was obtained. Undoubtedly, azobenzene was oxidized to azoxybenzene during the reduction of the dichloroazoxybenzene to 4,4′-dichloroazobenzene. The azoxybenzene would be converted into **1** under the reaction conditions. Azobenzene itself was recovered unchanged after exposure to fluorosulfonic acid at 93°.[11]

The presence of oxidizing material in Wallach rearrangement mixtures has been noted.[7b] About 25% of the theoretical active oxygen material could be titrated after 4,4′-dichloroazoxybenzene had been heated (steam bath) for 1 hr with fluorosulfonic acid. No oxygen was liberated, and the fate of the oxygen not

(10) K. Heumann, *Ber.*, **5**, 910 (1872).

(11) No fluorosulfation was observed here or in any other reactions of azobenzenes and fluorosulfonic acid.

(12) A mixed fluorosulfate–difluoramine would give rise to **3**.

(13) The 4,4′-disubstituted azobenzene actually isolated is the hydroxy fluorosulfate; the material oxidized may be 4-hydroxyazobenzene.

accounted for is not known, although oxidized organic materials may have been present.

Experimental Section

Melting points and boiling points are not corrected. ^{19}F spectra were run in carbon tetrachloride or deuteriochloroform on a Varian 4300 B spectrometer at 40 MHz; ϕ values are measured in parts per million (ppm) from internal CCl_3F standard. Proton nmr spectra were recorded on a Varian A-60 spectrometer. Fluorosulfonic acid was Baker and Adamson technical grade. Methylene chloride was passed through a silica gel column. Difluoramine, a dangerous explosive,[2,3] must be handled with skill and caution.

Reaction of Azoxybenzene and Fluorosulfonic Acid.—A mixture of 10 ml of fluorosulfonic acid and 10 ml of methylene chloride was stirred at ice-bath temperature while azoxybenzene (Eastman, purified by chromatography on silica gel followed by recrystallization from hexane), 5.0 g (25.2 mmol), in 25 ml of methylene chloride was added slowly. After 1 hr at 0°, the mixture was stirred at 25° for 2 hr. The mixture was poured over ice, and the methylene chloride layer was separated and washed with water. Other runs established that no amine fraction could be isolated by further extraction of the basic aqueous layer. The residue from the methylene chloride extract was chromatographed on silica gel (G. F. Smith Chemical Co.). The column was packed in pentane, and elution was carried out with methylene chloride (2, 10, 20, 33, and 50%) in pentane, with methylene chloride, with 10% ethyl acetate in methylene chloride, and with 10% methanol in methylene chloride. The first material eluted from the column, 0.12 g, was azobenzene, identified by its infrared spectrum. The next fraction, 5.05 g (71.4%), was 4-(fluorosulfato)azobenzene (**1**). One recrystallization from hexane gave 4.82 g of **1**, mp 96–98°; an additional recrystallization (ethanol) gave material of mp 98–100°.

Finally, 0.22 g (3%) of material, mp 102–104° (from hexane–chloroform), was eluted by methylene chloride. This presumably is 4-(fluorosulfato)-4′-hydroxyazobenzene. The ^{19}F nmr spectrum had a peak at ϕ − 38.0.

Anal. Calcd for $C_{12}H_9FN_2O_4S$: C, 48.6; H, 3.06; N, 9.46. Found: C, 48.8; H, 3.01; N, 9.42.

From some runs, *p*-phenylazophenol, mp and mmp 150–152°, could be obtained.

Reaction of Azoxybenzene, Fluorosulfonic Acid, and Difluoramine.—A mixture of 0.100 g (0.5 mmol) of azoxybenzene, 5 ml of methylene chloride, 1 ml of fluorosulfonic acid, and 112 cc (STP) (5 mmol) of difluoramine was stirred in a 25-ml sealed pressure tube[14] at ice-bath temperature for 1 hr and at ambient temperature overnight. The pressure tube was then vented *in vacuo* through traps cooled to −80, −110, and −196°. The −110° trap contained difluoramine, 7 cc (STP), and methylene chloride. The −196° trap contained 83 cc (STP) of (by mass spectrum) 23% difluoramine, 42% tetrafluorohydrazine, 30% silicon tetrafluoride, 2% methylene chloride, and 1% each of nitrogen, nitric oxide, and nitrous acids. Thus 26 cc (STP) of difluoramine and 35 cc (STP) of tetrafluorohydrazine was recovered. Another run of the same size under the same conditions gave 23 cc (STP) of recovered difluoramine and 33 cc (STP) of tetrafluorohydrazine. The residues from both runs were combined and poured over ice–dilute aqueous hydrochloric acid. The methylene chloride extract of the aqueous phase (both acidic and after neutralization with sodium hydroxide) was evaporated to dryness and chromatographed on silica gel with the eluents described above. In this way, 0.049 g (17.5%) of 4-(fluorosulfato)azobenzene (**1**) was obtained. The next fraction from the column, 0.027 g, was 4-amino-4′-(fluorosulfato)azobenzene (**3**), mp 171–173° dec (from hexane). The ^{19}F nmr spectrum had a single peak at ϕ −37.2.

Anal. Calcd for $C_{12}H_{10}FN_3O_3S$: C, 48.8; H, 3.41; N, 14.23. Found: C, 49.0; H, 3.33; N, 14.0.

The last fraction from the column (0.095 g, 45%) was 4,4′-diaminoazobenzene (**2**), mp 242–244°. The infrared spectrum was identical with that of Eastman's 4,4′-azodianiline of advertised mp 244–249°.

Anal. Calcd for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.41. Found: C, 67.59; H, 5.49; N, 26.08.

Another run, also conducted in duplicate, used 0.30 g (1.5 mmol) of azoxybenzene, 1 ml of HSO_3F, 5 ml of methylene chloride, and 110 cc (STP) (5 mmol) of difluoramine. The mass spectrum of the gases over the reactions indicated the following compositions: run 1, 2% HNF_2, 40% N_2F_4, 14% CH_2Cl_2, and 44% SiF_4; run 2, 2% HNF_2, 36% N_2F_4, 28% CH_2Cl_2, and 37% SiF_4. The reactions, combined, extracted, worked up, and chromatographed as above, gave 0.312 g (37%) of 4-(fluorosulfato)azobenzene, 0.174 g (19.6%) of 4-amino-4′-(fluorosulfato) azobenzene, and 0.160 g (25%) of 4,4′-diaminoazobenzene. A third set of conditions, involving 0.50 g (2.5 mmol) of azoxybenzene, 2 ml of fluorosulfonic acid, 5 ml of methylene chloride, and 110 cc (STP) (5 mmol) of difluoramine, gave 55% 4-(fluorosulfato)azobenzene, 5% 4-amino-4′-(fluorosulfato)azobenzene, and 15.6% 4,4′-diaminoazobenzene.

Reaction of 3,3′-Dichloroazoxybenzene, Fluorosulfonic Acid, and Difluoramine.—A mixture of 0.27 g (1 mmol) of 3,3′-dichloroazoxybenzene, 1 ml of fluorosulfonic acid, 3 ml of methylene chloride, and 110 cc (STP) of difluoramine in the 25-ml pressure tube[14] was stirred 1 hr at 0° and overnight at ambient temperature. The gas over the reaction mixture, by mass spectrum, was 7% HNF_2, 43% N_2F_4, 20% CH_2Cl_2, and 30% SiF_4. The reaction residue was poured over ice and worked up as described above. Chromatography of the organic material over silica gel gave 0.138 g (39.5%) of 3,3′-dichloro-4-(fluorosulfato)-azobenzene (**4**) (Table I) and 0.053 g (18.7%) of 3,3′-dichloro-4-amino-4′-(fluorosulfato)azobenzene (**6**), mp 115–116° (from hexane). The ^{19}F nmr spectrum had a singlet peak at ϕ −41.1.

Anal. Calcd for $C_{12}H_8Cl_2FN_3O_3S$: C, 39.6; H, 2.21; N, 11.5. Found: C, 39.8; H, 2.32; N, 11.3.

The last fraction eluted from the column was 4,4′-diamino-3,3′-dichloroazobenzene (**5**): yield, 0.145 g (39.0%); mp 215–217° (from methanol).

Anal. Calcd for $C_{12}H_{10}Cl_2N_4$: C, 51.26; H, 3.59; N, 19.93; Cl, 25.22. Found: C, 50.8; H, 3.38; N, 19.5; Cl, 25.8.

When the reaction was conducted under the same conditions using 0.54 g (2 mmol) of 3,3′-dichloroazoxybenzene, 1 ml of fluorosulfonic acid, 4 ml of methylene chloride, and 160 cc (STP) of difluoramine, 0.34 g (48.5%) of **4**, 0.135 g (18.5%) of **6**, and 0.162 g (22%) of **5** were isolated. The gases from the reaction mixture, trapped *in vacuo* in −110 and −196° traps, contained 30 cc of difluoramine and 49 cc of tetrafluorohydrazine.

A third run under the same conditions with 0.27 g of azoxy compound, 1 ml of fluorosulfonic acid, 4 ml of methylene chloride, and 160 cc (STP) of difluoramine gave 0.094 g (27%) of **4**, 0.037 g (13%) of **6**, and 0.101 g (28%) of **5**.

Reaction of 4′-Chloroazoxybenzene (7), Fluorosulfonic Acid, and Difluoramine.—A mixture of 0.47 g (2 mmol) of 4′-chloroazoxybenzene, 1 ml of fluorosulfonic acid, 5 ml of methylene chloride, and 160 cc (STP) of difluoramine was stirred overnight at ambient temperature. A total of 25 cc of difluoramine and 52 cc (STP) of tetrafluorohydrazine was obtained from the volatile gases in the tube. The organic residue, after the usual aqueous work-up, was chromatographed on silica gel. The first fraction isolated was 4-chloroazobenzene (0.039 g) identified by infrared spectrum. After this came 0.082 g of a mixture of 4-chloroazobenzene and 4-chloro-4′-(fluorosulfato)azobenzene and 0.033 g of clean 4-chloro-4′-(fluorosulfato)azobenzene. The next fraction was 4-amino-4′-chloroazobenzene (0.127 g, 18%), mp 148–150° from hexane (lit.[15] mp 147–148°.[15] The infrared spectrum of this material was identical with that of an authentic sample prepared from 4-chloronitrosobenzene and *p*-phenylenediamine.

Anal. Calcd for $C_{12}H_{10}ClN_3$: C, 62.2; H, 4.35; N, 18.14; Cl, 15.3. Found: C, 61.8; H, 4.34; N, 18.20; Cl, 14.9.

Reaction of Fluorosulfonic Acid, 4,4′-Dichloroazoxybenzene, and Azobenzene.—A mixture of 2.67 g (10 mmol) of 4,4′-dichloroazobenzene, 2.73 g (15 mmol) of azobenzene, and 20 ml of fluorosulfonic acid was heated on a steam bath for 1 hr. The mixture was cooled, poured over ice, and extracted with methylene chloride. The methylene chloride solution was washed with water and 10% aqueous sodium bicarbonate solution. The residue left by evaporation of the methylene chloride was chromatographed on silica gel; 5% methylene chloride in pentane was inserted into the usual list of eluents. The initial fractions contained a mixture

(14) Described by R. P. Rhodes, *J. Chem. Educ.*, **40**, 423 (1963).

(15) L. von Mechel and H. Stauffer, *Helv. Chim. Acta*, **24**, 151 (1941); *Chem. Abstr.*, **36**, 6808 (1941).

of azobenzene and 4,4′-dichloroazobenzene; these were not weighed or characterized. The next fraction (0.785 g, 28%) was 4-(fluorosulfato)azobenzene (1), crude mp 96–99° (mixture melting point with 1 from azoxybenzene was 97–99°). The infrared spectrum was identical with that of earlier samples of 1.

Registry No.—Fluorosulfonic acid, 7789-21-1; fluorosulfonic acid–difluoramine, 16704-22-6; **1**, 16704-23-7; 4-(fluorosulfato)-4′-hydroxyazabenzene, 16704-24-8; **3**, 16704-25-9; **5**, 16704-26-0; **6**, 16704-27-1.

Syntheses and Reactions of Triarylsulfonium Halides[1]

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Received November 24, 1967

Triarylsulfonium halides have been prepared by the reaction of diaryl sulfoxides with aromatic hydrocarbons in the presence of a large excess of aluminum halide. The structures of the salts were established by pyrolysis and subsequent glpc analysis of the pyrolysates. On the basis of product ratios produced in the pyrolysis reactions, it was possible to suggest what seemed to be the most plausible mechanism of thermal decomposition of the salts. The reaction of diphenyl-*p*-tolylsulfonium bromide with sodium *t*-butoxide was also investigated. The formation of acetone and a host of other products indicated the operation, at least in part, of a radical reaction in this instance.

In order to investigate the effects of substituents on the reactions of triarylsulfonium halides, it was first necessary to develop a reliable method of synthesis of such salts. One method that seemed potentially useful was that of Wildi, Taylor, and Potratz,[2] who prepared triphenylsulfonium bromide by treatment of diphenyl sulfoxide with phenylmagnesium bromide. However, when an attempt was made to prepare phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium bromide by causing phenyl *p*-tolyl sulfoxide to react with 2,5-dimethylphenylmagnesium bromide in benzene at 75°, no reaction occurred. This was probably due in part to the sterically hindered nature of the Grignard reagent. However, it was also found that no product was obtained when *p*-anisyl- or *p*-bromophenylmagnesium bromide was used. Also, aryllithiums are known not to give appreciable quantities of sulfonium salts when caused to react with diaryl sulfoxides.[3]

Another route that appeared promising was the treatment of a diaryl sulfide with a diazonium compound, as had been developed by Horner and Hoffmann[4] in their synthesis of tetraarylphosphonium salts. However, treatment of diphenyl sulfide with benzenediazonium chloride or *p*-toluenediazonium tetrafluoroborate produced no sulfonium compounds, even when cuprous chloride was added as a catalyst.

Courtout and Tung[5] have reported the syntheses of phenyl-*p*-tolyl-2,3-dimethylphenyl- and phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium chlorides by the reaction of phenyl *p*-tolyl sulfoxide with *o*- and *p*-xylene, respectively, in the presence of aluminum chloride at 40°. Our attempts to reproduce their results met with failure.

Finally, the desired sulfonium salts were prepared by using the method of Courtout and Tung[5] in a drastically modified form. Excess aluminum chloride and much higher reaction temperatures were found necessary to promote formation of the sulfonium salts. About a sixfold molar excess of aluminum chloride was found to work best, although the reason for this is not understood at this time. The most suitable reaction temperature was the reflux temperature of the aromatic hydrocarbon employed in excess as reactant and solvent. Aluminum bromide was also found suitable for use in this reaction, especially in preparation of the bromide salts. By use of this method, several asymmetric and a number of other triarylsulfonium salts were prepared in good yield and purity.

When benzene was employed as a reagent, the synthesis was unambiguous. However, because of the high reaction temperatures involved, a possible aluminum chloride induced migration of the methyl groups on the methyl-substituted benzenes was a possibility to be considered. Use of toluene or *m*-xylene also opened up possibilities of product mixtures arising from electrophilic substitution at various positions on the hydrocarbon in question. In practice, however, as demonstrated by pyrolysis studies to be described later, almost exclusive *para* substitution occurred with toluene, while *m*-xylene yielded exclusively the diaryl-2,4-dimethylphenylsulfonium salt. The results of these syntheses are summarized in Table I.

The melting point of phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium chloride, as noted in Table I, also brings the results of Courtout and Tung[5] into question. The melting point of this anhydrous salt was found by us to be 122–123°, whereas the French authors reported a value of 73–74°. This latter figure is quite close to that observed for the starting material, phenyl *p*-tolyl sulfoxide, mp 75–76°. Phenyl-*p*-tolyl-2,3-dimethylphenylsulfonium chloride, as obtained by these same workers, is reported to have a melting point of 74–76°, almost the same as that for phenyl *p*-tolyl sulfoxide. In our attempts to reproduce the results of Courtout and Tung,[5] we recovered at least a significant portion of the sulfoxides unchanged.

It is of practical value and theoretical interest that triarylsulfonium halides undergo pyrolysis at moderate temperatures to produce theoretical yields of diaryl sulfides and the corresponding aryl halides. ($R_3S^+ + X^- \rightarrow RX + R_2S$). The practical value lies in the fact that the products of pyrolysis are easily analyzed by vapor phase chromatography, and this constitutes the most convenient method for determining

(1) A preliminary report of this work has been published: G. H. Wiegand and W. E. McEwen, *Tetrahedron Lett.*, 2639 (1965).

(2) B. S. Wildi, S. W. Taylor, and H. A. Potratz, *J. Amer. Chem. Soc.*, **73**, 1965 (1961).

(3) K. K. Anderson and S. A. Yeager, *J. Org. Chem.*, **28**, 865 (1963).

(4) L. Horner and H. Hoffmann, *Ber.*, **91**, 45 (1958).

(5) C. Courtout and T. Y. Tung, *Compt. Rend.*, **197**, 1227 (1933).

TABLE I

PREPARATION OF TRIARYLSULFONIUM HALIDES

Sulfoxide	ArH	Aluminum halide	Sulfonium cation	Anion	Mp, °C	Yield, %
Phenyl *p*-tolyl	*p*-Xylene	$AlCl_3$	Phenyl-*p*-tolyl-2,5-dimethylphenyl	Cl^-	122–123	31
Phenyl *p*-tolyl	*p*-Xylene	$AlCl_3$	Phenyl-*p*-tolyl-2,5-dimethylphenyl	I^-	133.5–134	38–60
Phenyl *p*-tolyl	*p*-Xylene	$AlBr_3$	Phenyl-*p*-tolyl-2,5-dimethylphenyl	Br^-	124–125.5	50
Phenyl *p*-tolyl	*m*-Xylene	$AlCl_3$	Phenyl-*p*-tolyl-2,4-dimethylphenyl	I^-	186–186.5	45
Phenyl *p*-tolyl	*m*-Xylene	$AlBr_3$	Phenyl-*p*-tolyl-2,4-dimethylphenyl	I^-	184–186	30
Phenyl *p*-tolyl	*m*-Xylene	$AlBr_3$	Phenyl-*p*-tolyl-2,4-dimethylphenyl	Br^-	170.5–171	27
Phenyl *p*-tolyl	Benzene	$AlBr_3$	Diphenyl-*p*-tolyl	Br^-	246.5–248 dec	60
Diphenyl	*p*-Xylene	$AlBr_3$	Diphenyl-2,5-dimethylphenyl	Br^-	158–159	61
Diphenyl	Benzene	$AlBr_3$	Triphenyl	Br^-	288.5	55

the structure and purity of a given sample of a triarylsulfonium halide. The theoretical interest arises from the ratios of pyrolysis products obtained from triarylsulfonium halides in which at least two different aryl groups are present and the implications of these results with respect to the mechanism of reaction.

The results of a number of pyrolysis reactions conducted for 10–20 min at 250° are given in Table II. It

TABLE II

PYROLYSES OF TRIARYLSULFONIUM HALIDES AT 250°

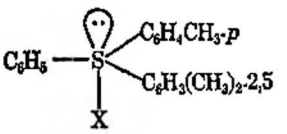
Sulfonium halide	Molar ratio of aryl halides		
Phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium chloride	C_6H_6Cl	*p*-$CH_3C_6H_4Cl$	2,5-$(CH_3)_2C_6H_3Cl$
	1.63	1.00	5.00
	1.38	1.00	5.00
Phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium bromide	C_6H_5Br	*p*-$CH_3C_6H_4Br$	2,5-$(CH_3)_2C_6H_3Br$
	1.91	1.00	11.6
	1.92	1.00	11.9
Phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium iodide	C_6H_5I	*p*-$CH_3C_6H_4I$	2,5-$(CH_3)_2C_6H_3I$
	3.40	1.00	12.4
	4.00	1.00	17.2
	2.40	1.00	17.6
Phenyl-*p*-tolyl-2,4-dimethylphenylsulfonium bromide	C_6H_5Br	*p*-$CH_3C_6H_4Br$	2,4-$(CH_3)_2C_6H_3Br$
	1.94	1.00	3.96
	1.88	1.00	4.32
Diphenyl-*p*-tolylsulfonium bromide	C_6H_5Br	*p*-$CH_3C_6H_4Br$	
	3.40	1.00	
	3.40	1.00	
Diphenyl-2,5-dimethylphenylsulfonium bromide	C_6H_5Br	2,5-$(CH_3)_2C_6H_3Br$	
	1.00	1.38	
	1.00	1.27	

is clear that the product ratios cannot be explained on the basis of either an aromatic SN1 mechanism or a bimolecular aromatic nucleophilic substitution process. For example, pyrolysis of phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium iodide would be expected to give aryl iodides in the order of preference of iodobenzene > *p*-iodotoluene > 2,5-dimethyliodobenzene if a simple bimolecular nucleophilic aromatic substitution mechanism were operative. An aromatic SN1 mechanism would be expected to produce aryl iodides in the order of preference of 2,5-dimethyliodobenzene > *p*-iodotoluene > iodobenzene. In a free-radical process the direction of carbon–sulfur bond cleavage might be expected to be relatively insensitive to the nature of the substituent groups present on the aromatic rings.[6] Furthermore, biaryls would probably be produced in a free-radical process, and none was found.

(6) This has been observed in the copper-catalyzed hydrolysis of unsymmetrical diaryliodonium salts, which is known to be a free-radical process; *cf.* M. C. Caserio, D. L. Glusker, and J. D. Roberts, Theoretical Organic Chemistry, papers presented to the Kekulé Symposium, Section of Organic Chemistry, London, Sept 1958, pp 103–113.

It is also instructive to observe the relative amounts of 2,5-dimethylhalobenzene formed by pyrolysis of the chloride, bromide, and iodide, respectively. The fact that the relative amount of 2,5-dimethyliodobenzene is greater than that of 2,5-dimethylbromobenzene, which, in turn, is distinctly greater than that of 2,5-dimethylchlorobenzene is also inexplicable in terms of any of the mechanisms cited above.

In our opinion, all of the results can best be explained in terms of the formation and subsequent intramolecular decomposition of a tetravalent sulfur compound, I. This decomposes preferentially in such a manner as to give maximum relief of steric strain; *i.e.*, the 2,5-dimethylhalobenzene and phenyl *p*-tolyl sulfide are formed in the greatest amount of the three possible pairs of products, and the effect is larger as the size of the halogen increases.



I

In each case the amount of the halobenzene produced exceeds that of the *p*-halotoluene. Since there are no major steric effects to consider in either of these alternative pathways of decomposition, the charge distribution in the transition state for the intramolecular decomposition of I is probably such that there is a greater electron density in the aryl groups than found in I; *i.e.*, the intramolecular decomposition has some degree of the character of a nucleophilic substitution reaction but should not be confused with an uncomplicated bimolecular aromatic nucleophilic substitution mechanism.[7]

It has recently been reported[8,9] that the reactions of triarylsulfonium halides with sodium alkoxides in alcohol solution give mixtures of aromatic hydrocarbons, diaryl sulfides, alkyl aryl ethers, and aldehydes (or ke-

(7) The possibility of two competing mechanisms was also considered, one involving nucleophilic attack of halide ion upon aromatic carbon to explain the halobenzene to *p*-halotoluene ratios, and the other the decomposition of the sulfonium cation to give primarily phenyl *p*-tolyl sulfide and xylenecnium ion, thus relieving the steric strain resulting from the presence of the *o*-methyl group. Since the yield of haloxylene was found to be large with respect to halobenzene and *p*-halotoluene, formation of xylenecnium ion would have to take precedence over nucleophilic attack if this argument were valid. Also, the order of nucleophilic reactivities would have to be $Cl^- > Br^- > I^-$, which is the known order in aprotic solvents. An unanswered question is whether or not a molten sulfonium salt is similar in this regard to an aprotic solvent.

(8) J. W. Knapczyk, G. H. Wiegand, and W. E. McEwen, *Tetrahedron Lett.*, 2971 (1965).

(9) J. W. Knapczyk, Ph.D. Dissertation, University of Massachusetts, Amherst, Mass., 1965.

tones, depending on the structure of the alkoxide ion used). It was suggested that these products arise, at least in part, by way of radical intermediates [$Ar_3S^+ + OR^- \rightleftharpoons Ar_3S{-}OR \rightleftharpoons (Ar_3S\cdot + RO\cdot) \rightarrow$ products]. In order to provide more direct evidence for the occurrence of radical processes, we decided to study the reaction of a triarylsulfonium halide with sodium *t*-butoxide in *t*-butyl alcohol.

It is known that the *t*-butoxyl radical decomposes into acetone and methyl radical.[10] If sodium *t*-butoxide were used in the decomposition of a triarylsulfonium salt and if the radical mechanism were operative, a *t*-butoxyl radical would be formed which would subsequently yield acetone. Also, products arising from attack of the methyl and *t*-butoxyl radicals upon the various species in solution would be expected. As summarized in Table III, these expectations were realized. Thus, it is evident that a free-radical mechanism is, at least in part, operative.

TABLE III

REACTION OF DIPHENYL-*p*-TOLYLSULFONIUM BROMIDE WITH SODIUM *t*-BUTOXIDE

	% volatile products				
Run	Low mol-wt[a] hydrocarbon	Acetone	Benzene[b]	Toluene[b]	*t*-Butyl phenyl ether
1	Trace	Trace	Trace	Trace	19.7
2	Trace	Trace	Trace	Trace	15.9
Average	Trace	Trace	Trace	Trace	17.8
Run	*t*-Butyl *p*-tolyl ether	Unknown[c] ether	Unknown[d]	Diphenyl sulfide	Phenyl *p*-tolyl sulfide
1	4.2	4.1	1.1	13.0	57.8
2	7.2	4.2	1.2	11.8	60.0
Average	5.7	4.2	1.2	12.4	58.9

[a] Probably ethane, propane, or butane (not methane). [b] More toluene than benzene was formed. [c] Possibly a *t*-butyl, *p*-tolyl, or *t*-butyl xylyl ether. Nmr spectroscopy of a very dilute solution showed the possible presence of a *t*-butyl group bonded to an aromatic carbon. [d] Possibly a sulfide with molecular weight between unknown ether and diphenyl sulfide.

Experimental Section

General.—All melting points are uncorrected. All boiling points were obtained by use of the micro boiling point method and are also uncorrected.

The procedure of Potratz and Rosen[11] was used in the preparation of cobaltous ammonium thiocyanate solution, which was used to detect the presence of the various sulfonium ions in solution.

Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by Dr. Franz Pascher, Mikroanalytisches Laboratorium, Bonn, West Germany.

Phenyl-*p*-tolyl-2,4-dimethylphenylsulfonium Iodide.—To a solution of 3.0 g (0.014 mol) of phenyl *p*-tolyl sulfoxide in 100 ml of *m*-xylene was added 12 g (0.09 mol) of anhydrous aluminum chloride. The mixture was refluxed for 6 hr and then cooled to room temperature, whereupon it was poured into 100 ml of ice containing 20 ml of concentrated hydrochloric acid. The resulting mixture was warmed on a steam bath for a few minutes. The aqueous phase was then removed and washed twice with benzene, excess potassium iodide was added, and the resulting yellow precipitate was extracted with three 50-ml portions of chloroform. After it had been dried over anhydrous sodium sulfate, the chloroform extract was evaporated to give an oil which was dissolved in acetone and treated with an excess of anhydrous benzene. When allowed to stand, white crystals formed and were collected by filtration to give 2.7 g (44%) of pure phenyl-*p*-tolyl-2,4-dimethylphenylsulfonium iodide, mp 186–186.5°. Analytical data for this and other new compounds are given in Table IV.

Phenyl-*p*-tolyl-2,4-dimethylphenylsulfonium Bromide.—To a solution of 2.0 g (0.009 mol) of phenyl *p*-tolyl sulfoxide in 50 ml of *m*-xylene was added 16 g (0.06 mol) of anhydrous aluminum bromide. The mixture was refluxed 24 hr, cooled, carefully poured onto a mixture of 100 ml of ice and 20 ml of concentrated hydrobromic acid, and warmed on a steam bath for a few minutes. After separation from the xylene layer, the aqueous layer was washed three times with benzene and extracted three times with 50-ml portions of chloroform. The chloroform extract was then dried over anhydrous sodium sulfate and evaporated to yield a light yellow oil. This oil was caused to crystallize by dissolving it in a minimum amount of chloroform, adding a few drops of acetone, and flooding the solution with dry benzene. This process was repeated twice to give 1.05 g (27%) of phenyl-*p*-tolyl-2,4-dimethylphenylsulfonium bromide, mp 170.5–171°. The infrared spectrum of this compound was identical with that of phenyl-*p*-tolyl-2,4-dimethylphenylsulfonium iodide.

Phenyl-*p*-tolyl-2,4-dimethylphenylsulfonium Chloride.—A solution containing 5.0 g (0.025 mol) of phenyl *p*-tolyl sulfoxide in 100 ml of *p*-xylene was treated with 16.2 g (0.12 mol) of anhydrous aluminum chloride, and the mixture was refluxed for 18 hr. After it has been cooled to room temperature, the mixture was poured slowly over 200 ml of ice containing 25 ml of concentrated hydrochloric acid; the resulting mixture was allowed to warm to room temperature. The aqueous layer was removed, washed once with benzene, and extracted four times with 50-ml portions of chloroform; the chloroform extract was dried over anhydrous sodium sulfate. After evaporation of the chloroform, a yellow viscous oil remained which was suspended in 100 ml of boiling benzene. Absolute ethanol was added to the boiling mixture until the oil just dissolved, and the resulting solution was added dropwise from a separatory funnel to 450 ml of rapidly stirred benzene at room temperature. Stirring was continued for 1 hr, whereupon 2.13 g (31%) of phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium chloride, a white solid, formed, mp 122–123°. The infrared spectrum of this compound was found to be almost identical with that of phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium iodide.

Other Triarylsulfonium Halides.—The other triarylsulfonium halides listed in Tables I and IV were prepared in essentially the same manner as described above, with the exception of periods of reflux and solvents used for recrystallizations. These differences are summarized in Table IV. It was found possible to convert the triarylsulfonium chlorides and bromides into the respective iodides by metathesis. For example, treatment of an aqueous solution of phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium bromide with an excess of potassium iodide, subsequent extraction with chloroform, drying of the chloroform extract with anhydrous sodium sulfate, and evaporation of the chloroform left an oil which, when crystallized from hot water, gave white needle-like crystals, mp 135.5–136°. That this substance was phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium iodide was shown by a mixture melting point test with an authentic sample. No depression was observed.

***p*-Tolyl 2,5-Dimethylphenyl Sulfide.**—To a solution of 135 ml of concentrated hydrochloric acid in 250 ml water was added 86 g of 2,5-xylidine (Technical, Matheson Coleman and Bell) with vigorous swirling to prevent the formation of lumps. Diazotization was carried out at 0–5° by use of a solution of 37 g of sodium nitrite in 150 ml of cold water, and the resulting solution was added slowly to a solution containing 65 g of *p*-toluenethiol and 82.5 g of sodium hydroxide in 750 ml of water maintained at 50°. After completion of the addition, the resulting mixture was stirred at 50° for 1 hr, and the oily layer was allowed to settle. The oily layer was collected, acidified, steam distilled, separated from the aqueous distillate, and distilled to yield 42 g (35%) of *p*-tolyl 2,5-dimethylphenyl sulfide, bp 147–150° (0.2 mm).

Anal. Calcd for $C_{15}H_{16}S$: C, 79.4; H, 7.1. Found: C, 79.1; H, 7.1.

Phenyl 2,5-Dimethylphenyl Sulfide.—The procedure used was the same as that for *p*-tolyl 2,5-dimethylphenyl sulfide, 59.0 g of benzenethiol being used in the preparation. The yield of phenyl 2,5-dimethylphenyl sulfide was 54 g (47%), bp 130–135° (0.2 mm).

Anal. Calcd for $C_{14}H_{14}S$: C, 78.6; H, 6.6; S, 15.0. Found: C, 78.5; H, 6.9; S, 15.2.

(10) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p 470.

(11) H. A. Potratz and J. M. Rosen, *Anal. Chem.*, **21**, 1276 (1949).

TABLE IV

REACTION CONDITIONS AND ANALYTICAL DATA FOR TRIARYLSULFONIUM HALIDES

$Ar_3S^+ X^-$	Time of reflux, hr	Recrystallization Solvent	Anal., % Calcd C	Calcd H	Calcd S	Calcd X	Found C	Found H	Found S	Found X
Phenyl-*p*-tolyl-2,4-dimethylphenylsulfonium iodide	6	Acetone–benzene	58.3	4.9	7.4	29.4	58.3	5.0	7.5	29.2
Phenyl-*p*-tolyl-2,4-dimethylphenylsulfonium bromide	24	Chloroform–acetone–benzene	...	...	...	...	...	...	...	...
Phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium iodide	28	Water	...	...	7.4	29.4	...	...	7.3	29.3
Phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium bromide	22	Chloroform–benzene or absolute ethanol–ethyl acetate	...	...	...	...	...	...	...	...
Phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium chloride	18	Absolute ethanol–benzene	...	...	...	...	...	...	...	...
Diphenyl-*p*-tolylsulfonium bromide	23	Chloroform–benzene	64.0	4.8	9.0	22.2	63.9	4.8	9.1	22.2
Diphenyl-2,5-dimethylphenylsulfonium bromide	22	Absolute ethanol–ethyl acetate	64.7	5.2	8.6	21.5	64.4	5.5	8.5	21.3
Triphenylsulfonium bromide[a]	24	Absolute ethanol–benzene	...	...	...	...	...	...	...	...

[a] Mp 288–289° (lit.[6] mp 285–286°).

p-Tolyl 2,4-Dimethylphenyl Sulfide.—This compound was prepared in the same manner as described above for *p*-tolyl 2,5-dimethylphenyl sulfide; 86.0 g of 2,4-xylidine (Technical, Matheson Coleman and Bell) was used in the reaction. The yield of *p*-tolyl 2,4-dimethylphenyl sulfide was 60 g (46%), bp 158° (0.3 mm). Vpc analysis, by use of an F & M Model 500 gas chromatograph equipped with a 2-ft silicone rubber column at 160°, showed the presence of an impurity, amounting to about 10–20%, which was probably isomeric material.

Anal. Calcd for $C_{15}H_{16}S$: C, 79.4; H, 7.1. Found: C, 79.4; H, 7.0.

Phenyl 2,4-Dimethylphenyl Sulfide.—This compound was prepared in the same manner as that described for *p*-tolyl 2,4-dimethylphenyl sulfide, 59.0 g of benzenethiol being used in the synthesis. The yield of phenyl 2,4-dimethylphenyl sulfide was 52 g (45%), bp 126° (0.3 mm). Vpc analysis, by use of an F & M Model 500 gas chromatograph equipped with a 2-ft silicone rubber column at 160°, showed the presence of an impurity, amounting to about 10–20%, which was probably isomeric material.

Anal. Calcd for $C_{14}H_{14}S$: C, 78.6; H, 6.6; S, 15.0. Found: C, 78.1; H, 6.6; S, 14.5.

p-Tolyl 2,5-Dimethylphenyl Sulfoxide.—To 25 ml of glacial acetic acid was added 2.28 g (0.01 mol) of *p*-tolyl 2,5-dimethylphenyl sulfide, and the resulting mixture was treated with 1.07 g (1 equiv) of 30% hydrogen peroxide solution and heated overnight on a steam bath. The mixture was then added to an excess of water, the aqueous solution was extracted with chloroform, and the chloroform extract was dried over anhydrous magnesium sulfate. Evaporation of the chloroform left an oil which was crystallized from a minimum amount of Skellysolve F solvent to give large, tan crystals. After four more recrystallizations from Skellysolve F solvent, a yield of 0.98 g (40%) of tan, crystalline *p*-tolyl 2,5-dimethylphenyl sulfoxide, mp 74–75°, was obtained. A fifth recrystallization from Skellysolve F solvent (Norit) gave the product as white needles, mp 79–80°.

Anal. Calcd for $C_{15}H_{16}SO$: C, 73.8; H, 6.6; S, 13.1. Found: C, 73.9; H, 6.6; S, 13.0.

Phenyl 2,5-Dimethylphenyl Sulfoxide.—This compound was prepared in the same manner as was *p*-tolyl 2,5-dimethylphenyl sulfoxide, 2.14 g (0.01 mol) of phenyl 2,5-dimethylphenyl sulfide being used as starting material. The yield was 0.90 g (39%) of pure phenyl 2,5-dimethylphenyl sulfoxide as white prisms, mp 65.5–66.5°.

Anal. Calcd for $C_{14}H_{14}SO$: C, 73.0; H, 6.1; S, 13.9. Found: C, 72.9; H, 6.6; S, 13.9.

Pyrolysis of Sulfonium Salts for Proof of Structure.—Each of the sulfonium salts listed in Table I, except triphenylsulfonium bromide, was pyrolyzed in a 4-mm Pyrex tube about 30 cm long, sealed at one end, at 250 ± 5° for 10–20 min until reaction was complete. Only about 2 cm of the sealed end of the tube was immersed in the oil bath used, the remainder of the tube being used as an air condenser. In all cases the compositions of the pyrolysates were determined by use of either an F & M Model 500 or an F & M Model 609 gas chromatograph, a 2-ft silicone rubber column being used. Identification of the products was accomplished by use of retention times. Where applicable, a small amount of the suspected material was added to the pyrolysate and an increase in peak height observed. It was found possible to separate the isomeric aromatic sulfides from one another by use of these conditions. The isomeric aromatic halides were also found separable, except for the 4- and 5-bromo-*m*-xylenes, which were separated by use of a 2-ft Apiezon L column.

In no case was any significant amount of unexpected product found, and all of the sulfonium salts, when pyrolyzed, gave the products expected from their thermal decomposition. Thus, the sulfonium salts listed in Table I, with the exception of triphenylsulfonium bromide, were found by pyrolysis and subsequent vpc analysis to have the structures given.

Pyrolysis of Sulfonium Salts. Product Ratios.—Resolution and appropriate shape of the halide peaks obtained in the chromatograms of the pyrolysates used for structure determinations were sufficient to permit determination of the relative ratios of the halides formed in each pyrolysate. In each experiment on an individual pyrolysate, the approximate relative amounts of the halides formed were determined by finding the approximate relative areas of the halide peaks obtained. Approximate peak areas were obtained by multiplying the peak height by the peak width at half-height. At least three standard solutions were then prepared having various compositions near the approximate values obtained. Vpc analysis was then performed on these standards; the approximate area ratios were obtained and plotted graphically with respect to composition. The actual product ratios of the halides in the pyrolysate were then obtained directly from the graphs.

The total aromatic halide to total aromatic sulfide ratio in the case of the pyrolysis of phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium bromide was obtained in the following manner. The column temperature was raised until the halide peaks coalesced into one peak and the sulfide peaks did likewise, the resulting two peaks being sharp and cleanly resolved. Standard mixtures were again prepared and subjected to vpc analysis. From this analysis, the ratio of total aromatic halide to total aromatic sulfide was found to be approximately 1:1.

t-Butyl Phenyl Ether.—The method of Baddeley, *et al.*,[12] was used in the preparation of this compound. A 15% yield of *t*-butyl phenyl ether, a colorless oil, bp 27° (0.15 mm), was obtained [lit.[13] bp 70–71° (11 mm)]. The nmr spectrum (neat) of this compound was in agreement with the structure given.

t-Butyl *p*-Tolyl Ether.—This compound was prepared in low yield by the same method as described above. It was obtained as a colorless oil, bp 38–40° (0.2 mm) [lit.[13] bp 79–81° (9 mm)]. Nmr and ir spectra (both neat) were consistent with the structure given.

p-Methylphenetole (Ethyl *p*-Tolyl Ether).—A sample of *p*-methylphenetole was vacuum distilled from a small amount of ferrous sulfate to give a colorless liquid, bp 51° (1 mm). A

(12) G. Baddeley, N. H. P. Smith, and M. A. Vickars, *J. Chem. Soc.*, 2455 (1956).

(13) S. O. Lawesson and N. C. Yang, *J. Amer. Chem. Soc.*, 81, 4230 (1959).

micro boiling point at atmospheric pressure gave a value of 190.5–191° (lit.[14] 189–191°).

5-Bromo-*m*-Xylene.—This compound was prepared by the method of Buehler, *et al.*,[15] in 27.6% yield, bp 33° (0.1 mm) [lit.[15] bp 70° (6 mm)].

Reaction of Diphenyl-*p*-Tolylsulfonium Bromide with Sodium *t*-Butoxide.—A sample of 0.357 g (0.001 mol) of diphenyl-*p*-tolylsulfonium bromide was mixed with 6 ml of an approximately 0.16 *M* (1 equiv) slurry of sodium *t*-butoxide in anhydrous *t*-butyl alcohol, and the mixture was refluxed under an efficient condenser for 24 hr. During this time a precipitate of sodium bromide formed. The reaction mixture was then subjected to vpc analysis. Quantitative determinations were carried out by use of an F & M Model 609 gas chromatograph equipped with a 2-ft Apiezon L column; a time–temperature program from 25 to 200° at 4.6°/min was employed. Standards were prepared as in the analyses of the pyrolysates, and the product percentages were determined graphically. Quantities of the unknown materials were estimated by measurement of their peak areas. The results of this analysis are listed in Table III.

Trace amounts of materials in the reaction mixture were identified by use of an Aerograph Autoprep Model A-700 gas chromatograph equipped with a 20-ft silicone rubber column. The minor products were identified by retention times. Where possible, a small amount of an authentic sample of the suspected material was added to a small quantity of the mixture and an increase in peak height was observed. An attempt was made to collect a sample of the unknown ether by preparative gas chromatography, the Autoprep being used. A very small amount of the material was collected and subjected to nmr analysis. A carbon tetrachloride solution of the substance gave a weak signal; however, the presence of *t*-butyl and aromatic methyl groups was indicated. The retention time was about that expected for a tolyl or xylyl *t*-butyl ether other than *t*-butyl *p*-tolyl ether, and the substance had the odor of an ether.

Although both were formed in small amounts, it was possible to see that toluene was formed in greater quantity than benzene. The presence of a polymeric material was also indicated by a very broad "peak" which was observed at long retention times.

(14) J. Pinette, *Ann.*, **243**, 32 (1888).

(15) C. A. Buehler, T. A. Magee, K. V. Nyak, and D. M. Glenn, *J. Org. Chem.*, **24**, 1307 (1959).

Registry No.—Phenyl-*p*-tolyl-2,4-dimethylphenylsulfonium iodide, 16720-21-1; phenyl-*p*-tolyl-2,4-dimethylphenylsulfonium bromide, 4063-74-5; phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium chloride, 4063-73-4; *p*-tolyl 2,5-dimethylphenyl sulfide, 16704-44-2; phenyl 2,5-dimethylphenyl sulfide, 16704-45-3; *p*-tolyl 2,4-dimethylphenyl sulfide, 16704-46-4; phenyl 2,4-dimethylphenyl sulfide, 16704-47-5; *p*-tolyl 2,5-dimethylphenyl sulfoxide, 16704-48-6; phenyl 2,5-dimethylphenyl sulfoxide, 16704-49-7.

Acknowledgments.—This work was supported by Grant GP 182 from the National Science Foundation. One of us (G. H. W.) also gratefully acknowledges support as a National Science Foundation Cooperative Graduate Fellow. The Varian A-60 nmr apparatus used in this work was purchased with funds donated to the University of Massachusetts by the National Science Foundation.

Ozonation of Amines. II. The Competition between Amine Oxide Formation and Side-Chain Oxidation

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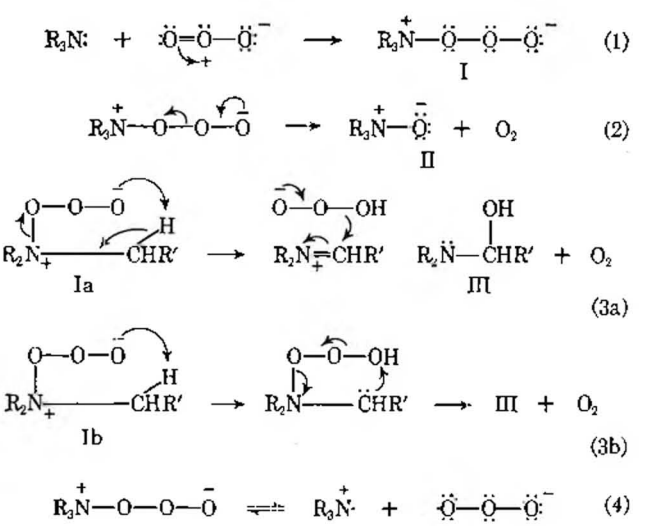
Received January 31, 1968

The competition between amine oxide formation and side-chain oxidation during ozonation of tri-*n*-butylamine in several different solvents has been studied, using ozone–nitrogen mixtures. To obtain a better understanding of the side-chain oxidation, 1-di-*n*-butylamino-2-butanone (XV) was synthesized and ozonized. A preference for attack at the methylene group between the amino and carbonyl groups was observed. The results, including solvent effects, are explained on the basis of competitive fates of an initial amine–ozone adduct.

In the first paper of this series[1] the hypothesis was presented that all known reactions between ozone (an electrophile) and amines (nucleophiles) can be explained on the basis of the initial formation of an adduct (I, eq 1) for which there are at least three major fates: (1) loss of molecular oxygen to give an amine oxide (II, eq 2) or further reaction products thereof; (2) an intramolecular side-chain oxidation (eq 3a or b) to give molecular oxygen and further reaction products of III; (3) dissociation to cation and anion radicals (eq 4), followed by stabilizing reactions thereof.

Equation 3a is based on a recent suggestion of Kolsaker and Meth-Cohn[2a] and is analogous to the accepted mechanism of the Polonovski reaction.[2b]



Equation 3b bears an analogy to the accepted mechanism of the Steven's rearrangement.[2c]

The conversion of tertiary amines into amine oxides

(1) P. S. Bailey, J. E. Keller, D. A. Mitchard, and H. M. White, paper presented at the International Oxidation Symposium, San Francisco, Calif., Aug 1967; Advances in Chemistry Series, American Chemical Society, Washington, D. C., in press.

(2) (a) P. Kolsaker and O. Meth-Cohn, *Chem. Commun.*, **18**, 423 (1965); (b) R. Huisgen, F. Bayerlein, and W. Heydkamp, *Chem. Ber.*, **92**, 3223 (1959); (c) C. R. Hauser and S. W. Kantor, *J. Amer. Chem. Soc.*, **73**, 1437 (1951).

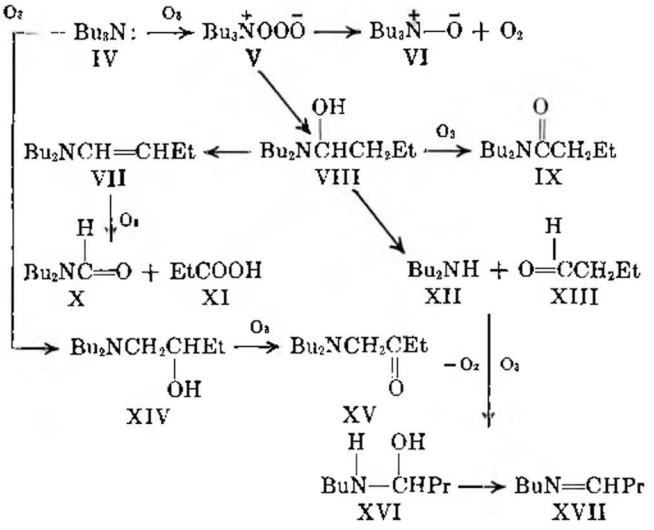
TABLE I
OZONATION OF TRI-*n*-BUTYLAMINE[a]

	Solvent						
	Pentane	CCl_4	CH_2Cl_2	$CHCl_3$	$CHCl_3$	$CHCl_3$	CH_3OH
Temp, °C	−45	−25	−45	−25	−45	−65	−45
O_3 reacting/amine reacting	1.6	1.4	1.4	1.3	1.2	1.1	1.2
O_2 evolved/O_3 reacting	0.9	...	...	...	1.0	...	...
$Bu_3\overset{+}{N}\overset{-}{O}$, %	6	11	36	38	53	65	53
$Bu_2\overset{+}{N}H_2Cl^-$, %	0	29	4	8	7	7	0
Bu_2NH_2, %	22	2	17	14	10	5	9
BuN=CHPr, %	4	1	1	2	2	1	2
$Bu_2NCH{=}CHEt$, %	27	1	15	13	12	3	11
$Bu_2NCH{=}O$, %	12	10	5	7	3	2	3
$Bu_2NC(=O)Pr$, %	9	12	9	8	6	4	6
$Bu_2NCH_2C(=O)Et$, %	1	1	1	1	1	...	1
PrCHO	*b*	*b*	*b*	*b*	*b*	*b*	*b*
EtCOOH	*b*	*b*	*b*	*b*	*b*	*b*	*b*
PrCOOH	*b*	*b*	*b*	*b*	*b*	*b*	*b*
Total yield, %	81	67	88	91	94	87	85

[a] The ozonations were carried out with 22 mmol of ozone in an ozone–nitrogen mixture on solutions of 22 mmol of tributylamine in 50 ml of solvent. Yields were based on the amount of amine which reacted (unrecovered). [b] Present.

(eq 1 and 2),[3-8] phosphines and arsines into similar oxides,[5,8] phosphites into phosphates,[9] sulfides into sulfoxides,[8] and sulfoxides into sulfones,[8] by means of ozone, is well known. The solvents generally employed in the conversion of tertiary amines into amine oxides have been chloroform or methanol.[4,5] Following a clue from Strecker and Baltes,[3] Henbest and Stratford[6] reported a strong solvent effect in the ozonation of tri-*n*-butylamine (IV). Whereas in methanol and chloroform, 52 and 61% yields, respectively, of the amine oxide were reported, the oxide yields were only 2 and 0.5% in butyl chloride and pentane, respectively, at the same temperature (−45°). The other products (IX, X, and XII) were from oxidation of a butyl side chain, presumably *via* intermediate VIII, as shown in Scheme I. Temperature effects also have been noted in the ozonation of tertiary amines.[6,7]

SCHEME I



The present paper deals with evidence for the fate of the amine–ozone adduct (Ia or b) described by eq 3a or b, as an explanation for side-chain oxidation, and with the competition between amine–oxide formation and side-chain oxidation (eq 2 and 3). Since Henbest and Stratford[6] carried out their ozonations with ozone–oxygen mixtures, the possibility was not eliminated that the side-chain oxidation observed resulted from autoxidation. Thus, the ozonation of tributylamine (IV) has been studied with ozone–nitrogen mixtures in pentane, methylene chloride, chloroform, carbon tetrachloride, and methanol. The chloroform experiments were carried out at three different temperatures. The results of experiments in which the best accounting of starting material was obtained are shown in Table I.

It is perhaps noteworthy that our yields of tri-*n*-butylamine oxide (VI) in chloroform at −45° were not so high as those of Henbest and Stratford[6] in the same solvent and at the same temperature, although we accounted for 94% of the starting material and they only 67%. This is probably due to the fact that Henbest and Stratford[6] did not realize that di-*n*-butylammonium chloride was a product, and it was included in their yield of amine oxide, which they extracted with water and converted into a picrate. Horner, *et al.*,[5] reported even higher oxide yields (70% for VI). The work-up procedure described does not preclude the possibility that unreacted starting material (as the picrate) was included in the amine oxide yield. In our determination of the amine oxide (VI) the more exact and specific titanium trichloride method[10] was employed. Other differences in our results and those of Henbest and Stratford[6] include our determination of products VII and XVII (Scheme I), which made possible a considerably greater accounting of starting material than obtained by the earlier workers.

Preliminary experiments in our laboratory showed that there were only minor differences in results using ozone–nitrogen and ozone–oxygen mixtures, especially in regard to the ratios of ozone to amine reacting and of

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TABLE II
OZONATION OF Bu_2NCH_2COEt (XV)[a]

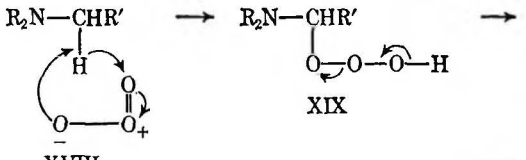
	Solvent: Chloroform, mmol (%)	Solvent: Pentane, mmol (%)	Source
O_3	5.2	5.0	
XV reacting	4.1	4.0	
O_3/XV (reacting ratio)	1.3	1.3	
$Bu_2\overset{O^-}{\overset{\vert}{N}}CH_2COEt$	0.24 (6)	0.12 (3)	
Bu_2NH_2 (XII)	0.89 (22)[b,c]	0.61 (15)[c]	Eq 6, 10
Bu_2NCHO (X)	0.36 (18)[d]	0.41 (20)[d]	Eq 6, 8, 10–12
$Bu_2NCOCOEt$ (XXIV)	0.38 (9)	0.62 (16)	Eq 6, 9
$PrCON(Bu)CH_2COEt$ (XXII)	0.57 (14)	0.40 (10)	Eq 6, 7
$PrCONBu_2$ (IX)	0.02 (1)[d]	0.02 (1)[d]	Eq 6, 8, 10, 11
PrCHO (XIII)	1.25 (30)	0.74 (19)	Eq 6, 8, 10, 13
Other products	[e]	[e]	
Total yield, %	100	84	

[a] All ozonations were carried out with ozone–nitrogen mixtures on 10-mmol samples of XV in 20 ml of solvent at −45°. [b] Includes 0.15 mmol (4%) in form of dibutylammonium chloride. [c] Includes 0.02 mmol of a further oxidation product of dibutylamine (*i.e.*, BuN=CHPr; see eq 14). [d] Since these products are secondary products derived from two different primary sources, the percentage yield in accounting for the starting material is twice that based on the yield in millimoles (see eq 11 and 12). [e] Propionic acid (XXV), 17–18%, was also obtained, but is not counted in total yield since it must come from same source as certain other products (see eq 10 and 12).

amine oxide to side-chain oxidation products obtained. This result seems to exclude the possibility of a radical-type hydrogen abstraction as a step in the side-chain oxidation. If such occurred, the yield of side-chain oxidation products should be greater in the presence of oxygen than in its absence owing to the initiation of autoxidation,[11] at least in chloroform solvent where such a difference would be noticeable.

The results shown in Table I, obtained with ozone–nitrogen mixtures, not only confirm the solvent and temperature effects reported by earlier workers,[6,7] but give more information concerning them. The amine oxide yields were greatest in methanol and chloroform, next in methylene chloride, and least in carbon tetrachloride and pentane. In chloroform the amine oxide yields increased as the temperature was decreased. The ozone to amine reacting ratio varied from 1.1 to 1.6 and increased as the yield of side chain oxidation products increased. In both chloroform and pentane, the ratio of molecular oxygen evolved to ozone reacting was approximately unity.

Besides the mechanisms for side-chain oxidation of amines described by eq 3a and b, another major possibility must be considered. This is the 1,3-dipolar insertion reaction (XVIII → XIX → III) proposed recently[11] to account for results obtained upon ozonation of aromatic aldehydes,[11] aliphatic ethers,[12] anthrones,[13] and hydrocarbons.[14] To distinguish between the two possibilities, 1-di-*n*-butylamino-2-butanone (XV) was synthesized and ozonized in chloroform and in pentane. If the insertion mechanism is correct, the ozone attack should occur predominantly at the least acidic carbon–hydrogen bonds in the molecule.[11,13] These would be in the *n*-butyl groups. If, however, one of the mechanisms of eq 3a and b is operative, the most acidic nearby carbon–hydrogen bond should be attacked. This would be the methylene group between the nitrogen and carbonyl groups. The results of this study are shown in Table II.



$$R_2NCHR' \quad (5)$$
$$\overset{|}{OH}$$
III

The probable sources of the products listed in Table II are shown by eq 6–14. The minimum and maximum percentages in which these products could originate from the butyl and butanone groups of the starting material (XV) are shown in Table III. It can be seen from Table III that a minimum of 43% of the product yield arises from attack on the butanone group (*via* XXI) of 1-di-*n*-butylamino-2-butanone (XV) in both chloroform and pentane solvents and that this conceivably could be as high as 85–90%. The principal uncertainty is in regard to the source of butyraldehyde (XIII). As can be seen from eq 8, butyraldehyde (XIII) is a pri-

$$PrCH_2\overset{Bu}{\overset{|}{N}}CH_2\overset{O}{\overset{\|}{C}}Et \xrightarrow[-O_2]{O_3}$$
XV

$$\left[PrCH\overset{Bu}{\overset{|}{N}}CH_2\overset{O}{\overset{\|}{C}}Et\right]_{OH} + \left[PrCH_2\overset{Bu}{\overset{|}{N}}CH\overset{O}{\overset{\|}{C}}Et\right]_{OH} \quad (6)$$
XX XXI

$$XX \xrightarrow{O_3} PrC\overset{Bu}{\overset{|}{N}}CH_2CEt + H_2O + O_2 \quad (7)$$
XXII

$$XX \longrightarrow PrCHO + \left[BuN\overset{H}{\overset{|}{C}}H_2\overset{O}{\overset{\|}{C}}Et\right] \quad (8)$$
XIII XXIII

$$XXI \xrightarrow{O_3} Bu_2NC\overset{O}{\overset{\|}{C}}Et + H_2O + O_2 \quad (9)$$
XXIV

$$XXI \longrightarrow Bu_2NH + \left[HC\overset{O}{\overset{\|}{C}}Et\right]_{O} \xrightarrow{O_3} EtCOOH \quad (10)$$
XII XXV

$$XII + XIII \longrightarrow Bu_2N\overset{OH}{\overset{|}{C}}HCH_2Et \xrightarrow{O_3} IX \quad (11)$$
VIII

$$VIII \xrightarrow{-H_2O} VII \xrightarrow{O_3} X + XXV \quad (12)$$

$$XII \xrightarrow[-O_2]{O_3} \left[BuN\overset{H}{\overset{|}{C}}HPr\right]_{OH} \longrightarrow [BuNH_2] + XIII \quad (13)$$
XXVI

$$XXVI \longrightarrow BuN{=}CHPr \quad (14)$$
XXVII

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TABLE III

ORIGINS OF PRODUCTS IN TABLE II

	Chloroform				Pentane			
	Butyl (*via* XX)		Butanone (*via* XXI)		Butyl (*via* XX)		Butanone (*via* XXI)	
	Min[a]	Max[a]	Min[a]	Max[c]	Min[a]	Max[a,b]	Min[a]	Max[a,b]
Bu_2NH (XII)	0	0	23	23	0	0	15.5	(>15.5)
Bu_2NCHO (X)	0	9.5	9.5	19	0	(>10)	10	(>20)
$Bu_2NCOCOEt$ (XXIV)	0	0	10	10	0	0	16.5	(>16.5)
XXII	15	15	0	0	10	(>10)	0	0
$PrCONBu_2$ (IX)	0	0.5	0.5	1	0	(>0.5)	0.5	(>1)
PrCHO (XIII)	0	32	0	32	0	(>20)	0	(>20)
Total	15	57	43	85	10	(57.5)	42.5	(90)

[a] The values are percentages of minimum and maximum attack on the above group in XVs, based on the percentages of each product present in the mixture of side-chain oxidation products. [b] Since in pentane only an 84% accounting of starting material was obtained, the maximum values could all be larger than the isolated yields, as indicated in the parentheses. Thus, the total maximum values listed are equal to 100% minus the respective minimum values shown for attack on the other group.

mary decomposition product of amino alcohol XX, which must be the initial product from oxidation of a butyl side chain (eq 6). The substance (XXIII) which should be simultaneously produced with butyraldehyde (XIII) could not be identified; perhaps it polymerizes or in some other way is destroyed.[15] Another possible source of butyraldehyde, however, is as a secondary product from oxidation of the butanone group of tributylamine. This involves decomposition of intermediate XXI to dibutylamine (eq 6 and 10), oxidation of dibutylamine (XII) to amino alcohol XXVI, and decomposition of XXVI to butylamine and butyraldehyde (eq 13). A similar uncertainty of origin is associated with products IX and X, since the most reasonable source of these products is *via* interaction of dibutylamine and butyraldehyde (eq 6, 8, 10, and 11) and further reactions of intermediate VIII (eq 11 and 12). We have shown qualitatively that ozonation of dibutylamine does produce butyraldehyde as a major product and that dibutylamine is more reactive toward ozone than is 1-di-*n*-butylamino-2-butanone (XV). Thus, some of the butyraldehyde (XIII), and also of products IX and X, undoubtedly does arise from intermediate XXI and the true value for attack on the butanone group must be somewhere between the minimum and maximum values of 43 and 85 or 90% shown in Table III. There is some indication that the true value is closer to the maximum than to the minimum value in spite of the fact that butyraldehyde is a primary product of decomposition of XX, but only a secondary product from further reactions of XXI. This will be discussed later.

Since there are two butyl groups and only one butanone group in XV, a statistical attack on these groups with no preference for one or the other should result in 67% attack on the butyl groups, to give XX, and only 33% attack on the butanone group, to give XXI (eq 6). Thus, even the minimum value of 43% attack on the butanone group signifies a greater rate of attack on the butanone than on the butyl groups, by a factor of 1.5 to 1. If the true value for attack on the butanone group is as high as 80%, as will be defended shortly, the rate of attack on the butanone group must be greater than that on the butyl groups by a factor of 8 to 1. Thus, these results furnish strong evidence for one of the mechanisms of side-chain oxidation described by eq 3 rather than by the insertion mechanism (eq 5).

In the light of such a mechanism the solvent and temperature effects in the ozonation of tributylamine (Table I) become understandable. The ability of a solvent to promote amine oxide formation certainly does not appear to be connected with its polarity. Butyl chloride was no better in this respect than pentane.[6] Instead, it appears to be due to its solvating power, or, as expressed by Henbest and Stratford,[6] its hydrogen-bonding capacity. Solvents such as chloroform and methanol, with which the highest yields of amine oxide were obtained, solvate the amine–ozone adduct (Ia or b, eq 3) and inhibit the abstraction of a proton required by eq 3. Thus, the major fate of the adduct (I) is loss of molecular oxygen to give the amine oxide, as shown by eq 2. With solvents like pentane, butyl chloride,[6] and carbon tetrachloride, however, there is no appreciable solvation and the major fate of the amine–ozone adduct (Ia or b) involves the side-chain oxidation (eq 3). The fact that methylene chloride gives results in between is in line with expectations based on its acidity and consequential ability to solvate Ia or b. The temperature effect observed both by the authors and by Shulman (with dimethyllaurylamine)[7] is also reasonable on the basis of the mechanisms of eq 3. The ability for the intramolecular hydrogen abstraction to occur in eq 3 should increase with increasing temperature in solvents such as chloroform, since at higher temperatures the deterring effect of solvation of the negative pole of Ia or b (eq 3) should be less. Amine oxide formation, therefore, should increase with decreasing temperature and side-chain oxidation should increase with increasing temperature in solvating solvents, like chloroform, at least up to a point, as found.

A striking difference in the results of ozonation of tributylamine (IV) and 1-di-*n*-butylamino-2-butanone (XV) is that there is no appreciable solvent effect with XV (*cf.* Tables I and II). This is understandable on the basis that the increased acidity of the methylene hydrogens of the butanone group causes hydrogen abstraction to occur so rapidly, by one of the mechanisms of eq 3, that amine oxide formation is essentially precluded in all solvents. Perhaps hydrogen bonding within the amine–ozone complex, between the negative oxygen and the hydrogens of the acidic methylene group, is more important than solvation by solvents like chloroform. Such reasoning leads to the conclusion that there must be an overwhelming preference for oxidation of the butanone group and that the maximum values of 85–90% in Table III are closer to the true value for attack on the butanone group than is the minimum value of 43%. To say the least, however, the fact is significant that with neither tri-*n*-butylamine

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nor 1-di-*n*-butylamino-2-butanone does any appreciable attack occur at the β, γ, or δ carbons of the butyl groups. These should bear the least acidic hydrogens, and should be, therefore, the preferred positions of attack by the insertion mechanism.[11,13]

In addition to products VII, IX, X, XII, and XVII, from ozonation of tributylamine (IV), traces of XV were found, indicating a very minor attack at a β position of one of the butyl groups of IV. It seems possible that the mechanisms of eq 3 could occur at a β position, although not so easily as at an α position, since the transition state should involve a seven rather than a six-membered ring. Alternatively, this result may represent the extent to which the insertion mechanism competes with a mechanism of the type shown by eq 3.

The fact that some dibutylammonium chloride was produced from ozonations of tributylamine (IV) and 1-dibutylamino-2-butanone (XV) in chlorinated solvents (Tables I and II) is indicative that the fate of the amine–ozone adduct represented by eq 4 occurs to some extent.[16] The salts of IV and XV probably are initially produced, after which these amines are displaced from their salts by the stronger base, dibutylamine. It is interesting that this fate of the amine–ozone adduct (eq 4) does not occur to so great an extent, at least in methylene chloride and chloroform, as it does with *t*-butylamine.[16] This is not especially surprising, however, since there is no possibility for the occurrence of reactions 3a and b with *t*-butylamine. A greater mystery is the high yield of the ammonium salt from ozonation of IV in carbon tetrachloride (Table I). Although it has been reported that amines, themselves, react with carbon tetrachloride to give ammonium salts, the yields were very low even after 72 hr at room temperature.[17] We have shown that the reaction is negligible under our ozonation conditions. Thus, for some reason not yet apparent, the fate of the amine–ozone adduct described by eq 4 increases at the expense, primarily, of the fate described by eq 3, with tributylamine in carbon tetrachloride solvent. A comparison with the chloroform reaction at −25° (Table I) shows that this is not a temperature effect.

Finally, it should be mentioned that the stoichiometry observed in the ozonations of tributylamine (Table I) fit the reaction schemes of eq 1, 2, and 3 and Scheme I very well. In amine oxide formation, 1 mol equiv of ozone is required and 1 mol equiv of molecular oxygen is evolved. This is also true with certain of the side chain oxidation products (VII, XII), but not all. In the formation of X, IX, and XVII more ozone is required and, at least in the case of X, no oxygen would be evolved. Thus, the ozone–amine ratio should increase as the amount of side-chain oxidation increases, as observed. Similar observations can be made concerning Table II.

Experimental Section

The ozonation setup and procedures, using either ozone–oxygen or ozone–nitrogen, and the method for determining molecular oxygen yields are described in earlier publications.[18,19] Nmr spectra were taken with a Varian Associates A-60 spectrometer using carbon tetrachloride as the solvent and tetramethylsilane as an internal standard.

Gas Chromatography.—Most analyses were made with an Aerograph Model 1520B with hydrogen flame detector and equipped with a disk integrator. A 0.125 in. × 10 ft column of 30% silicone gum rubber SE-30 on Chromosorb W was used at an initial temperature of 75°, which was increased at a rate of 8°/min up to 250°. N,N-Dibutylpropionamide was used as an internal standard in the tributylamine (IV) studies and tributylamine was the internal standard in the 1-butylamino-2-butanone (XV) studies. In all experiments except those employing chloroform as a solvent butyraldehyde was determined separately on the same 1520B chromatograph, using the same column and a benzene or dioxane internal standard. For the chloroform runs, an F & M 500 gas chromatograph and a 0.25 in. × 20 ft column packed with 15% Carbowax 20M on Chromosorb W was employed at 100°. The F & M machine was also used for propionic acid, employing a 0.25 in. × 10 ft 5% dimer acid silicon oil 550 on Haloport F column at 100°. Yields were obtained by comparisons with standard solutions of known compounds. Preparative vpc work was carried out on a Wilkins A-90-P3 Autoprep, using a 0.375 in. × 20 ft column of 15% Carbowax 20M on Chromosorb W at 250°.

Chemicals.—The tri-*n*-butylamine, di-*n*-butylamine, N,N-di-*n*-butylpropionamide, N,N-di-*n*-butylformamide, butyraldehyde, and propionic acid used were the best commercial grades available. All solvents were pure and anhydrous.

1-Di-*n*-butylamino-2-butanone (XV).—1-Chloro-2-butanone was prepared from propionyl chloride, diazomethane, and dry hydrogen chloride by the general method of McPhee and Klingsberg[20] [bp 66–68° (55 mm); n^{16}D 1.4330; 75% yield]. This (45 g, 0.42 mol) was added to a solution of dibutylamine (163 g, 1.27 mol) in 150 ml of ethanol, and the resulting solution was refluxed for 1.5 hr. About one-half of the solvent was removed by distillation, and the residue was cooled in an ice bath. The precipitated di-*n*-butylammonium chloride was separated by filtration. The reaction mixture was diluted with ether (1–2 l.) and extracted with three 400-ml portions of dilute hydrochloric acid. The combined extracts were neutralized with potassium hydroxide pellets and extracted with three 300-ml portions of ether. The ether extract was washed with saturated salt solution, dried over anhydrous magnesium sulfate, and evaporated. The residue was distilled. After removal of a low-boiling fraction, 47 g (56% yield) of 1-dibutylamino-2-butanone (XV) was obtained: bp 92° (5 mm); n^{25}D 1.4355. The infrared spectrum of a neat sample showed a strong carbonyl band at 1715 cm^{-1}; the nmr spectrum in carbon tetrachloride included peaks at τ 6.95 (singlet, two protons, O=C—CH_2N<), 7.52 (quartet, two protons, CH_3CH_2C=O), and 7.57 (triplet, four protons, >N-CH_2Pr) ppm.

Anal. Calcd for $C_{12}H_{25}NO$: C, 72.31; H, 12.64; N, 7.03. Found: C, 72.15; H, 13.05; N, 7.15.

1-Di-*n*-butylamino-1-butene (VII) was prepared as described by Henbest and Stratford:[6] bp 75° (0.7 mm); n^{25}D 1.4480.

N,N-Di-*n*-butylbutyramide (IX) was prepared from di-*n*-butylamine and butyric anhydride:[21] bp 113–115° (5 mm); n^{25}D 1.4445.

Butylidene butylamine (XVII) was prepared from butylamine and butyraldehyde:[22] bp 52° (21 mm); n^{25}D 1.4176.

1-Di-*n*-butylamino-1,2-butanedione (XXIV) was isolated from the ozonation reaction mixture of 1-dibutylamino-2-butanone (XV) by preparative vpc. Its infrared spectrum (liquid film) showed carbonyl peaks at 1715 (keto) and 1645 cm^{-1} (amide). Its nmr spectrum (neat liquid) included peaks at τ 6.59 (triplet, four protons, $PrCH_2N$—C=O), 7.17 (quartet, two protons, CH_3CH_2—C=O) ppm. Peaks in the mass spectrum appeared at *m/e* 214 (mol wt + 1), 156 (mol wt − *n*-Bu or EtCO), and 128 (mol wt − EtCOCO), but not at *m/e* 142 (mol wt − PrCO).

Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.22; H, 10.68; N, 6.84.

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1-(*n*-Butyl-*n*-butyrylamino)-2-butanone (XXII) was isolated from the ozonation reaction mixture of 1-dibutylamino-2-butanone (XV) by preparative vpc. Its infrared spectrum (liquid film) showed carbonyl peaks at 1730 (ketone) and 1642 cm^{-1} (amide). Its nmr spectrum (neat liquid) included peaks at τ 5.98 (singlet, two protons, O=C—CH_2N<), 6.70 (triplet, two protons, >NCH_2Pr), 7.66 (complex, four protons, EtCH_2—C=O and CH_3CH_2C=O), and 8.55 (complex, six protons, O=$CCH_2CH_2CH_3$ and -$CH_2CH_2CH_2CH_3$) ppm. Peaks appeared in the mass spectrum at *m/e* 214 (mol wt + 1), 213 (mol wt), 184 (mol wt − Et), 156 (mol wt − EtCO or Bu), and 142 (mol wt − PrCO).

Anal. Calcd for $C_{12}H_{23}NO_2$: N, 6.57. Found: N, 6.24.

Ozonation of Tri-*n*-butylamine (IV).—A solution of 4 g (21.6 mmol) of tributylamine (IV) in 50 ml of the solvent was treated with 1 mol equiv of ozone from an ozone–nitrogen mixture at −45°. The ozone absorption was quantitative. The reaction mixture was allowed to warm to room temperature and was analyzed for aldehydes by vpc. If the solvent was pentane, the reaction mixture was then extracted with three 15-ml portions of water. When the solvent was methanol, chloroform, methylene chloride, or carbon tetrachloride, the solvent was first removed under reduced pressure and 50 ml of pentane was added before the water extraction. Otherwise the separation of amine oxide from other products was incomplete. The water extract was diluted to 50 ml. The aqueous solution (5 ml) was used for the amine oxide determination by the titanium chloride method.[10] In those cases where the original solvent was a chlorinated hydrocarbon, 5 ml of the aqueous solution was used for the amine hydrochloride (ammonium salt) determination, by titration with 0.1 *N* silver nitrate solution after addition of 0.5 ml of saturated sodium bicarbonate solution and some potassium chromate indicator. The remaining water extract was made basic with sodium hydroxide and continuously extracted with ether for 24 hr. Analysis of the ether extract by vpc showed largely dibutylamine. The basic extract was acidified with hydrochloric acid and continuously extracted with ether for 24 hr. The ether extract was analyzed for carboxylic acids by vpc. The pentane layer was analyzed by vpc for the other volatile products and unreacted tributylamine.

Ozonation of 1-di-*n*-butylamino-2-butanone (XV) was carried out in the same manner as described for tributylamine.

Registry No.—IV, 102-82-9; XV, 16656-38-5; XXII, 16656-39-6; XXIV, 16656-40-9.

Acknowledgment.—The authors are grateful for grants from the National Science Foundation and the Robert A. Welch Foundation which made this work possible.

Ozonation of Amines. III. *t*-Butylamine[1]

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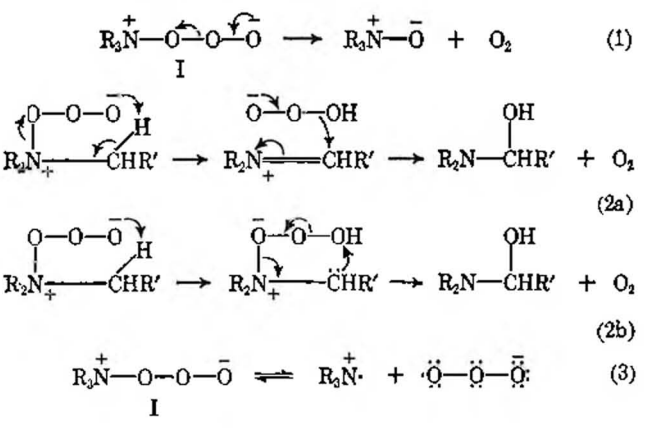
Received January 31, 1968

Ozonation of *t*-butylamine in chlorinated solvents gave as major products *t*-butylammonium chloride, 2-methyl-2-nitropropane, and *t*-butyl isocyanate. In isooctane, the nitroalkane and azoxyisobutane were produced, along with 2,4,4-trimethyl-2-pentanol. All amine ozonations were carried out under conditions whereby neither ozone nor the amine alone reacted appreciably with the solvent. The results are explained in terms of an initial electrophilic ozone attack on the amine to give an adduct which can either lose molecular oxygen or dissociate to nitrogen cation radicals and the ozonate anion radical.

In the preceding paper[1] of this series, evidence was presented to show that the competition observed between amine oxide formation and side-chain oxidation during ozonation of certain tertiary amines involves two competing fates of an initial amine–ozone adduct (I), as illustrated in eq 1 and 2a or b. In the first paper of the series[2] a third fate of adduct I was proposed, namely, dissociation into nitrogen cation radicals and the ozonate anion radical (eq 3), followed by further reactions of these species. The formation of Wurster's salts by ozonation of phenylene diamines[3] and of ammonium ozonate by ozonation of liquid ammonia[4] are apparent examples of this reaction course open to I.

To gain further information concerning the possibility of the fate of I exemplified by eq 3, the ozonation of *t*-butylamine in several different solvents was studied. In this case there is little possibility of the occurrence of routes 2, since they would have to involve a β position. The principal competition, therefore, should be between the reactions described by eq 1 and 3.

Since our first report on this work, at the International Oxidation Symposium in 1967,[2] Bachman and Strawn[5] have reported the oxidation of several different primary amines to the corresponding nitro compounds by means of ozone. The present paper describes a more thorough study of a primary amine in which all products are described and reasonable reaction paths thereto suggested. Together, these two works constitute the first detailed study of the ozonation of primary amines.[6]



Experimental Section

Equipment and Procedures.—The ozonation setup and procedures, using ozone–oxygen or ozone–nitrogen, and the method of determining molecular oxygen yields are described in earlier

(1) For paper II of this series, see P. S. Bailey, D. A. Mitchard, and A. Y. Khashab, *J. Org. Chem.*, **33**, 2675 (1968).

(2) P. S. Bailey, J. E. Keller, D. A. Mitchard, and H. M. White, Advances in Chemistry Series, American Chemical Society, Washington, D. C., in press; paper presented at the International Oxidation Symposium, San Francisco, Calif., Aug 1967.

(3) R. W. Layer, *Rubber Chem. Technol.*, **39**, 1584 (1966).

(4) I. J. Solomon, K. Hattori, A. J. Kacmarek, G. M. Platz, and M. J. Klein, *J. Amer. Chem. Soc.*, **84**, 34 (1962).

(5) G. B. Bachman and K. G. Strawn, *J. Org. Chem.*, **33**, 313 (1968).

(6) For a historical background, see ref 1 and 5 and P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

TABLE I
OZONATION OF *t*-BUTYLAMINE IN VARIOUS SOLVENTS

Expt	Amine,[a] mmol	O_3,[b] mmol Passed	O_3,[b] mmol Reacted	Solvent (ml)	Temp, °C	O_2 evolved, mmol	*t*-BuNO$_2$ mmol	*t*-BuNO$_2$ Yield, %	*t*-BuN=C=O mmol	*t*-BuN=C=O Yield, %	*t*-BuNH$_3^+$Cl$^-$ mmol	*t*-BuNH$_3^+$Cl$^-$ Yield, %	Total yield, %
1	5	6.1	3.9	$CHCl_3$ (50)	−60	3.5	0.9	18	0.8	16	3.2	64	98
2	5	6.0	4.2	$CHCl_3$ (25)	−65	...	0.9	18	0.9	18	3.0	60	100[c]
3	5	6.0	4.9	CH_2Cl_2 (50)	−78	4.5	1.5	30	0.5[d]	10	2.9	58	98
4	20	30	27.9	CH_2Cl_2 (50)	−70	...	5.9	30	1.5	8	10.9	55	93
5	20	40	40	CCl_4 (50)	−20	...	8.9	45	2.5[d]	13	6.2	31	89
6	20	45	43.4	CCl_4 (50)	−20	...	8.5	43	2.0[d]	10	5.5	28	81
7	10	30	23.6	CH_3Cl (25)	−70	...	3.6	36	0.2	2	2.1	21	59
8	2.5	6.2	6.2	Isobutane (10)	−78	...	1.1	44[e]	...	...	...	...	44
9	3	9.6	8.1	Isooctane (25)	−78	...	1.8	60[f]	...	...	...	...	104[f]

[a] Preliminary studies indicated that all of the amine reacted under the conditions used and yields of products were calculated on this basis. [b] In all experiments except 9, ozone–nitrogen streams were employed. The amount reacted is amount passed minus that appearing in KI trap. [c] In addition 2% acetone, 1% *t*-butyl alcohol, and 1% isobutane were produced. [d] From one-third to one-half of this material was actually N,N′-di-*t*-butylurea, but the yield was calculated on basis of isocyanate. [e] *t*-Butyl alcohol (0.7 mmole) also was a product. [f] Other products were 2,4,4-trimethyl-2-pentanol (0.34 mmol) and azoxyisobutane (XV, 0.66 mmol or 44%). The determination of XV was crude, explaining the higher than 100% total yield.

publications.[7] Vpc determinations in most cases were carried out on a F & M Model 500 gas chromatograph using a 0.25 in. × 20 ft column of 20% Carbowax 20M on Chromosorb P. In one case (expt 2, Table I) an Aerograph 1520B chromatograph with an 0.125 in. × 20 ft 20% Carbowax 20M column was employed. A column temperature of 75° was used for *t*-butyl isocyanate (XI), acetone (shoulder on isocyanate peak), *t*-butyl alcohol, nitrosoisobutane (IV), and isobutane, whereas 125° was used for nitroisobutane (V) and azoxyisobutane (XV). Yields were determined on the F & M chromatograph by comparison with standard solutions of known compounds. With the Aerograph 1520B, an internal standard of benzene was used at 75° and a standard of *p*-xylene was used at 125°. For preparative chromatography an Aerograph 90-P3 chromatograph and a 0.375 in. × 20 ft 30% Carbowax 20M column were employed. Nmr spectra were obtained with a Varian Associates A-60 spectrometer, using a tetramethylsilane internal standard.

Materials.—Distillation Products No. 6772 *t*-butylamine was dried over potassium hydroxide pellets and distilled from fresh pellets: bp 46°. *t*-Butylhydroxylamine (III),[8a] nitrosoisobutane (IV),[8b] nitroisobutane (V),[8c] *t*-butylisocyanate (XI),[9] N,N′-di-*t*-butylurea (XII),[10] and 2,4,4-trimethyl-2-pentanol[11] were prepared by known literature procedures. Solvents were pure and anhydrous.

Ozonation of *t*-Butylamine (VI).—In a typical experiment a solution of 0.365 g (5.00 mmol) of *t*-butylamine in 50 ml of chloroform was cooled to −60° and treated with an ozone–nitrogen stream containing 6 mmol of ozone; the exit gases were analyzed for molecular oxygen.[7] From the beginning of the ozonation, a slight blue color, due to nitrosoisobutane (IV), appeared but was replaced at the end of the ozonation by the purple color of unreacted ozone. A precipitate of *t*-butylammonium chloride (VIIIa and b) formed during the ozonation. The excess ozone was purged with nitrogen and the colorless solution above the precipitate was analyzed by vpc for all products except the *t*-butylammonium chloride and N,N′-di-*t*-butylurea (XII). The reaction mixture was then evaporated to dryness and the *t*-butylammonium chloride was determined by dissolving it in water and titrating for chloride ion. In those cases where the urea (XII) was a product, it was left behind when the *t*-butylammonium chloride was dissolved in water and was identified by infrared spectral comparison with a known sample. Ozonations in the other solvents were similar except that there was no salt precipitate formed in isooctane or isobutane. The results are shown in Table I.

When the pure solvents, except chloroform, were treated with ozone at the temperatures used in the amine ozonations, 99–100% of the ozone employed passed into the KI trap. A vpc determination of 25 ml of isooctane treated with 10 mmol of ozone at −78° showed nothing but isooctane. In the case of chloroform, 0.9 mmol of 5.9 mmol of ozone passed into 50 ml of solvent underwent reaction. However, in another experiment, 10 mmol of ozone was passed through 50 ml of chloroform at −60°, and the exit gases were passed into 10% sodium carbonate solution. The chloroform was then washed with the carbonate solution, which was then acidified with nitric acid and treated with silver nitrate. Only a faint turbidity was produced. Treatment of 50 ml of chloroform with 20 mmol of *t*-butylamine at either room temperature or −65° for 3 hr produced only 5 mg of *t*-butylammonium chloride. Similar treatment of carbon tetrachloride gave 6 mg of the salt at −20° and 16 mg of salt at room temperature. Collins[12] reports only a 2% yield of triethylammonium chloride from treatment of carbon tetrachloride with triethylamine at room temperature for 72 hr.

Ozonation of 25 ml of neat *t*-butylamine was carried out at −50° with 60 mmol of ozone. The reaction mixture was treated with excess hydrochloric acid, and the resulting solution was extracted with ether. The products, qualitatively identified by vpc, were nitrosoisobutane (IV), nitroisobutane (V), and azoxyisobutane (XV). The azoxyisobutane was isolated by preparative vpc: bp 148°; n^{26}D 1.4171;[13] nmr showed two peaks of equal intensity at τ 8.58 and 8.76 ppm. This was used as a standard in later vpc determinations.

Anal. Calcd for $C_8H_{18}N_2O$: C, 60.72; H, 11.47; N, 17.70; mol wt, 158. Found: C, 60.44; H, 11.21; N, 17.78; mol wt, 153.

Ozonations of *t*-butylhydroxylamine (III) and nitrosoisobutane (IV) were carried out and products were determined as described for *t*-butylamine. These results are shown in Table II.

Results and Discussion

The results of ozonation of *t*-butylamine (VI) in several different solvents are shown in Table I. The major products in the chlorinated solvents were *t*-butylammonium chloride (VIIIa and b), 2-methyl-2-nitropropane (V), and either *t*-butyl isocyanate (XI) or, sometimes, N,N′-di-*t*-butylurea (XII).

As stated in the first paper of this series,[2] the only initial reaction likely to occur between ozone (an electrophile) and an amine (a nucleophile) is formation of an adduct (I). The route from there to the nitroiso-

(7) (a) P. S. Bailey, *J. Amer. Chem. Soc.*, **78**, 3811 (1956); (b) P. S. Bailey, *J. Org. Chem.*, **22**, 1548 (1957); (c) P. S. Bailey and A. M. Reader, *Chem. Ind.* (London), 1063 (1961); (d) P. S. Bailey, P. Kolsaker, B. Sinha, J. R. Ashton, F. Dobinson, and J. E. Batterbee, *J. Org. Chem.*, **29**, 1400 (1964); (e) A. M. Reader, P. S. Bailey, and H. M. White, *ibid.*, **30**, 784 (1965).

(8) (a) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739 (1957); (b) W. D. Emmons, *ibid.*, **79**, 6522 (1957); (c) N. Kornblum, R. J. Clutter, and W. J. Jones, *ibid.*, **78**, 4003 (1956).

(9) B. Brauner, *Chem. Ber.*, **12**, 1874 (1879).

(10) N. Bortnick, L. S. Luskin, M. D. Hurwitz, and A. W. Rytina, *J. Amer. Chem. Soc.*, **78**, 4358 (1956).

(11) J. J. Ritter, *ibid.*, **70**, 4253 (1948).

(12) R. F. Collins, *Chem. Ind.* (London), 704 (1957).

(13) J. P. Freeman [*J. Org. Chem.*, **28**, 2508 (1963)] reports bp 50° (20 mm) and n^{20}D 1.4208.

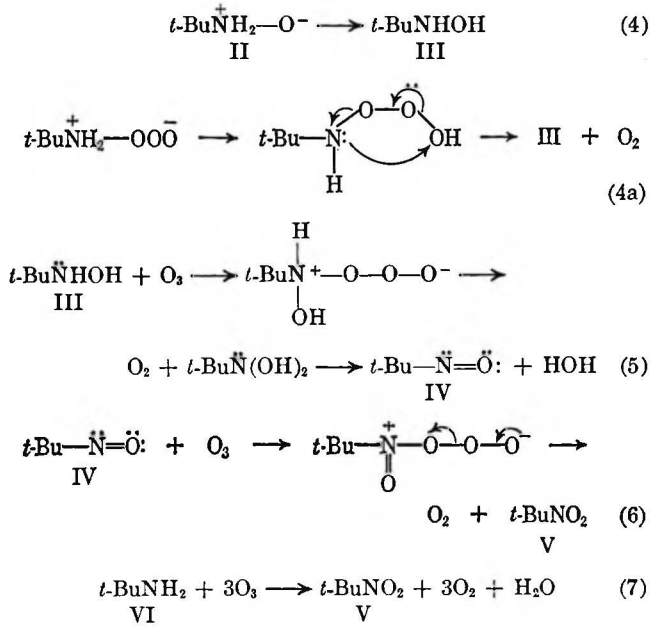
TABLE II

OZONATION OF *t*-BUTYLHYDROXYLAMINE (III) AND NITROSOISOBUTANE (IV)

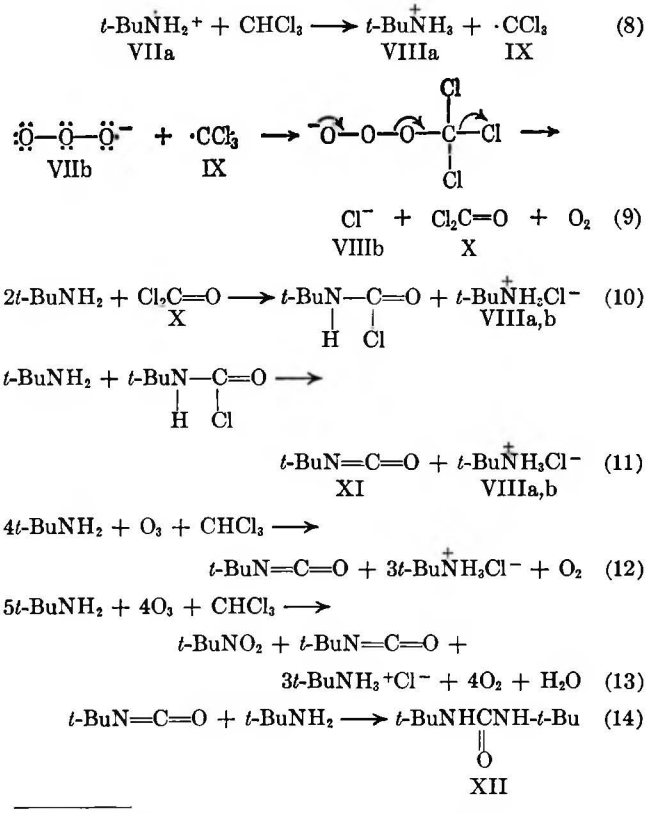
Compd ozonized	Compd, mmol	—O_3,[a] mmol— Passed	Reacted	Solvent (ml)	Temp, °C	O_2 evolved, mmol	—*t*-$BuNO_2$— mmol	Yield, %	Other products	Total yield, %	O_3[b]/ S.M.	O_2[c]/ *t*-$BuNO_2$
III	2.5	6.0	3.8	CH_2Cl_2 (50)	−50	2.6	1.2	48	*t*-$BuNH_2OH$ Cl^- 35%	83	1.5	2.2
III	2.3	5.0	3.8	CCl_4 (50)	−18	3.9	1.7	74		74	1.7	2.3
III	2.5	6.0	4.4	Isooctane[d] (100)	−60	4.4	2.3	92		92	1.8	1.9
IV	2.0	3.0	1.4	Isooctane (50)	−78	1.4	1.8	90	Some unreacted IV	90	0.7	0.8

[a] From an ozone–nitrogen stream. [b] Millimoles of ozone to millimoles of starting material (S.M.) reacting. [c] Millimoles of oxygen evolved to millimoles of nitroisobutane obtained. [d] More than the usual amount of solvent was necessary because of solubility difficulties.

butane (V) in all solvents should logically involve the reaction course described by eq 1. Since, however, the amine oxide produced in this case (II) is primary, it is not stable and most likely rearranges to a hydroxylamine (III). A similar set of reactions should convert III into the nitrosoisobutane (IV) and IV into the nitroisobutane (V). These reactions, described by eq 1 and 4–6 are summed up in eq 7. An alternative to the reactions of eq 1 and 4 is shown by eq 4a. Results from separate ozonations of *t*-hydroxylamine (III) and nitrosoisobutane (IV), shown in Table II, are in agreement with this reaction scheme, as are the facts that the blue color of the nitroso compound (IV) was observed throughout most of each ozonation and that IV was identified by vpc as a product of the ozonation of neat *t*-butylamine.

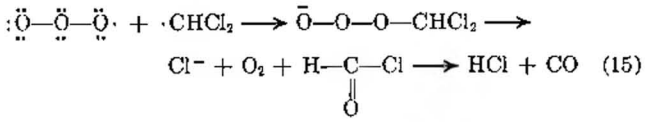


It was shown in separate experiments that at the ozonation reaction temperatures no appreciable amount of hydrogen chloride was produced by passage of ozone through the solvents in the absence of the amine, nor was any appreciable amount of ammonium salt (VIIIa and b) produced by reaction of the amine with the solvent in the absence of ozone, even at room temperature. Thus, the logical route to *t*-butylammonium chloride (VIIIa and b) is *via* nitrogen cation radical (VIIa) and the ozonate anion radical (VIIb) produced in minute equilibrium amounts through dissociation of the amine–ozone adduct (eq 3). In the case of chloroform solvent, the proposed reaction course is shown by eq 3 and 8–11 and is summed up in eq 12. Nitrogen cation radical VIIa stabilizes itself by abstraction of hydrogen from a solvent molecule to give ammonium cation VIIIa and solvent radical IX, (eq 8). The ozonate anion radical (VIIIb) and the solvent radical (IX) then interact to give chloride anion (VIIIb) and phosgene (X, eq 9). Phosgene and *t*-butylamine interact to produce *t*-butyl isocyanate (XI) and additional salt *via* reactions 10 and 11. This reaction was verified in a separate experiment at the ozonation temperature. Only at room temperature is the isocyanate (XI) converted into N,N-di-*t*-butylurea (XII, eq 14) by excess *t*-butylamine. Equation 13 is a summation of 7 and 12, assuming the two fates of the amine–ozone adduct (I) to occur equally. The fact that the results of expt 1 and 2 of Table I agree well with the stoichiometry of eq 13 increases confidence in the validity of the mechanism. The production of ammonium salts by ozonation of amines in chloroform has been reported previously,[14,15] but it was not shown that such did not arise either by action of the amine on the solvent or through oxidation of the solvent by ozone.



(14) W. Strecker and M. Baltes, *Chem. Ber.*, **54**, 2693 (1921).
(15) G. P. Shulman, *Can. J. Chem.*, **43**, 3069 (1965).

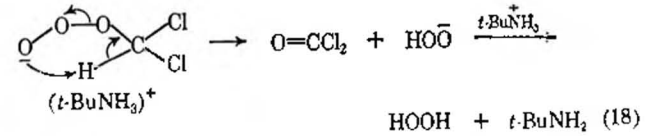
The results from the other chlorinated solvents are more difficult to interpret, especially in regard to the production of the isocyanate (XI) or the urea (XII) in the methylene chloride and methyl chloride reactions. However, if it is assumed that the major reactions occurring are analogous to those suggested for chloroform, reasonable correlations with experimental results can be obtained. For methylene chloride, the over-all reaction analogous to reaction 12 is represented by eq 17, which is a summation of eq 3, the analog of 8 (to give $\cdot CHCl_2$), 15, and 16.



$$t\text{-BuNH}_2 + HCl \longrightarrow t\text{-Bu}\overset{+}{\underset{\cdot\cdot}{N}}H_3Cl^- \quad (16)$$

$$2t\text{-BuNH}_2 + O_3 + CH_2Cl_2 \longrightarrow 2t\text{-Bu}\overset{+}{\underset{\cdot\cdot}{N}}H_3Cl^- + O_2 + CO \quad (17)$$

A likely explanation for the formation of *t*-butyl isocyanate (XI) in the methylene chloride reaction is *via* eq 18 followed by 10 and 11.[16] A summation of these with eq 17 and two times eq 7 gives eq 19, which fits the data of expt 3 and 4 of Table I reasonably well.



$$HOOH + t\text{-BuNH}_2 \quad (18)$$

$$7t\text{-BuNH}_2 + 8O_3 + 2CH_2Cl_2 \longrightarrow 2t\text{-BuNO}_2 + 4t\text{-Bu}\overset{+}{\underset{\cdot\cdot}{N}}H_3Cl^- + t\text{-BuN=C=O} + 7O_2 + CO + H_2O_2 + 2H_2O \quad (19)$$

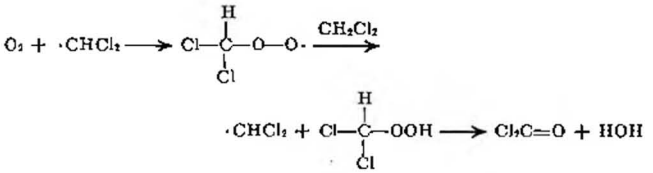
For the ozonation in methyl chloride the reaction analogous to those represented by eq 12 and 17 is described by eq 20. Although the results in methyl chloride are far from quantitative, reaction 7 appears to be twice as important as reaction 20. Such a summation gives eq 21, which at least fits the amine–ozone stoichiometry of expt 7, Table I. The isocyanate obtained in the methyl chloride experiment must have come from chloroform, methylene chloride, or carbon tetrachloride impurities.

$$t\text{-BuNH}_2 + O_3 + CH_3Cl \longrightarrow t\text{-BuNH}_3{}^+Cl^- + O_2 + H_2C{=}O \quad (20)$$

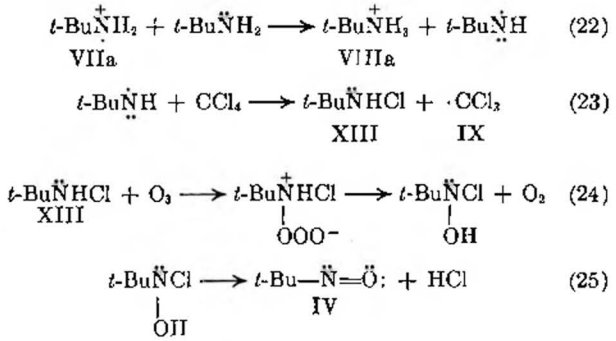
$$3t\text{-BuNH}_2 + 7O_3 + CH_3Cl \longrightarrow 2t\text{-BuNO}_2 + t\text{-Bu}\overset{+}{\underset{\cdot\cdot}{N}}H_3Cl^- + 7O_2 + 2H_2O + H_2C{=}O \quad (21)$$

The reactions in carbon tetrachloride leading to the ammonium salt are, of necessity, somewhat different from those in the other chlorinated solvents, since the nitrogen cation radical (VIIa) from eq 3 must find some source of hydrogen other than the solvent, presumably

(16) An alternative explanation for the formation of phosgene is shown by the following equation, suggested by the work of J. I. G. Cadogan, D. H. Hey, and P. G. Hibbert, *J. Chem. Soc.*, 3939 (1959).



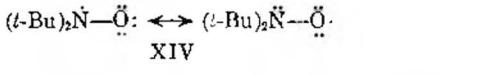
another amine molecule as shown in eq 22. There are, of course, several possible routes from this point on to products. The one most attractive to us is similar to the mechanistic course suggested by Lautenberger, *et al.*,[17] for the photochemical reaction of amines with carbon tetrachloride. It is described by eq 23, 9, 24, 25, 16, 10, 11, and 6. One difference in our scheme and that of Lautenberger, *et al.*, is that species XIII cannot react in the same way as proposed by the other authors since the alkyl group in XIII is tertiary. We suggest that it is attacked by ozone to give nitrosoisobutane (IV) as is shown in eq 24 and 25. A summation of the above equations with eq 3 provides eq 26. If this occurs to the extent of 20% and eq 7 to 80%, the result is eq 27, which fits fairly well the data of expt 5, in which 89% of the starting amine was accounted for. There obviously are other competing reactions leading to these and other products which prevent better agreement between our results and eq 27.



$$6t\text{-BuNH}_2 + 3O_3 + CCl_4 \longrightarrow t\text{-BuNO}_2 + 4t\text{-Bu}\overset{+}{\underset{\cdot\cdot}{N}}H_3Cl^- + t\text{-BuN=C=O} + 3O_2 \quad (26)$$

$$10t\text{-BuNH}_2 + 15O_3 + CCl_4 \longrightarrow 5t\text{-BuNO}_2 + 4t\text{-Bu}\overset{+}{\underset{\cdot\cdot}{N}}H_3Cl^- + t\text{-BuN=C=O} + 15O_2 + 4H_2O \quad (27)$$

In addition to the major products already discussed, small amounts of di-*t*-butyl nitroxide (XIV),[18] acetone, *t*-butyl alcohol, and isobutane also were obtained from ozonation of *t*-butylamine in the chlorinated solvents. Details of the production of these substances and results of ozonation of XIV will be given in a later paper.



Ozonation of *t*-butylamine in isobutane and isooctane gave largely the nitroisobutane (V, eq 7). The best results were obtained in isooctane (expt 9, Table I) from which azoxyisobutane (XV) also was isolated. This probably arises from interaction of *t*-butylhydroxylamine and nitrosoisobutane (eq 28). This summed with twice eq 1 and 4, eq 5, and two times eq 7 gives eq 29, which fits fairly well the stoichiometry of expt 9. The extra ozone reacting accounts for the alcohol side product (also found in expt 8). Since there was no apparent reaction between ozone and the solvent alone at the reaction temperature of expt 8 and 9 of Table I, we suggest eq 3 and 30–32 as the origin of the

(17) W. J. Lautenberger, E. N. Jones, and J. G. Miller, *J. Amer. Chem. Soc.*, **90**, 1110 (1968).

(18) (a) A. K. Hoffmann, W. G. Hodgson, D. L. Maricle, and W. H. Jura, *ibid.*, **86**, 631 (1964); (b) G. Chapelet-Letourneux, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, 3283 (1965).

alcohol products. It is noteworthy that, although the amine plays a prominent role in this oxidation of the alkane, it is not used up in the series of reactions.

$$t\text{-BuNHOH} + t\text{-BuN=O} \longrightarrow t\text{-BuN=}\overset{+}{\underset{\underset{\underset{\text{XV}}{\text{O}^-}}{|}}{\text{N}}}\text{-}t\text{-Bu} + \text{H}_2\text{O} \quad (28)$$

$$4t\text{-BuNH}_2 + 9\text{O}_2 \longrightarrow$$

$$2t\text{-BuNO}_2 + t\text{-BuN=}\overset{+}{\underset{\underset{\text{O}^-}{|}}{\text{N}}}\text{-}t\text{-Bu} + 4\text{H}_2\text{O} + 9\text{O}_2 \quad (29)$$

$$t\text{-Bu}\overset{+}{\text{N}}\text{H}_2 + \text{RH} \longrightarrow t\text{-Bu}\overset{+}{\text{N}}\text{H}_3 + \cdot\text{R} \quad (30)$$
VIIa

$$\text{R}\cdot + \cdot\text{O}_3^- \longrightarrow \text{ROOO}^- \longrightarrow \text{RO}^- + \text{O}_2 \quad (31)$$

$$\text{RO}^- + t\text{-Bu}\overset{+}{\text{N}}\text{H}_3 \longrightarrow \text{ROH} + t\text{-BuNH}_2 \quad (32)$$

Thus, the results of ozonation of *t*-butylamine in the various solvents furnish strong evidence for two different fates of an initial amine–ozone adduct, as summarized by general eq 33. The results in carbon tetrachloride, in which an ammonium salt is produced even though the solvent does not contain hydrogen, and in isooctane, in which the solvent is converted into an alcohol even though it does not react with ozone alone, constitute especially strong evidence for nitrogen cation radical intermediates. The dissociation of I to cation and anion radicals, however, appears to become important only if the nitrogen cation radical is stabilized by resonance, as with Wurster's salts,[3] or can readily abstract a hydrogen atom from its environment.

$$\text{R}_3\overset{+}{\text{N}}\text{-}\bar{\text{O}} + \text{O}_2 \longleftarrow \underset{\text{I}}{\text{R}_3\overset{+}{\text{N}}\text{-OO}\bar{\text{O}}} \rightleftharpoons \text{R}_3\overset{+}{\text{N}}\cdot \cdot\ddot{\text{O}}\text{-}\ddot{\text{O}}\text{-}\ddot{\text{O}}\text{:}$$

Registry No.—III, 16649-50-6; IV, 917-95-3; VI, 75-64-9; XV, 16649-52-8.

Acknowledgments.—This work was supported by grants from the National Science Foundation, the Robert A. Welch Foundation, and the Petroleum Research Fund of the American Chemical Society, for which the authors are very grateful.

Regiospecificity. A Useful Terminology in Addition and Elimination Reactions[1]

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Received January 22, 1968

The prefix *regio* is proposed to complement that of *stereo* to describe orientational or directional preference in reaction specificity and selectivity involving bond making or breaking. Examples of regiospecific and regioselective additions, eliminations, ring opening, and cycloadditions are discussed.

The terms stereospecificity and stereoselectivity[2] are deeply entrenched in the chemical vocabulary, particularly in that of the organic chemist. While these terms are useful in describing stereochemical preference in organic reactions, namely, the propensity to a certain relative spatial arrangement of reacting groups (*e.g. cis* or *trans* additions), there seems to be no general term in use for describing selectivity or specificity of orientational or directional preference in chemical reactions.

For instance the addition of an unsymmetrical reagent X–Y to an unsymmetrical olefin RCH=CH_2 often occurs in a highly specific manner, with one segment of the reagent (*i.e.*, X) being directed to assume one of two possible positions in the final product (eq 1 and 2).

$$\text{RCH=CH}_2 + \text{X-Y} \longrightarrow \underset{\text{Y}\quad\text{X}}{\text{RCH—CH}_2} \quad (1)$$

or

$$\underset{\text{X}\quad\text{Y}}{\text{RCH—CH}_2} \quad (2)$$

The problem is a general one, namely, that of describing the preferential making or breaking of bonds in one of two possible orientations.

We have proposed that the course of such reactions be referred to as *regiospecific*,[3] the term being derived from the latin ward *regio* denoting direction. Regiospecificity then refers to the directional preference of bond formation. If a reaction proceeds without skeletal rearrangement to give exclusively (within experimental error) one of two or more possible isomers, it is called *regiospecific*. If there is a significant preponderance of one isomer formed it is said to be *regioselective*.[4] A nearly equimolar isomer distribution is the result of a *nonregiospecific* reaction.

These terms are useful not only in addition reactions but equally in a variety of chemical processes including eliminations, ring opening, and cycloaddition reactions as illustrated below.

Although regiospecificity, like stereospecificity, describes an important characteristic of reactions by itself, selected modifying terms can greatly enhance the definition of such reactions. The terms Markovnikov[5] and anti-Markovnikov to modify the type of regiospecificity are archaic and sometimes inadequate. For instance the ionic addition of hydrobromic acid to

(1) Stereochemistry. XXXIV. For paper XXXIII, see F. W. Fowler and A. Hassner, *J. Amer. Chem. Soc.*, **90**, 2875 (1968).

(2) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., New York, N. Y., 1962.

(3) (a) A. Hassner, and F. Boerwinkle, *J. Amer. Chem. Soc.*, **90**, 216 (1968). (b) The pronunciation *reejio* is proposed. (c) The need for such a term has recently also been recognized by H. G. Viehe [*Angew. Chem. Intern. Ed. Eng.*, **6**, 767 (1967)] who proposed the slightly more cumbersome term directiospecific.

(4) Unlike in stereospecificity where one is faced with the problem of two isomeric substrates leading to the same product, in regiospecificity one deals with only one substrate leading to two (or more) possible regioisomers. This permits the designation regioselectivity to be used for partial regiospecificity.

(5) V. W. Markovnikov, *Compt. Rend.*, **81**, 668 (1875).

styrene follows Markovnikov's rule (eq 3). It is not clear whether HBr addition to ethyl vinyl ketone (eq 4)[6] should be said to be anti-Markovnikov or

$$C_6H_5CH{=}CH_2 + HBr \longrightarrow C_6H_5\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 \qquad (3)$$

$$C_2H_5\overset{\displaystyle O}{\overset{\|}{C}}CH{=}CH_2 + HBr \longrightarrow C_2H_5\overset{\displaystyle O}{\overset{\|}{C}}CH_2\underset{\displaystyle Br}{\underset{|}{C}}H_2 \qquad (4)$$

whether the rule should be modified to take account of the stability of intermediate carbonium ions rather than the attachment of H^+ to the less substituted carbon. If specificity exists in additions to olefins of type 1 (as ineq 9), then Markovnikov's rule breaks down completely.

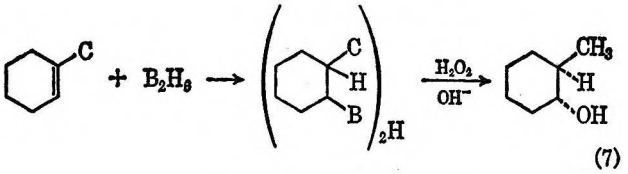
We feel it desirable that an empirical classification of orientations be employed and that the terms be chosen without knowledge of the mechanistic pathway.

As modifying terms in regiospecific addition reactions the indication of two vicinal groups in the product (one derived from the reagent and one from the unsaturated substrate—in that order) is proposed. Thus eq 3 shows Br–phenyl regiospecificity and eq 4 shows H–carbonyl[7] regiospecificity.

Further illustrations are given by the S–H regiospecific nucleophilic addition of thioalkoxide to acetylenes[8] (eq 5), the Br–phenyl regiospecific free-radical addition of bromine azide[3] (eq 6), and the H–CH_3 regiospecific hydroboration of methylcyclohexene[9] (eq 7).

$$C_6H_5C{\equiv}CH + CH_3SNa \longrightarrow C_6H_5CH{=}CHSCH_3 \qquad (5)$$

$$C_6H_5CH{=}CH_2 + BrN_3 \xrightarrow{N_3\cdot} C_6H_5\underset{\displaystyle Br}{\underset{|}{C}}HCH_2N_3 \qquad (6)$$



(7)

The advantage of this convention is that mechanistic interpretations can be added if desired. Thus, the N_3-butyl regiospecificity in IN_3 addition to 1-hexene[10] (eq 8) is attributable to electronic factors whereas the I-*t*-butyl regiospecificity[11] in eq 9 is sterically controlled (and may be termed sterically regiospecific).

$$n\text{-Bu}{-}CH{=}CH_2 + IN_3 \longrightarrow n\text{-Bu}{-}\underset{\displaystyle N_3}{\underset{|}{C}}H{-}\underset{\displaystyle I}{\underset{|}{C}}H_2 \qquad (8)$$

$$t\text{-Bu}{-}CH{=}\underset{1}{C}HCH_3 + IN_3 \longrightarrow t\text{-Bu}{-}\underset{\displaystyle I}{\underset{|}{C}}H{-}\underset{\displaystyle N_3}{\underset{|}{C}}HCH_3 \qquad (9)$$

This terminology can also be used profitably in elimination reactions. Thus, if elimination of HBr from 2 occurs preferentially in one of the two possible directions,[12] the reaction is said to be regioselective.

(6) M. M. Maire, *Bull. Chem. Soc. Fr.*, [4] **3**, 281 (1908).

(7) Br–H regiospecificity is equally valid.

(8) W. E. Truce and J. A. Simms, *J. Amer. Chem. Soc.*, **78**, 2756 (1956).

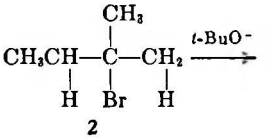
(9) H. C. Brown, "Hydroboration," W. A. Benjamin Inc., New York, N. Y., 1962.

(10) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, **89**, 2077 (1967).

(11) A. Hassner and F. W. Fowler, *J. Org. Chem.*, **33**, 2686 (1968).

(12) H. C. Brown and I. Montani, *J. Amer. Chem. Soc.*, **78**, 4112 (1953).

For such reactions we prefer the well-established modifying terms *Saytzeff* and *Hofmann*.[13] If elimination of HX proceeds in the direction of the more substituted olefin, the reaction may be said to be Saytzeff regiospecific. Preferential elimination to the less substituted olefin, *e.g.*, eq 10, is Hofmann regioselective.

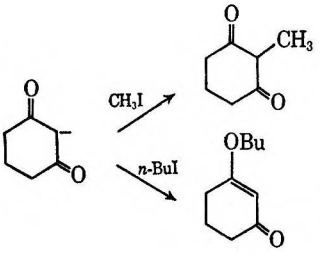


2

$$\underset{72\%}{CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2} + \underset{28\%}{CH_3CH{=}\overset{\displaystyle CH_3}{\overset{|}{C}}CH_3} \qquad (10)$$

The concept of regiospecificity can be usefully employed in an even wider sense. Unique modifying terms can be used in describing particular reactions, some examples of which follow.

Reactions of ambident ions can be described in this context. Thus, eq 11 is a C-regiospecific alkylation, while 12 is O regioselective.[14] Using inorganic ions as an example, the displacement of alkyl halides with nitrite ion can be N over O regioselective.[15]

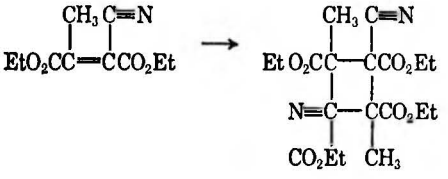


(11)

(12)

main product

Cycloadditions, dimerizations, 1,3-dipolar additions, and Diels–Alder reactions can be regiospecific or regioselective. Equation 13 is an example of a nonvicinally regiospecific dimerization.[16] Diels–Alder reactions usu-



(13)

ally are vicinally regioselective[17] (eq 14). The term vicinal is to be employed when the two identical groups or the two largest groups originally on separate molecules are found in the closest of the two possible positions in the product. Additional clarification may be

(13) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953; J. S. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co. Inc., New York, N. Y., 1956; E. S. Gould, "Mechanism and Structure in Organic Chemistry," H. Holt and Co., New York, N. Y., 1959.

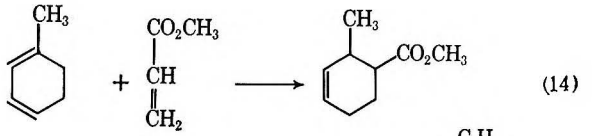
(14) H. Stetter and W. Dierichs, *Ber.*, **85**, 61 (1952).

(15) N. Kornblum, R. A. Smiley, and R. B. Blackwood, *J. Amer. Chem. Soc.*, **77**, 6269 (1955).

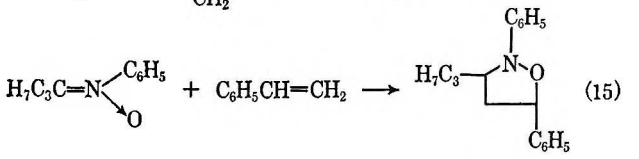
(16) C. K. Ingold, E. A. Perren, and J. F. Thorpe, *J. Chem. Soc.*, **121**, 1765 (1922).

(17) R. Huisgen, R. Grashey, and J. Sauer, "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, Inc., London, 1964, Chapter 11, p 915.

required on occasion as for the phenyl–propyl nonvicinally regiospecific dipolar addition shown in eq 15[18] below.

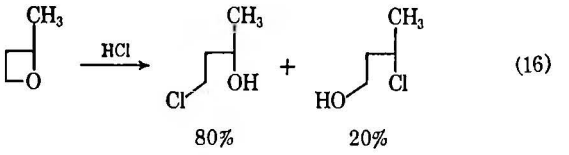


(14)



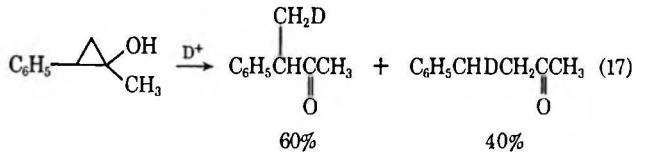
(15)

Ring-opening reactions of heterocycles such as aziridines, epoxides, larger ring ethers, lactams, and lactones as well as of other ring compounds can occur in a regiospecific or selective manner, *i.e.*, the Cl–H over Cl–CH_3 regioselective opening of oxetanes (eq 16)[19] and the D–H over D–phenyl regioselectivity in the opening of cyclopropanols[20] (eq 17).



(16)

80% 20%



(17)

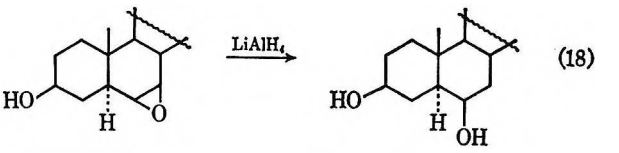
60% 40%

(18) R. Grashey, R. Huisgen, and H. Leitermann, *Tetrahedron Lett.*, 9 (1960).

(19) S. Searles, K. A. Pollart, and F. Blaock, *J. Amer. Chem. Soc.*, **79**, 952 (1957).

(20) C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *ibid.*, **88**, 3347 (1966).

Hydride opening of 6β,7β-epoxycholestane is H–(C-7) regiospecific, consistent with diaxial opening of epoxides[21] (eq 18).



(18)

Electrophilic, nucleophilic, or free-radical aromatic substitutions may be *ortho*, *meta*, or *para* regioselective.

In inorganic chemistry examples of regioselective reactions can be found among others in alkylations[22] or deuterium exchange[23] involving decaboranes and halogenation of B_5H_9.[24]

Finally the concept can be applied to positional isomerism, so that **3** and **4** can be termed regioisomers (synonymous with position isomers).[25]



3 **4**

Acknowledgment.—The author is indebted to Professors P. D. Bartlett, C. H. DePuy, A. Dreiding, E. L. Eliel, J. S. Meek, V. Prelog, J. D. Roberts, J. Sicher, and P. S. Skell for discussions and to Mr. F. Boerwinkle, F. W. Fowler, R. J. Isbister, and G. J. Matthews for valuable suggestions and discussions. This work was supported by U. S. Public Health Service Grant CA-04474 from the National Cancer Institute.

(21) E. J. Corey, *ibid.*, **76**, 175 (1954).

(22) I. Dunston, R. C. Williams, and N. J. Blay, *J. Chem. Soc.*, 5012 (1960).

(23) J. A. Dupont and M. F. Hawthorne, *J. Amer. Chem. Soc.*, **84**, 1804 (1962).

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(25) M. Svoboda, J. Zavada, and J. Sicher, *Collect. Czech. Chem. Commun.*, **32**, 2104 (1967).

A General Synthesis of Vinyl Azides from Olefins. Stereochemistry of Elimination from β-Iodo Azides[1a]

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Received January 22, 1968

Treatment with base of β-iodo azides, prepared by the addition of iodine azide to olefins, resulted generally in vinyl azides, suggesting a directive effect of the azido function. Terminal olefins, vicinally disubstituted olefins, and unsaturated carbonyl compounds all led regiospecifically to the vinyl azides. Indene, 1,2-dihydronaphthalane, cyclooctene, and 1,3-cyclooctadiene also gave the vinyl azides. However, the iodine azide adducts of cyclopentene and cyclohexene produced the allyl azides. Apparently, the stereoelectronic preference for *trans* elimination is greater than the directive effect of the azido function. An assignment of *cis* configuration to the double bond in the eight-membered-ring vinyl azides, made on the basis of nmr data, suggests *syn* elimination of hydrogen iodide in these systems. Regioselectivity in IN_3 additions to olefins is discussed.

The simplest vinyl azide, azidoethylene, was prepared by Forster and Newman[2] as early as 1910. However, since then very few vinyl azides have been reported[3] and, although some have been found to be valuable intermediates for the synthesis of 1-azirines,[4] their chemistry has not been explored very extensively. Consequently a general synthesis of vinyl azides (Table I) would be desirable for it should allow for the investigation of this relatively unknown class of com-

(1) (a) Stereochemistry. XXXV. For paper XXXIV, see A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968). (b) NASA Predoctoral Fellow, 1965–1967.

(2) M. O. Forster and S. H. Newman, *J. Chem. Soc.*, **97**, 2570 (1910).

(3) (a) J. H. Boyer and F. C. Cantes, *Chem. Rev.*, **54**, 1 (1954); (b) E. Lieber, J. S. Curtice, and C. N. R. Rao, *Chem. Ind.* (London), 586 (1966).

(4) (a) G. Smolinsky, *J. Amer. Chem. Soc.*, **83**, 4483 (1961); (b) G. Smolinsky, *J. Org. Chem.*, **27**, 3557 (1962); (c) A. Hassner and F. W. Fowler, *J. Amer. Chem. Soc.*, **90**, 2875 (1968).

TABLE I
SYNTHESIS OF ACYCLIC IODO AZIDES AND VINYL AZIDES[a]

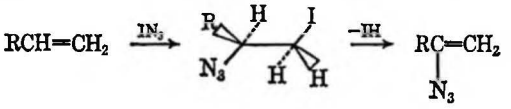
	Olefin, series a	β-Iodo azide, series b	Unsaturated azide, series c
1.	$PhCH=CH_2$	$PhCH(N_3)CH_2I$[b]	$PhC(N_3)=CH_2$[c]
2.	t-$BuCH_2CH=CH_2$	t-$BuCH_2CH(N_3)CH_2I$[d]	t-$BuCH_2C(N_3)=CH_2$
3.	t-$BuCH=CH_2$	t-$BuCH(I)CH_2N_3$[b]	t-$BuCH=CHN_3$[b]
4.	$CH_3CH=CHCH_3$ (*cis*)	$CH_3CH(N_3)CH(I)CH_3$ (*threo*)[b]	$CH_3C(N_3)=CHCH_3$ (*trans*)
5.	$(CH_3)_2CHCH=CHCH_3$ (*cis*)	$(CH_3)_2CHCH(I)CH(N_3)CH_3$[d] (*threo*)	$(CH_3)_2CHC(N_3)=CHCH_3$ (*trans*)
6.	$CH_3CH=CHCH_3$ (*trans*)	$CH_3CH(I)CH(N_3)CH_3$ (*erythro*)[b]	$CH_3C(N_3)=CHCH_3$ (*cis*)
7.	EtCH=CHEt (*trans*)	$EtCH(N_3)CH(I)Et$[d]	$EtC(N_3)=CHEt$ (*cis*)[c]
8.	$PhCH=CHCH_3$ (*trans*)	$PhCH(N_3)CH(I)CH_3$[d]	$PhC(N_3)=CHCH_3$ (*cis*)[c]
9.	t-$BuCH=CHCH_3$ (*trans*)	t-$BuCH(N_3)CH(I)CH_3$[d]	t-$BuC(N_3)=CHCH_3$ (*cis*)
10.	$CH_3CH=CHCO_2Et$ (*trans*)	$CH_3CH(I)CH(N_3)CO_2Et$	$CH_3C(N_3)=CHCO_2Et$ (*cis*)[c]
11.	$PhCH=CHCO_2CH_3$ (*trans*)	$PhCH(N_3)CH(I)CO_2CH_3$	$PhC(N_3)=CHCO_2CH_3$[c]
12.	$CH_2=CHCO_2CH_3$	$CH_2CH(N_3)CO_2CH_3$ (12b) + $CH_2CH(I)CO_2CH_3$ (13b)	$HC(N_3)=CHCO_2CH_3$[d] (12c) + $CH_2=C(N_3)CO_2CH_3$ (13c)
14.	$(CH_3)_2CHCH=CH_2$	mixture	$(CH_3)_2CHCH=CHN_3$ (14c)[d] + $(CH_3)_2CHC(N_3)=CH_2$ (15c)[d]

[a] All compounds gave nmr spectra consistent with their structure and indicative of high purity; the mass spectra of these compounds often show absence of parent peaks but are consistent with their structure. [b] See ref 5. [c] Converted into an azirine by photolysis.[4c] [d] Gave correct elemental analyses.

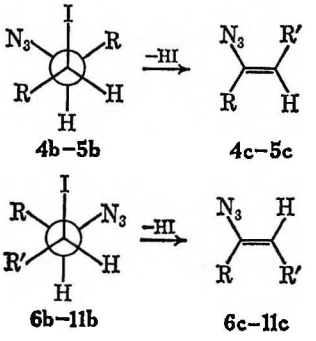
pounds and of possible nitrene intermediates as well as provide a synthesis of 1-azirines.

We have previously reported that iodine azide adds to olefins to give high yields of β-iodo azides.[5] If the elimination of hydrogen iodide occurs regiospecifically[6] in the direction of the azido function, β-iodo azides could provide a general synthesis of vinyl azides.

The addition of iodine azide usually occurred in an N_3–R regiospecific[6] manner to terminal olefins (except for **3a**, see later discussion), and elimination of hydrogen iodide with potassium *t*-butoxide in ether from these β-iodo azides presented no problem for the synthesis of 2-azido-1-alkenes (*e.g.*, **1c**, **2c**).



With vicinal iodo azides derived from internal olefins the elimination of hydrogen iodide can occur in two directions to give either the allyl azide, vinyl azide, or a mixture. Brown and coworkers[7] reported that treatment of 2-iodobutane with potassium *t*-butoxide in *t*-butyl alcohol gives 33% of 1-butene and 67% of 2-butene (*cis* and *trans*). If the azido function has little or no directive effect on the elimination of hydrogen iodide then a mixture of allyl and vinyl azide would be expected. Fortunately, the elimination of hydrogen iodide was Saytzeff regiospecific since the iodo azide adducts derived from the 2-butenes gave exclusively the vinyl azides. Moreover, the elimination was stereospecific, the iodo azides derived from *cis*-2-butene (**4a**) and *trans*-2-butene (**6a**) giving *trans*- and *cis*-2-azido-2-butenes **4c** and **6c**, respectively. Iodo azides **6b**–**11b** derived from *trans* olefins led to vinyl azides **6c**–**11c** of high purity, even



(5) F. W. Fowler, A. Hassner, L. A. Levy, *J. Amer. Chem. Soc.*, **89**, 2077 (1967).

(6) We have recently introduced the term regiospecific to denote orientationally specific reactions. See paper XXXIV.[1a]

(7) H. C. Brown and R. L. Klimisch, *J. Amer. Chem. Soc.*, **87**, 5517 (1965).

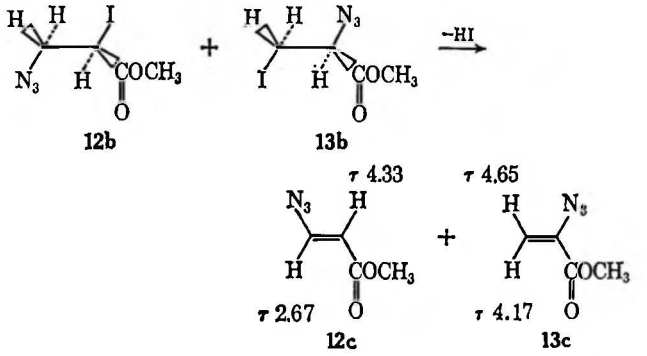
though *trans* elimination of hydrogen iodide required eclipsing of the alkyl groups in the transition state.

Trisubstituted olefins reacted with iodine azide in an electronically regiospecific manner so that the azido function occupied the tertiary position.[5] The unavailability of a hydrogen geminal to the azido function precluded the synthesis of vinyl azides from these adducts.

Iodine azide added to ethyl crotonate to give ethyl 3-azido-2-iodopropionate **10b** in good yield and elimination of hydrogen iodide gave vinyl azide **10c**. This vinyl azide appeared to be identical with that previously prepared by another route by Harvey and Ratts.[8]

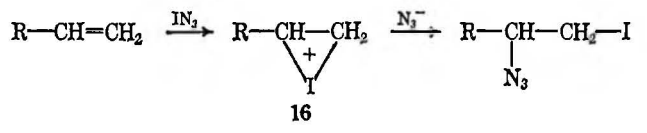
Owing to complications, such as ester cleavage, potassium *t*-butoxide proved to be unsatisfactory for the elimination of hydrogen iodide in these systems. We have observed that the elimination can be carried out very efficiently using 1,4-diazabicyclo[2.2.2]octane (DABCO) in acetone.

The addition of IN_3 to methyl acrylate (**12a**) proceeded in good yield to a mixture of **12b** and **13b** from which elimination of hydrogen iodide gave a mixture of vinyl azides **12c** and **13c**. This conclusion was based on the appearance of two typical absorptions in its nmr spectrum. One, centered at τ 3.56 (J = 14 Hz), accounted for *ca.* 12% of the total product and is attributed to **12c**. The other, centered at τ 4.40 (J = 1.6 Hz), accounted for the remaining 88% and arises from structure **13c**. The possibility that the eliminated product was just a *cis–trans* mixture is unlikely since a coupling constant of only 1.6 Hz would be too small for either the *cis* or the *trans* compound. However,



this coupling constant is consistent with the nonequivalent geminal vinylic protons of vinyl azide **13c**. Vinyl azides **12c** and **13c** were separated by chromatography over alumina.

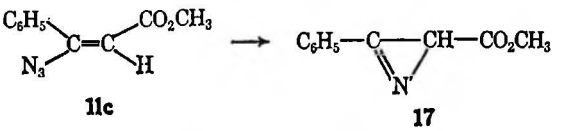
The regiospecific addition of IN_3 to terminal olefins most likely involves the intermediacy of a three-membered ring iodonium ion **16** that is opened at the more substituted carbon for electronic reasons.[5] When R is alkyl or phenyl, inductive effects would be expected to stabilize an incipient positive charge better at the secondary than at the primary carbon in **16**. The



opposite should be true in case of carbonyl substituents which destabilize an adjacent positive center. Accordingly, iodine azide addition to ethyl crotonate gave **10b** exclusively. The regioselective, although not specific, addition of iodine azide to methyl acrylate, appears to constitute an exception. Possibly the preferential formation of **11** can be accounted for in terms of the well-known ease of biomolecular displacement of α halogen in α-halo ketones and esters. This reflects the dual nature of the iodonium ion. That is, while being an ionic species, its ring opening resembles to a certain extent a nucleophilic displacement reaction. On the other hand, ionic addition of hydrogen halides to methyl acrylate give exclusively the β-halo adduct.

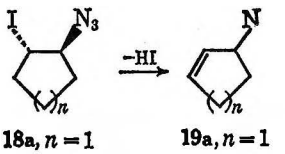
The importance of steric factors in controlling the regioselectivity of IN_3 additions may be seen by comparing the conversion of 3-*t*-butyl-1-propene (**2a**) into **2b** with the conversion of *t*-butylethylene (**3a**) into **3b**. This complete reversal of regiospecificity can be attributed to steric effects in the opening of **16**. Similar steric control on the regiochemistry of addition is seen in the orientation of **5b** and **9b** as opposed to **8b**. The steric effect of the isopropyl group in **14a** is not sufficient to cause I–*i*-Pr regiospecific addition. The nmr spectrum of the dehydroiodination product indicates the presence of 36% of **14c** and 64% of **15c**. The mixture of the two vinyl azides analyzed correctly. If the electronic effects are balanced by symmetrical dialkyl substitution as in olefin **5a** then the steric effect of the isopropyl group becomes dominant and the addition is I–*i*-Pr regiospecific.

Although iodine azide adds well to conjugated carbonyl compounds in general, the vinyl azide can not always be isolated. For example, we have reported[5] that when 2-iodo-3-azido-3-phenylpropiophenone was treated with DABCO only 3,5-diphenylisoxazole was obtained. However, when methyl 2-iodo-3-azido-3-phenylpropionate was treated with DABCO at 5° it does give the vinyl azide **11c**, as evidenced by the ir and nmr spectrum of the crude product. This vinyl azide could not be isolated because it rapidly lost nitrogen at room temperature giving the 1-azirine **17**.[4c]



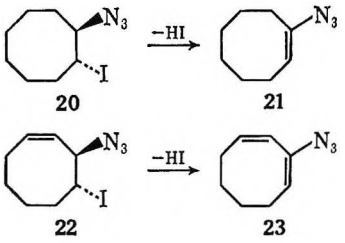
Since the starting methyl cinnamate possessed *trans* stereochemistry, its IN_3 adduct was the *erythro* isomer which on *trans* elimination of hydrogen iodide gave the *cis*-vinyl azide **11c**. The instability of these vinyl azides is probably due to the presence of large or polar *cis* substituents. *cis*-Azidostilbene derived from the iodo azide adduct of *trans*-stilbene[5] is likewise unstable at 0°. If this is the situation, then possibly stable vinyl azides with large substituents could be obtained if the starting olefin has *cis* stereochemistry. This problem is presently under investigation.

Unfortunately, the iodo azides derived from simple cyclic olefins do not yield vinyl azides; instead allyl azides **19** are obtained. Here the stereoelectronic



(8) G. R. Harvey and K. W. Ratts, *J. Org. Chem.*, **31**, 3907 (1966).

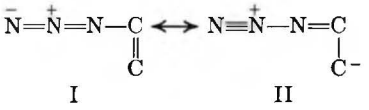
preference for *trans* elimination is greater than the directive effect of the azido function. However, with cyclooctene iodo azides **20** and **22**, where *trans* elimination of hydrogen iodide[9] to a *trans*-vinyl azide is possible, vinyl azides were obtained. The elimination



of hydrogen iodide in these system was very slow and the product from iodo azide **20** was contaminated with 10–15% cyclooctene. The formation of cyclooctene in this reaction is indicative of iodine azide elimination, a phenomenon sometimes observed with β-iodo azides.

Although it is tempting to assign the *trans* configuration to the double bond in 1-azidocyclooctene this does not appear to be justified on the basis of nmr data as well as from the fact that *trans*-cycloocten.es are unstable and react with azides at −100°.[9b]

The nmr absorption of vinylic protons vicinal to the azido substituent occur at relatively high field compared to normal vinylic protons. This is consistent with the nmr spectra of vinyl ethers[10] and can be attributed to contributions from resonance structures such as II which increase the electron density at the vicinal carbon atom. We have previously reported[5] that the proton *cis* to the azido function in azidostilbenes and azido-2-butenes has its nmr absorption shifted upfield from the corresponding proton in the *trans*



isomer. It is now apparent that with simple aliphatic vinyl azides these absorptions for the *cis* and *trans* isomers fall in a very narrow range (see Table II) and are well separated from each other. Evidently, 1-azidocyclooctene possesses the *cis* stereochemistry (**21**) unless some unexpected factor is operative in the cyclic *trans*-vinyl azide causing a downfield shift of the *trans* proton.

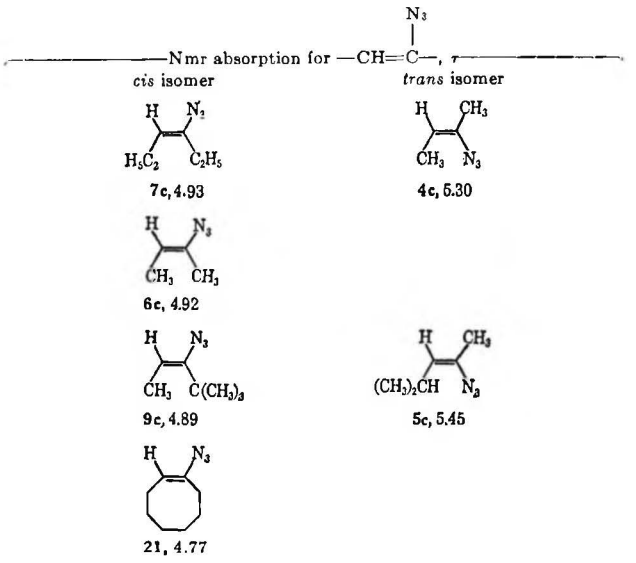
The vinyl azide obtained by hydrogen iodide elimination from **22** can likewise be assigned the *cis,cis* configuration **23**. The vinylic proton vicinal to the azido function occurs as a triplet and is shifted upfield from the other vinylic protons to τ 4.68. Irradiation at 192 cps upfield causes this triplet to collapse into a singlet.

These results could be explained by *cis* addition of IN_3 followed by *anti* elimination of hydrogen iodide. However, there is no precedent for *cis* addition of IN_3 to an olefin. Initial elimination of hydrogen iodide to the allyl azide followed by isomerization to the vinyl

(9) (a) A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Amer. Chem. Soc.*, **75**, 3212 (1953); (b) A. C. Cope, C. F. Howell, J. Bower, R. C. Lord, and G. M. Whitesides, *ibid.*, **89**, 4024 (1967).

(10) J. M. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance," Vol. 2, Pergamon Press Inc., New York, N. Y., 1966, p 721.

TABLE II



azide is unlikely with the cyclooctene iodo azide since this type of isomerization was not observed with the cyclopentene and cyclohexene iodo azides. In fact, the proton geminal to the azido function in allyl azide **19b** does not exchange after prolonged treatment with potassium deuteroxide in deuterium oxide–acetone-d_6. A better rationalization is that hydrogen iodide was eliminated in a *syn* manner from the *trans*-iodo azide to give the vinyl azide.

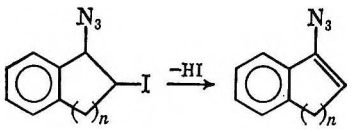
Sicher and coworkers have recently studied the elimination of hydrogen bromide from bromocycloalkanes with potassium *t*-butoxide in *t*-butyl alcohol.[11] In the larger rings it was postulated that the *cis* olefin was produced by ionic *anti* elimination of hydrogen bromide whereas an ion-pair *syn* mechanism was postulated for production of the *trans* olefin. In eight-membered rings *anti* elimination is known to be very slow.[11] Since an ion pair should be more stable with respect to the ions in ether than *t*-butyl alcohol, the *syn* mechanism should play a more important role in ether. This fact, coupled with the known directive effect of an azido substituent, supports the *syn* mechanism for the elimination to the vinyl azides in these systems.

Brown and coworkers[12] have recently reported that E2 elimination from *trans*-2-methylcyclooctyl tosylate with potassium *t*-butoxide gave a 1:1 mixture of the 1- and 3-methylcyclooctene.[12] Although no stereochemical assignment was made to the 1-methylcyclooctene, its isolation is consistent with our results and may indicate a *syn* elimination.

Two other cyclic olefins that we have successfully converted into vinyl azides are indene and 1,2-dihydronapthalene. Possibly a *syn* elimination of hydrogen iodide is also operative with these systems. However, a plausible pathway consistent with the elimination in the cyclopentene and cyclohexene series would involve initial elimination to the allyl azides. Owing to the greater acidity of the allylic hydrogens which in these systems are also benzylic, the allyl azides can rearrange in the presence of base to the vinyl azides **25a** and **b**.

(11) J. Zavada, J. Krupilka, and J. Sicher, *Chem. Commun.*, 67 (1967).

(12) H. C. Brown and R. L. Klimisch, *J. Amer. Chem. Soc.*, **88**, 1430 (1966).



24a, $n = 1$ **25a**, $n = 1$
b, $n = 2$ **b**, $n = 2$

Experimental Section[13]

General.—Both iodo and azido functions are quite labile in the iodo azide adducts and elemental analysis was generally precluded with the higher molecular weight olefins, since extensive decomposition occurred on attempted distillation. However, evidence that addition did take place can be obtained from an examination of the infrared spectrum which shows very strong asymmetric stretching absorption at *ca.* 2100 cm^{-1}. The nmr spectrum in the olefinic region can be used to ascertain whether any unreacted olefin is present and, if it is, generally the amount is quite small. Most iodo azides were converted by reduction into aziridines in good yield.[14] The general procedure for iodine azide addition was followed as described.[5]

A note of caution: We have observed that addition of iodine azide to sulfur-containing olefins results in violent decomposition of the reagent.

The general procedure for the formation of unsaturated azides from iodo azides was as described.[5] The crude unsaturated azides were purified by passage through neutral Woelm aluminum oxide activity I with dry Skellysolve F or A. Removal of the solvent *in vacuo* at room temperature gave the pure unsaturated azide (ir, 2100 ± 20 (vs), 1635 ± 10 cm^{-1} (s)). For possible deviations from these general procedures see the section below for each specific compound. The vinyl azides were likewise unstable and distillation was not advisable. The nmr data for all vinyl azides are consistent with the assigned structures. Most vinyl azides were converted in good yield into azirines or derivatives by photolysis.[4c]

α-Azidostyrene (**1c**) was prepared from α-azido-β-iodoethylbenzene[5] (**1b**) in 67% yield: nmr (CCl_4), τ 2.4–2.9 (m, five aromatic protons), 4.72 (d, 1 (J = 2.4 Hz), C=C**H**), and 5.19 (d, 1 (J = 2.4 Hz), C=C**H**).

1-Iodo-2-azido-4,4-dimethylpentane (**2b**) was prepared from 4,4-dimethyl-1-pentene in 79% yield: nmr ($CDCl_3$), τ 6.2–6.8 (m, 3, C**H**C**H**CN_3H_2) and 9.00 (s, 9, $(CH_3)_3C$).

Anal. Calcd for $C_7H_{14}IN_3$: C, 31.48; H, 4.28. Found: C, 31.51; H, 5.22.

2-Azido-4,4-dimethyl-1-pentene (**2c**) was prepared from 1-iodo-2-azido-4,4-dimethylpentane (**2b**) in 61% yield: nmr ($CDCl_3$), τ 5.25 (s, 1, C=C**H**), 5.38 (s, 1, C=C**H**), 8.08 (s, 2, $-CH_2$), and 9.03 (s, 9, $(CH_3)_3C$).

trans-**2-Azido-2-butene** (**4c**) was prepared from *threo*-2-azido-3-iodobutane (**4b**)[5] in 53% yield: nmr (CCl_4), τ 5.30 (one-proton quartet (J = 7 Hz) of quartets, J = 1.5 Hz, C=C**H**), 8.05 (quintet, 3, J = 1.5 Hz, CN_3CH_3), and 9.12 (three-proton doublet (J = 7 Hz) of quartets (J = 1.5 Hz), $CHCH_3$).

threo-**2-Azido-3-iodo-4-methylpentane** (**5b**) was prepared from *cis*-4-methyl-2-pentene in 95% yield: nmr ($CDCl_3$), τ 6.06 (t, 1 (J = 5.2 Hz), C**H**I), 6.58 (quintet, 1 (J = 6 Hz), CN_3H), 7.8–8.8 (m, *ca.* 1, $(CH_3)_2CH$), 8.62 (d, 3 (J = 6.6 Hz), CH_3CHN_3), and 8.97 (d, 6 (J = 6.5 Hz), $(CH_3)_2CH$).

Anal. Calcd for $C_6H_{12}IN_3$: C, 28.47; H, 4.78. Found: C, 28.71; H, 4.75.

trans-**2-Azido-4-methyl-2-pentene** (**5c**) was prepared from *threo*-2-azido-3-iodo-4-methylpentane (**5b**) in 81% yield: nmr ($CDCl_3$), 5.45 (one-proton doublet (J = 9.0 Hz) of quartets (J = 1.0 Hz), C=C**H**), 7.0–7.8 (m, 1, $(CH_3)_2CH$), 8.07 (d, 3 (J = 1.0 Hz), CH_3C=C), and 9.08 (d, 6 (J = 6.6 Hz), $(CH_3)_2CH$).

cis-**2-Azido-2-butene** (**6c**) was prepared from *erythro*-2-azido-3-iodobutane (**6b**)[5] in 52% yield: nmr (CCl_4), τ 4.89 (one-proton quartet (J = 6.5 Hz) of quartets (J = 1.0 Hz), C=C**H**), 8.28 (m, 4.5), and 8.42 (q, 1.5 (J = 1.0 Hz)).

erythro-**3-Azido-4-iodohexane** (**7b**) was prepared from 3-hexene in quantitative yield: nmr (CCl_4), τ 5.95 (q, 1 (J = 6.5 Hz), C**H**I), 6.5–7.0 (m, 1, C**H**N_3), and 7.9–9.2 (m, 10).

Anal. Calcd for $C_6H_{12}IN_3$: C, 28.47; H, 4.78. Found: C, 28.54; H, 4.94.

cis-**3-Azido-3-hexene** (**7c**) was prepared from *erythro*-3-azido-4-iodohexane in 77% yield: nmr (CCl_4), τ 4.94 (t, 1 (J = 7.0 Hz), C=C**H**), 7.6–8.2 (m, 4), and 8.7–9.2 (m, 6).

erythro-**1-Azido-2-iodo-1-phenylpropane** (**8b**) was prepared from *trans* 1-phenyl-1-propene in quantitative yield: nmr (CCl_4), τ 5.30 (d, 1 (J = 6.0 Hz), C**H**N_3), 5.75 (quintet, 1 (J = 6.5 Hz), C**H**I), 8.17 (d, 3 (J = 6.5 Hz), CH_3), and 2.6–2.9 (m, five aromatic protons).

Anal. Calcd for $C_9H_{10}IN_3$: C, 37.63; H, 3.48. Found: C, 37.87; H, 3.31.

cis-**1-Azido-1-phenyl-1-propene** (**8c**) was prepared from *erythro* 1-azido-2-iodo-1-phenylpropane (**8b**) in 86% yield: nmr (CCl_4), τ 2.80 (s, five aromatic protons), 4.67 (q, 1 (J = 7.0 Hz), C=C**H**CH_3), and 8.35 (t, 3 (J = 7.0 Hz), $CHCH_3$).

erythro-**2-Azido-3-iodo-4,4-dimethyl-2-pentane** (**9b**) was prepared from *trans*-4,4-dimethyl-2-pentene (**9a**) in 87% yield: nmr ($CDCl_3$), τ 5.74 (d, 1 (J = 3 Hz), C**H**I), 6.75 (one-proton quartet (J = 6.5 Hz) of doublets (J = 3 Hz), C**H**N_3), 8.62 (d, 3 (J = 6.5 Hz), CH_3), and 8.85 (s, 9, $(CH_3)_3C$).

cis-**2-Azido-4,4-dimethyl-2-pentene** (**9c**) was prepared from *erythro*-2-azido-3-iodo-4,4-dimethyl pentane (**9b**) in 72% yield: nmr ($CDCl_3$), τ 4.89 (q, 1 (J = 1.0 Hz), C=C**H**), 8.15 (d, 3 (J = 1 Hz), CH_3), and 8.89 (s, 9, $(CH_3)_3C$).

Azido-3-methyl-1-butene (**14c and 15c**). The iodine azide adduct to 3-methyl-1-butene (**14a**) was obtained in 92% yield; nmr spectra indicated the presence of primary iodide and azide at τ 6.7, as well as of secondary iodide (τ 5.8) and azide (τ 6.3). Treatment with K-*t*-BuO at 0° gave azido olefin indicated by nmr integration to be a mixture of 36% **14c** and 64% **15c**: nmr ($CDCl_3$) for **14c**, τ 6.17 (d, J = 13.5 Hz), 6.7 (q, J = 13.5 and 6.5 Hz); for **15c**, τ 5.3 (d, J = 1.5 Hz), 5.43 (d, J = 1.5 Hz), and isopropyl group at 7.73 (septet) and 8.9 and 9.1 (two doublets).

Anal. Calcd for $C_5H_9N_3$: C, 54.03; H, 8.16. Found: C, 53.85; H, 8.17.

erythro-**Ethyl 2-iodo-3-azidobutanoate** (**10b**) was prepared from ethyl crotonate in 81% yield: nmr (CCl_4), τ 5.5–6.4 (m, 4) and 8.4–8.9 (m, 6).

cis-**Ethyl β-Azidocrotonate** (**10c**).—To 12.00 g of ethyl α-iodo-β-azidobutanoate (**10b**) was added 6.00 g of 1,4-diazabicyclo-[2.2.2]octane in 120 ml of dry benzene. The reaction was allowed to stand at room temperature for 3 days. The reaction was then washed with 5% hydrochloric acid and dried with magnesium sulfate. Removal of the ether at reduced pressure produced 6.64 g of a yellow liquid. This was passed through *ca.* 80 g of aluminum oxide (Merck No. 71707) with petroleum ether (bp 40–60°) which gave, after removal of the solvent, 4.10 g of a pale yellow liquid (50%).

The nmr spectrum was identical with that previously reported.[8] The triphenylphosphine imine derivative was prepared as previously described, mp 135–136° (lit.[8] 135–135.5°).

Addition of IN_3 to Methyl Acrylate.—The adduct was prepared according to the general procedure in 86% yield. The nmr spectrum showed peaks at τ 5.4–6.6 (multiplet with strong singlet at 6.20).

The elimination of HI was carried out on 25.5 g of the adduct in 250 ml of acetone using 1,4-diazabicyclo[2.2.2]octane as a base at 5° for 16.5 hr. The mixture was then added to *ca.* 500 ml of water and 200 ml of a saturated salt solution. This was then extracted with ether. The ether extracts were combined and washed with water, 5% HCl solution, and again with water. The ethereal solution was dried. Removal of the solvent at reduced pressure gave 7.3 g (61%) of an orange liquid. The nmr spectrum showed this to be a 1:4 mixture of methyl β- and α-azido acrylates, respectively. To a dry column of 120 g of silica gel (grade 62, 60–200 mesh, Grace Davidson Chemical, Baltimore, Md.) was added 3.58 g of the above mixture. This was eluted with 10% v/v (150 ml), 20% (200 ml), 40% (200 ml), and 60% (200 ml) of methylene chloride in pentane. The first fractions (300 ml) gave 2.35 g of a pale yellow liquid which proved to be methyl α-azido acrylate (**13c**). This pale yellow liquid rapidly turned orange at room temperature. The nmr spectrum ($CDCl_3$) showed τ 4.17 (d, 1 (J = 1.6 Hz), C=C**H**),

(13) All melting points were determined on a Fisher-Johns melting point block and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer IR-21 spectrometer. Nuclear magnetic resonance spectra were recorded with either a Varian A-60 or A-60A spectrometer. Microanalyses were performed by either A. Bernhardt, Mülheim, Germany, or Galbraith Laboratories, Knoxville, Tenn. In nmr descriptions, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

(14) G. J. Matthews and A. Hassner, unpublished results.

4.65 (d, 1 (J = 1.6 Hz), C=CH), and 6.15 (s, 3, OCH_3). The ir spectrum showed strong broad bands at 2150 (N_3), 1745 (C=O), and 1625 cm^{-1} (C=C).

The following fractions (150 ml) of eluent produced 0.56 g of a pale yellow solid that proved to be methyl β-azido acrylate (12c). Recrystallization from pentane gave the analytical sample, mp 58–58.5° sublimes. The nmr spectrum ($CDCl_3$) showed peaks at τ 2.67 (d, 1 (J = 14 Hz), C=CH), 4.33 (d, 1 (J = 14 Hz), C=CH), and 6.25 (s, 3, OCH_3). The ir spectrum (KBr) showed absorptions at 2137 (N_3), 1715 (C=O), and 1631 cm^{-1} (C=C).

Anal. Calcd for $C_4H_5N_3O_2$: C, 37.80; H, 3.97. Found: C, 37.66; H, 3.87.

cis-Methyl β-Azidocinnamate (11c).—To 11.0 g of methyl *erythro*-3-azido-2-iodophenylpropionate[6] (11b) was added 100 ml of reagent acetone and 7.0 g of DABCO. The reaction mixture was kept at 5° for 38 hr and then 250 ml of H_2O was added. The mixture was extracted with ether. The ethereal extracts were combined and washed with H_2O followed by 5% HCl solution. The ethereal solution was dried with $MgSO_4$. Removal of the ether at reduced pressure gave 7.5 g of an orange liquid which slowly loses nitrogen. The nmr spectrum showed, in addition to absorptions due to methyl α-iodocinnamate,[4c] absorptions at τ 2.69 (s, five aromatic protons), 4.33 (s, 1, C=CH), and 3.47 (s, 3, OCH_3).

Pyrolysis of 7.2 g of the above orange liquid gave 6.7 g of 3-carbomethoxy-2-phenyl-1-azirine (17) and methyl α-iodocinnamate. (See ref 4c for a more complete description of this reaction.)

trans-1-Azido-2-iodocyclopentane (18a) was prepared from cyclopentene in 89% yield: nmr (CCl_4), τ 5.7–6.1 (m, 2, CHN_3—CHI) and 7.5–8.7 (m, 6).

3-Azidocyclopentene (19a) was prepared from *trans*-1-azido-2-iodocyclopentane (18a) in 82% yield as a colorless liquid: bp 85° (15 mm), *distillation exploded violently;* nmr (CCl_4), τ 3.8–4.4 (m, 2, CH=CH), 5.5–6.1 (m, 1, CHN_3), and 7.4–8.6 (m, 4).

Anal. Calcd for $C_5H_7N_3$: C, 55.03; H, 6.47. Found: C, 54.84; H, 6.53.

3-Azidocyclohexene (19b).—The elimination on 18b[5] was carried out using potassium hydroxide in methanol and gave a 74% yield of a colorless liquid: nmr (CCl_4), τ 4.17 (four-proton quartet (J = *ca.* 9 Hz) of multiplets, CH=CH), 6.0–6.4 (m, 1, CHN_3), and 7.8–8.6 (m, 6).

Attempted Deuterium Exchange of 19b.—To 0.305 g of 19b was added 2.888 g of acetone-d_6 and 0.330 g of a 25% NaOD–D_2O solution. The reaction mixture was refluxed for 5 days. The nmr spectrum was unchanged.

trans-1-Azido-2-iodocyclooctane (20) was prepared from *cis*-cyclooctene in 87% yield: nmr (CCl_4), τ 5.5–6.3 (m, 2, CHN_3—CHI) and 7.6–8.9 (m, 14).

Anal. Calcd for $C_8H_{14}IN_3$: C, 34.42; H, 5.05. Found: C, 35.56; H, 5.19.

1-Azidocyclooctene (21) was prepared from 1-azido-2-iodocyclooctane (20) in 80% yield: nmr (CCl_4), τ 4.77 (t, 1 (J = 8.5 Hz)) and 7.5–8.7 (m, 12).

3-Azido-4-iodocyclooctene (22) was prepared from 1,3-cyclooctadiene in 72% yield: nmr (CCl_4), τ 3.7–4.8 (m, 2, CH=CH), 5.2–6.1 (m, 2, CHN_3—CHI), and 7.4–8.9 (m, 8).

2-Azido-1,3-cyclooctadiene (23) was prepared from 3-azido-4-iodocyclooctene (22) in 50% yield: nmr (CCl_4), τ 3.8–4.4 (m, 3, vinylic protons), 4.68 (t, 1 (J = 7 Hz), CN_3=CH), and 7.5–8.9 (m, 8).

Anal. Calcd for $C_8H_{11}N_3$: C, 64.40; H, 7.43; Found: C, 65.90; H, 8.01.

1-Azido-2-iodotetralin (24b) was prepared from 1,2-dihydronaphthalene in 90% yield: mp 45–46°, from ethanol; nmr (CCl_4), τ 5.27 (d, 1 (J = 4 Hz), CHN_3), 2.82 (s, 4, aromatic protons), 5.54 (q, 1 (J = 4 Hz), CHI), 7.1–7.3 (m, 2), and 7.7–8.1 (m, 2).

Anal. Calcd for $C_{10}H_{10}N_3I$: C, 40.15; H, 3.37; N, 14.05. Found: C, 40.07; H, 3.62; N, 13.77.

1-Azido-3,4-dihydronaphthalene (25b) was prepared from 1-azido-2-iodotetralin (24b) in 70% yield: nmr (CCl_4), τ 2.2–3.1 (m, 4, aromatic protons), 4.43 (t, 1 (J = 4.5 Hz), C=CH), and 7.1–8.0 (m, 4).

1-Azido-2-iodoindan (24a) was prepared from indene in 76% yield: nmr, τ 2.6–2.8 (m, 4, aromatic protons), 4.99 (d, 1 (J = 5 Hz), CHN_3), 5.72 (q, 1 (J = 6 Hz), CHI), and 6.58 (t, 2 (J = 7 Hz)).

Anal. Calcd for $C_9H_8N_3I$: C, 37.92; H, 2.83. Found: C, 37.74; H, 2.92.

1-Azidoindene (25a) was prepared from 1-azido-2-iodoindan (24a). To 10.00 g of the iodo azide was added 100 ml of benzene and 5.00 g of 1,4-diazabicyclo[2.2.2]octane. The reaction was refluxed for 17.75 hr and then was washed with 5% hydrochloric acid. A polymeric solid formed which was removed by filtration through Celite. The benzene layer was washed again with 10% hydrochloric acid and dried with magnesium sulfate. The benzene was removed at reduced pressure. The residue was dissolved in pentane and decolorized with activated carbon. Removal of the pentane produced 3.48 g of a pale yellow liquid (83%): nmr (CCl_4), τ 2.77 (s, 5, aromatic protons), 4.15 (t, 1 (J = 2.5 Hz), C=CH), and 6.78 (d, 2 (J = 2.5 Hz), CH_2).

Registry No.—1c, 16717-64-9; 2b, 16717-65-0; 2c, 16717-661-1; 4c, 16717-67-2; 5b, 16717-68-3; 5c, 16717-69-4; 6c, 16717-70-7; 7b, 16717-71-8; 7c, 16717-72-9; 8b, 16717-73-0; 8c, 16717-74-1; 9b, 16717-75-2; 9c, 16717-76-3; 10b, 16717-77-4; 12c, 16717-78-5; 13c, 16717-79-6; 14c, 16717-80-9; 15c, 16717-81-0; 18a, 16717-82-1; 19a, 16717-83-2; 19b, 16717-84-3; 20, 16717-85-4; 21, 16719-52-1; 22, 16719-53-2; 23, 16719-54-3; 24a, 16719-55-4; 24b, 16719-56-5; 25a, 16719-57-6; 25b, 16719-58-7.

Acknowledgment.—Support of this study by Petroleum Research Fund Grant 2004A1, 4 from the American Chemical Society and by U. S. Public Health Service Grant CA-04474 by the National Cancer Institute is gratefully acknowledged. We are indebted to Dr. Gary J. Matthews for valuable assistance during this work.

Perhalo Ketones. XV.[1] The Preparation and Some Reactions of Perhalocyclopentanones and -hexanones

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Received September 22, 1967

Two convenient routes are described for the preparation of perhalogenated cyclopentanones and -hexanones from the corresponding 1,2-dichloroperfluorocyclo olefins. The ketones were converted into a number of derivatives, several of which were obtained through additions to their highly reactive carbonyl groups.

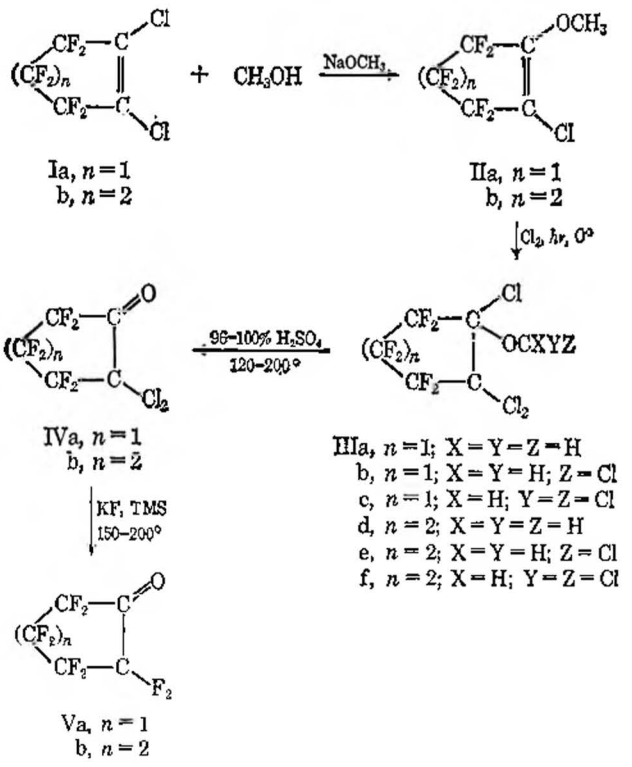
The chemistry of perfluorinated ketones has evoked much interest in recent years as indicated by the large number of patents and publications in this area. The present paper describes the synthesis and some reactions of perhalogenated cyclopentanones and cyclohexanones. Related chemistry in the perhaloacetone and -cyclobutanone areas has been discussed by various workers.[2]

Other preparations of perfluorocyclopentanone and -hexanone have appeared in the literature,[3] but few of their reactions have been reported.

Discussion

The syntheses of 2,2-dichloroperfluorocyclopentanone (IVa) and -hexanone (IVb) were effected in a three-step reaction sequence starting with 1,2-dichloroperfluorocyclopentene (Ia) and -hexene (Ib), respectively. Thus, treatment of these olefins with sodium hydroxide in methanol provided the corresponding 1-chloro-2-methoxyperfluorocycloalkenes (IIa and IIb). Photochlorination of IIa and IIb resulted in saturation of the double bond and partial replacement of the methoxyl hydrogen atoms by chlorine.[4] Hydrolysis of the resulting ethers (IIIa–f) with concentrated sulfuric acid gave the related ketones (IVa and b) in excellent yields; the ethers with partially chlorinated methoxyl groups exhibited increased rates of hydrolysis. The use of 100% sulfuric acid resulted in optimum ketone yields; 95% sulfuric acid gave solutions of ketone hydrates (*vide infra*). The treatment of IVa and IVb with potassium fluoride in polar solvents, such as dimethylformamide and tetramethylene sulfone (TMS), proved to be a good route to perfluorocyclopentanone (Va) and -hexanone (Vb), respectively (see Scheme I).

SCHEME I



Ketones Va and Vb were also prepared by another reaction sequence starting from the 1,2-dichloroperfluoro olefins Ia and Ib. Thus, these materials were epoxidized with basic hydrogen peroxide to provide 1,2-dichloroperfluorocyclopentene epoxide (VIa) and 1,2-dichloroperfluorocyclohexene epoxide (VIb); VIb was obtained in approximately 40% yield, whereas the yield for VIa was somewhat lower. A pure sample of VIb was tested for thermal stability by refluxing for several hours at 114°; there was no indication of decomposition. Treatment of this epoxide with potassium fluoride in tetramethylene sulfone (TMS) afforded a mixture of ketone Vb and 2-chloroperfluorocyclohexanone (VII). A similar treatment of VIa gave Va in very low yields (see Scheme II).

Reactions of Perhalo Ketones.—2,2-Dichloroperfluorocyclohexanone (IVb) was pyrolyzed by passing it through an Alundum tube packed with glass helices and heated to 375°. The recovered products were identified as 2-chloroperfluorocyclohexenone (VIIIa), 2,3-dichloroperfluorocyclohexenone (VIIIb), and silicon tetrafluoride. Compound VIIIb could be converted into VIIIa by treatment with hydrogen fluoride over Cr_2O_3 at 375°. The boiling point and ^{19}F nmr and in-

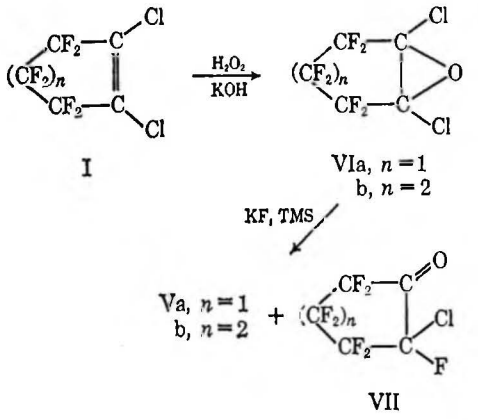
(1) (a) Part XIV: J. J. Murray, *J. Org. Chem.*, in press. (b) R. F. Sweeney, B. Veldhuis, E. E. Gilbert, L. G. Anello, R. J. DuBois, and W. J. Cunningham, *ibid.*, **31**, 3174 (1966).

(2) (a) D. C. England, *J. Amer. Chem. Soc.*, **83**, 2205 (1961); (b) D. C. England, U. S. Patents 3,036,091 (1961), 3,039,995 (1962), 3,040,058 (1963), 3,140,298 (1964), and 3,148,220 (1964); (c) British Patent (Du Pont) 904,877 (1962); (d) I. L. Knunyants, C. Ch'ing-yun, and N. P. Gambaryan, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk*, 686 (1960); (e) I. L. Knunyants and Yu. A. Cheburkov, *ibid.*, 678 (1960); (f) I. L. Knunyants and Yu. A. Cheburkov, *ibid.*, 2168 (1960); (g) V. F. Plakhova and N. P. Gambaryan, *ibid.*, 681 (1961); (h) A. G. Pittman and D. L. Sharp, *Polymer Letters*, **3**, 379 (1965); (i) A. G. Pittman and D. L. Sharp, *Text. Res. J.*, **35**, 190 (1965); (j) A. G. Pittman, D. L. Sharp, and B. A. Ludwig, Polymer Preprints of Papers, presented at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p 1093; (k) R. P. Graham, *J. Org. Chem.*, **31**, 957 (1966); (l) D. P. Carlson and A. S. Milian, Syntheses and Reactions of Some Perfluorocarbon Expoxides, Presented at the Fourth International Fluorine Symposium on Fluorine Chemistry, Estes Park, Colorado, July 24–28, 1967.

(3) (a) F. F. Holub and H. A. Bigelow, *J. Amer. Chem. Soc.*, **72**, 4879 (1950); (b) W. T. Miller, U. S. Patents 2,712,514 and 2,712,555 (1955); (c) British Patent (Du Pont) 1,019,788 (1966).

(4) R. F. Sweeney, L. G. Anello, and D. Werner, Abstracts, the 154th National Meeting of the Amerian Chemical Society, Chicago, Ill., Sept 1967, p K001.

SCHEME II



frared spectra of VIIIb were identical with those reported earlier.[1b]

Hydrates of the saturated ketones are formed readily; thus the exothermic reaction of IVa, IVb, Va, and Vb with water gave the respective 1:1 adducts (IXa–d) which were well-defined, distillable compounds.

The reduction of IVa, IVb, Va, and Vb with sodium borohydride gave the corresponding secondary alcohols Xa–d.

Ketones Va and Vb undergo reaction with potassium fluoride in polar solvents to afford the perfluorinated alkoxides XIa and XIb which may be isolated, and are stable at ambient temperature.

Hydroxy acids (XIIa and XIIb) are produced upon admixture of Va and b with malonic acid in pyridine.

Ketone Vb was found to undergo the Wittig reaction smoothly. Accordingly, ethyl perfluorocyclohexylidenyl acetate (XIII) was obtained when the ketone was heated with carbethoxymethylenetriphenylphosphorane in ether (see Scheme III).

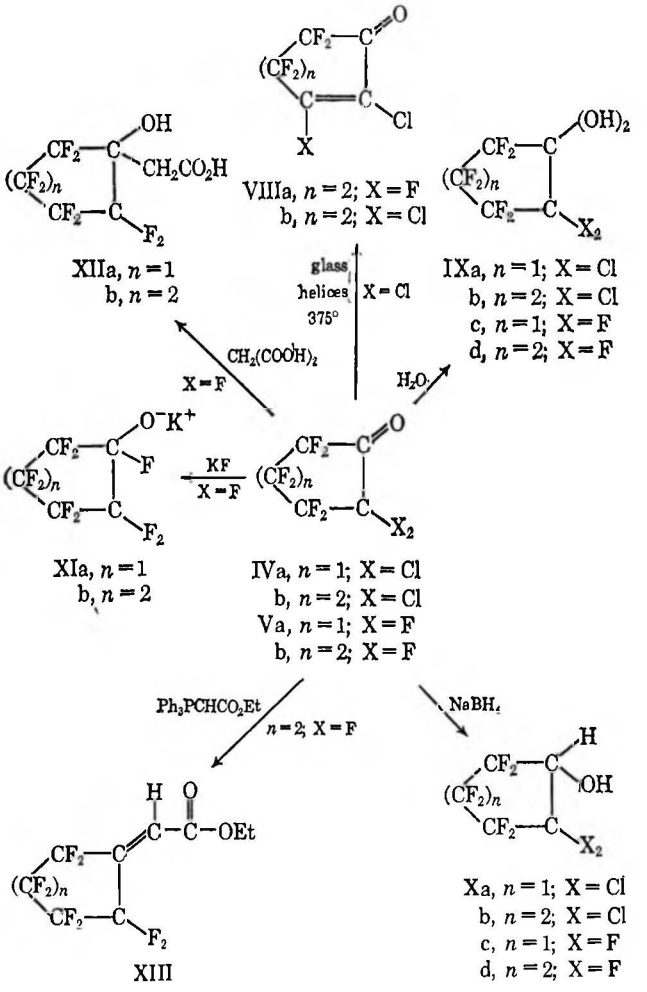
Acrylate Derivatives.—An interesting series of acrylate monomers (XIVa–d) was prepared by the reactions of alcohols Xc and Xd, and alkoxides XIa and XIb with acrylyl chloride. When the alcohols were employed, a by-product, arising from the addition of HCl across the acrylate double bond, was also formed; this was minimized by the use of quinoline as an acid acceptor.

The various acrylates were converted into their corresponding polymers (XVa–d) by free-radical polymerization in aqueous dispersions.

Malonic Acid Derivatives.—When hydroxy acids XIIa and XIIb were heated at 40–60° with thionyl chloride and catalytic amounts of pyridine, their respective acid chlorides (XVIa and XVIb) were formed. Compound XVIa could be isolated readily by glpc separation. In contrast, XVIb decomposed on the column to give primarily the lactone XVII (*vide infra*). Separation of XVIb from unreacted XIIb was achieved by extraction with cold carbon tetrachloride.

Both XVIa and XVIb gave a mixture of products upon heating with catalytic amounts of pyridine at 75°, or upon prolonged heating at lower temperatures. Examination of the product mixture from XVIb showed lactone XVII to be a major constituent. Compound XVII is also the main product when XIIb is heated with phosphorus pentoxide. On the other hand, dehydration of XIIb with 100% sulfuric acid

SCHEME III



leads to the unsaturated acid, XVIII. In an attempt to convert XVIII into its acid chloride, it was heated with thionyl chloride and a trace of pyridine. Surprisingly enough, the product proved to be the acid fluoride XIX in 47% yield. The acid XVIII was successfully converted into its acid chloride (XX) in high yield upon heating with benzotrichloride. Both XIX and XX reverted to XVIII upon exposure to moisture and gave XIII when warmed with ethanol (see Scheme IV).

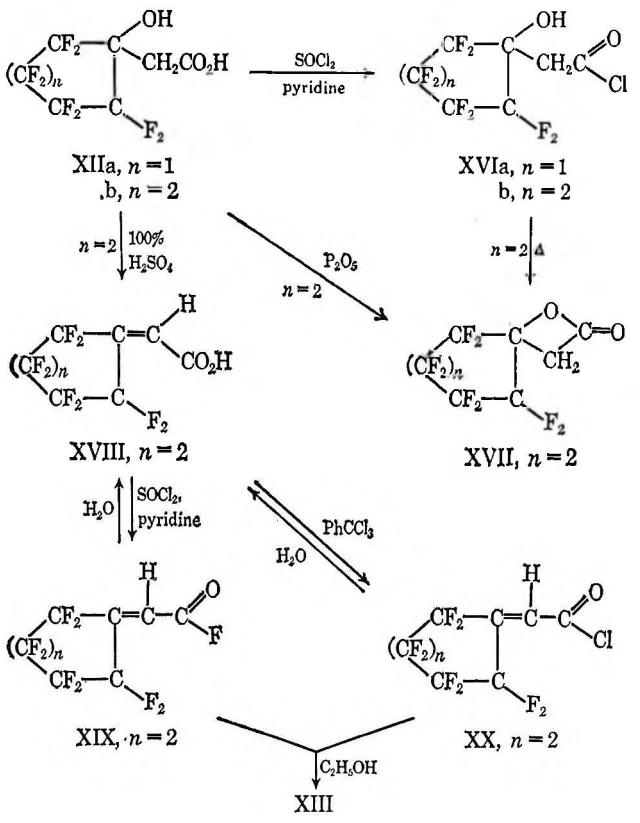
Experimental Section[5]

1-Chloro-2-methoxyperfluorocyclohexene (IIb).—A solution of 142 g (2.53 mol) of potassium hydroxide in 400 g of absolute methanol was added over a period of 4 hr to 748 g (2.53 mol) of 1,2-dichloroperfluorocyclohexene in 100 g of absolute methanol. The rate of addition was regulated to maintain the reaction mixture at about 45°. The product was drowned in a large excess of water; the organic layer was separated, extracted with ether, and dried over P_2O_5. Distillation gave 379 g (51%) of IIb, bp 135–136°.

Anal. Calcd for $C_7H_3OClF_8$: C, 12.2; F, 52.3. Found: Cl, 12.2; F, 52.8.

(5) Boiling points and melting points are uncorrected; melting points were taken on a Fisher-Johns hot stage melting point apparatus. The elemental analyses were by the Galbraith Analytical Laboratories and Messrs. G. E. Mohler, R. J. Tepper, and W. Zazulak of the Industrial Chemicals Analytical Laboratory, Morristownship, N. J. Infrared spectra were determined in carbon tetrachloride (unless otherwise noted) on a Perkin-Elmer Model 137 Infracord spectrophotometer. Gas–liquid partition chromatographic analyses and separations were carried out with an Aerograph Autoprep, Model A-700, equipped with a 20-ft column containing 20% QF-1 on 42–60 mesh firebrick.

SCHEME IV



1-Chloro-2-methoxyperfluorocyclopentene (IIa).—Following the procedure described above, 315 g (1.29 mol) of 1,2-dichloroperfluorocyclopentene was treated with 724 g (1.29 mol) of potassium hydroxide in 1980 ml of absolute methanol to give 225.8 g (85%) of IIa, bp 130–132°.

Photochlorination of 1-Chloro-2-methoxyperfluorocyclohexene.—Compound IIb (362 g, 1.25 mol), contained in an ice–water-cooled Vycor immersion apparatus, was irradiated with a 450-W, high pressure mercury lamp (Hanovia 79A36L) as chlorine gas (1.6 mol) was bubbled in over a 6-hr period; 0.44 mol of hydrogen chloride was evolved. A 100-g sample of the product was withdrawn and a small portion analyzed by glpc; the remainder was distilled. The analysis showed that the mixture consisted of 11.6 vol % of IIb, 62 vol % of 1,1,2-trichloro-2-methoxyperfluorocyclohexane (IIId), and 18.5 vol % of 1,1,2-trichloro-2-chloromethoxyperfluorocyclohexane (IIIe). Distillation of the product mixture gave mainly IIId (55 g), bp 187° and mp 101–103°, and 22 g of a higher boiling liquid.

Anal. Calcd for $C_7H_3Cl_3F_8O$: H, 0.83; Cl, 29.5; F, 42.0. Found: H, 0.80; Cl, 29.7; F, 41.5.

The chlorination of the remaining material was continued with 0.93 mol of chlorine being passed in over 3.5 hr; 0.47 mol of hydrogen chloride was evolved. Another 100-g sample of the reaction mixture was withdrawn and a portion was analyzed by glpc while the remainder was distilled. The analysis showed that the mixture consisted of 5.3% IIb, 18.4% IIId, 68% IIIe, and 8% higher boiler. Distillation of the product mixture gave mainly IIIe (62 g), bp 83–84° (10 mm), and 11 g of a higher boiling liquid.

Anal. Calcd for $C_7H_2Cl_4F_8O$: H, 0.31; Cl, 35.9; F, 38.4. Found: H, 0.45; Cl, 35.6; F, 37.9.

Chlorination of the remaining product mixture was continued with 0.50 mol of chlorine being passed in over a 2-hr period as 0.35 mol of hydrogen chloride evolved. A small portion of the product (278 g) was analyzed by glpc and a 139-g aliquot was distilled. The analysis showed that the product mixture consisted of 50.5% IIIe and 48% 1,1,2-trichloro-2-dichloromethoxyperfluorocyclohexane, IIIf. Distillation gave IIIe (72 g) and IIIf (64 g), bp 94° (10 mm).

Anal. Calcd for $C_7HCl_5F_8O$: H, 0.23; Cl, 41.2; F, 35.0. Found: H, 0.22; Cl, 40.7; F, 35.2.

Photochlorination of 1-Chloro-2-methoxyperfluorocyclopentene.—Using the techniques described above, the photochlorination of IIa gave three analgous compounds.

A.—1,1,2-Trichloro-2-methoxyperfluorocyclopentane IIIa had bp 172–175° and mp 95–100°.

Anal. Calcd for $C_6H_3Cl_3F_6O$: C, 23.1; H, 0.96. Found: C, 23.4; H, 0.80.

B.—1,1,2-Trichloro-2-monochloromethoxyperfluorocyclopentane IIIb had bp 76–78° (8 mm).

Anal. Calcd for $C_6H_2Cl_4F_6O$: H, 0.58; Cl, 41.0. Found: H, 0.50; Cl, 40.6.

C.—1,1,2-Triehloro-2-dichloromethoxyperfluorocyclopentane IIIc decomposed before boiling.

Anal. Calcd for $C_6HCl_5F_6O$: H, 0.26; Cl, 46.6; F, 30.0. Found: H, 0.25; Cl, 46.5; F, 30.0.

2,2-Dichloroperfluorocyclohexanone (IVb).—A mixture of 445 g (0.11 mol) of 1,1,2-trichloro-2-chloromethoxyperfluorocyclohexane and 200 g of 100% H_2SO_4 was slowly heated to 160–185°. At this temperature a rapid evolution of HCl occurred. The reaction was considered to be complete when the flask contents reached 200°. The organic product was distilled as formed using a 36-in. vacuum-jacketed column packed with glass helices. The product (46 g) was redistilled to give a 3-g forecut and 38 g (76%) of 2,2-dichloroperfluorocyclohexanone (IVb), bp 116–117°. The infrared spectrum showed a C=O band at 5.6 μ.

Anal. Calcd for $C_6Cl_2F_8O$: Cl, 22.8; F, 49.0. Found: Cl, 22.9; F, 49.0.

2,2-Dichloroperfluorocyclopentanone (IVa).—A mixture of 1,1,2-trichloro-2-chloromethoxyperfluorocyclopentane and 1,1,2-trichloro-2-dichloromethoxyperfluorocyclopentane, treated as in the previous experiment, gave the ketone IVa (88% yield), bp 87–88°.

Perfluorocyclohexanone (Vb).—2,2-Dichloroperfluorocyclohexanone (68 g, 0.22 mol) was added over a 3-hr period to a stirred mixture of 50 g (0.86 mol) of anhydrous potassium fluoride and 150 g of tetramethylene sulfone at 150°. The product was distilled from the reaction vessel as formed. The product was redistilled through an 18-in. spinning-band column to give a 1.0-g forecut (bp 41–54°), 31 g (74%) of perfluorocyclohexanone (Vb), bp 54–56°, and 22 g of starting material. The infrared spectrum showed a C=O band at 5.55 μ.

Anal. Calcd for $C_6F_{10}O$: C, 25.84; F, 68.34. Found: C, 25.52; F, 67.6.

Perfluorocyclopentanone (Va).—2,2-Dichloroperfluorocyclopentanone, treated as in the previous experiment, gave the ketone Va (50%), bp 23–24°. The infrared spectrum showed a C=O band at 5.49 μ.

Anal. Calcd for C_5F_8O: C, 26.32; F, 66.67. Found: C, 26.15; F, 66.85.

1,2-Dichloroperfluorocyclohexene Epoxide (VIb).—1,2-Dichloroperfluorocyclohexene (90 g, 0.3 mol) was added dropwise over a 75-min period at 0° to a solution of 57 g (1.02 mol) of potassium hydroxide and 151.5 g (1.35 mol) of 30% hydrogen peroxide in 450 ml of methanol. After stirring for an additional 80 min, the mixture was diluted with 400 ml of water, whereupon the lower layer (42.4 g) was separated and dried over sodium sulfate. Infrared analysis indicated that 89% of this layer was the desired epoxide (42% yield); the remainder was mainly the starting olefin.

A pure sample of the epoxide (bp 114°) could be obtained by further subjecting this mixture to treatment with basic hydrogen peroxide.

Anal. Calcd for $C_6Cl_2OF_8$: C, 23.2; H, 0.00; Cl, 22.8; F, 48.9. Found: C, 23.13; H, 0.00; Cl, 22.7; F, 49.0.

The infrared spectrum exhibited an absorption band at 7.58 μ which appears to be characteristic of halogenated epoxides.

1,2-Dichloroperfluorocyclopentene Epoxide (VIa).—Following the procedure described above, 245 g of 1,2-dichloroperfluorocyclopentene was treated with 224 g of KOH and 510 ml of 30% hydrogen peroxide in 950 ml of methanol to provide 54 g (19%) of epoxide VIa, bp 86.5–88°.

Anal. Calcd for $C_5F_8Cl_2O$: H, 0.00; F, 43.8. Found: H, 0.00; F, 41.8.

Perfluorocyclohexanone Vb and 2-Chloroperfluorocyclohexanone (VII) from Epoxide VIb.—Potassium fluoride (35 g, 0.6 mol) was slurried in 175 g of tetramethylene sulfone. The temperature was raised to 160° and a slow stream of nitrogen was passed through the system. Epoxide VIb (100 g, 0.32 mol) was added dropwise to this mixture and the resulting products were distilled as they formed. When epoxide addition was complete, the temperature was increased slowly to 200°. A total of 70 g of distillate was collected; subsequent fractional distillation gave, in the early fractions, 22.8 g (27% yield) of

perfluorocyclohexanone (Vb), bp 50–55°. In later fractions, approximately 6 g (8% yield) of pure 2-chloroperfluorocyclohexanone (Vb) was obtained. Redistillation provided an analytical sample, bp 85–86.5°.

Anal. Calcd for C_6ClOF_9: C, 24.5; Cl, 12.0; F, 58.0. Found: C, 22.7; Cl, 11.6; F, 59.0.

The infrared spectrum exhibited a carbonyl absorption at 5.52 μ.

In a similar experiment, a mixture of 5.85 g (0.02 mol) of epoxide and about 4.0 g of the olefin was added to a slurry of 8.7 g (0.15 mol) of potassium fluoride in tetramethylene sulfone while the reaction temperature was increased from 130 to 180°. A total of 0.78 g (18% yield) of Vb and 1.94 g (42% yield) of VII were obtained.

Perfluorocyclopentanone (Va) from Epoxide VIa.—Following the above procedure, 15 g of epoxide VIa (containing some of the parent 1,2-dichloroperfluorocyclopentene as an impurity) was treated with 15 g of potassium fluoride in 175 g of tetramethylene sulfone at 160–170° to provide 0.7 g (7%) of ketone Va.

Pyrolysis of 2,2-Dichloroperfluorocyclohexanone.—During a period of 2.75 hr, 55 g (0.18 mol) of 2,2-dichloroperfluorocyclohexanone vapors were passed through a $^5/_8$ in. i.d. × 36 in. long Alundum reactor packed with glass helices; the temperature was maintained at 375° over a 30-in. length by an electric furnace. The products were passed into −78 and −198° cooled traps from which the reaction products were isolated by fractional distillation. The −198° trap contained 28 g of material which was identified by infrared analysis to be almost pure SiF_4, contaminated with traces of CO and CF_2Cl_2. The −78° trap contained 52 g of product which, upon distillation, gave a 1.0-g forecut, 7 g (16%) of 2-chloroperfluoro-2-cyclohexanone (VIIIa), bp 107°, 10 g of 2,2-dichloroperfluorocyclohexenone (IVb), bp 116°, and 28 g (70%) of 2,3-dichloroperfluoro-2-cyclohexenone VIIIb, bp 135–136°. The infrared spectrum of VIIIa showed a C=O absorption at 5.7 and a C=C band at 6.05 μ.

Anal. Calcd for C_6ClF_7O: C, 28.07; Cl, 13.83; F, 51.85. Found: C, 27.65; Cl, 13.64; F, 52.05.

The infrared spectrum of VIIIb showed a C=O band at 5.71 and a C=C band at 6.32 μ.

Anal. Calcd for $C_5Cl_2F_6O$: C, 26.4; Cl, 26.0; F, 41.8. Found: C, 26.1; Cl, 25.7; F, 41.2.

2,2-Dichloroperfluorocyclohexanone Hydrate (IXb).—Water (5 g, 0.28 mol) was slowly added to 25 g (0.08 mol) of 2,2-dichloroperfluorocyclohexanone. After all the water was added, the reaction mixture became a semisolid. Distillation gave a 5-g forecut (mainly water mixed with hydrate) and 22 g (84%) of 2,2-dichloroperfluorocyclohexanone hydrate (IXb), bp 116–118° and mp 95–96°. The infrared spectrum showed an OH band at 3.0 μ.

Anal. Calcd for $C_6H_2Cl_2F_8O_2$: H, 0.61; Cl, 21.6; F, 46.2. Found: H, 0.45; Cl, 21.0; F, 45.8.

2,2-Dichloroperfluorocyclopentanone Hydrate (IXa).—2,2-Dichloroperfluorocyclopentanone, treated as in the previous experiment, gave the hydrate IXa (47%), bp 107–108° and mp 38–40°. The infrared spectrum showed an OH band at 3.0 μ.

Anal. Calcd for $C_5H_2Cl_2F_6O_2$: H, 0.72; Cl, 25.45; F, 40.86. Found: H, 0.85; Cl, 25.1; F, 41.2.

Perfluorocyclohexanone Hydrate (IXd).—Perfluorocyclohexanone, treated as previously described, gave the hydrate IXd (85%), mp 129–131°. The infrared spectrum showed an OH band at 3.0 μ.

Anal. Calcd for $C_6H_2F_{10}O_2$: H, 0.68; F, 64.2. Found: H, 0.71; F, 63.3.

Perfluorocyclopentanone Hydrate (IXc).—Perfluorocyclopentanone, treated as previously described, gave the hydrate IXc (97%), bp 124–125° and mp 75–76°. The infrared spectrum showed an OH band at 3.0 μ.

Anal. Calcd for $C_5F_8H_2O_2$: C, 24.39; F, 61.78; H, 0.81. Found: C, 24.75; F, 62.02; H, 0.85.

1-Hydro-2,2-dichloroperfluorocyclohexanol (Xb).—To a mixture of 8 g (0.21 mol) of $NaBH_4$ and 50 ml of anhydrous ether was slowly added 59 g (0.19 mol) of 2,2-dichloroperfluorocyclohexanone. After the addition was complete, the mixture was refluxed for 6 hr. The excess reagent and $NaBH_4$ complex were decomposed by the addition of aqueous sulfuric acid. The lower layer was separated and the upper aqueous layer was extracted with ether. The oil layer and ethereal extracts were combined, dried, and distilled to give 30 g (50%) of 1-hydro-2,2-dichloroperfluorocyclohexanol (Xb), bp 72° (40 mm). The infrared spectrum showed on OH band at 3.0 μ.

Anal. Calcd for $C_6H_2Cl_2F_8O$: C, 23.80; H, 0.64; Cl, 22.68; F, 48.56. Found: C, 22.5; H, 0.78; Cl, 22.2; F, 47.8.

1-Hydro-2,2-dichloroperfluorocyclopentanol (Xa).—2,2-Dichloroperfluorocyclopentanone, treated as in the previous experiment, gave the alcohol Xa (74%), bp 67–69° (76 mm). The infrared spectrum showed an OH band at 3.0 μ.

Anal. Calcd for $C_5H_2Cl_2F_6O$: C, 22.80; H, 0.76; Cl, 26.99; F, 43.34. Found: C, 22.5; H, 0.84; Cl, 26.5; F, 42.7.

1-Hydroperfluorocyclohexanol (Xd).—Perfluorocyclohexanone treated as previously described gave the alcohol Xd (91%), bp 106–108° and mp 66–68°. The infrared spectrum showed an OH band at 3.0 μ.

Anal. Calcd for $C_6F_{10}H_2O$: C, 25.71; F, 67.86; H, 0.71. Found: C, 26.01; F, 67.75; H, 0.80.

1-Hydroperfluorocyclopentanol (Xc).—Perfluorocyclopentanone, treated as previously described, gave the alcohol Xc (77%), bp 86–87°. The infrared spectrum showed an OH band at 3.0 μ.

Anal. Calcd for $C_5H_2F_8O$: H, 0.86; F, 65.5. Found: H, 1.0; F, 66.3.

Perfluorocyclohexanone–Potassium Fluoride Adduct (XIb).—A mixture of 7.0 g (0.17 mol) of anhydrous acetonitrile, 1.5 g (0.025 mol) of potassium fluoride, and 7.0 g (0.025 mol) of perfluorocyclohexanone was stirred at 55° for 1 hr. The resulting product was cooled to room temperature and the organic volatile products were removed under vacuum. A white, crystalline solid (XIb, 92%) was isolated. The infrared spectrum showed no C=O absorption in the 5.5–5.9-μ region.

Anal. Calcd for $C_6F_{11}KO$: C, 21.43; F, 62.20. Found: C, 19.9; F, 61.2.

(1-Hydroperfluorocyclopentyl)acetic Acid (XIIa).—Perfluorocyclopentanone (147 g, 0.64 mol) was added dropwise to a stirred mixture of 93.5 g (0.90 mol) of malonic acid and 180 ml of pyridine; the temperature was maintained at about 10 to 25°. After stirring for an additional 18 hr at ambient temperature, the mixture was diluted with 900 ml of water and then acidified with 192 ml of 12 *N* hydrochloric acid. The resulting solution was extracted with five 200-ml portions of ether. The organic fractions were combined, washed with 150 ml of water, and dried over sodium sulfate. The solvent was removed under reduced pressure. Recrystallization of the residue from carbon tetrachloride afforded 163 g (89% yield) of colorless crystals. Repeated recrystallization provided an analytical sample, mp 117–119°.

Anal. Calcd for $C_7H_4O_3F_8$: C, 29.2; H, 1.4; F, 52.8. Found: C, 30.18; H, 1.87; F, 53.18.

The infrared spectrum (KBr) exhibited absorption bands at 2.8, 3.3, and 5.83 μ corresponding to the hydroxyl and acid functions.

(1-Hydroxyperfluorocyclohexyl)acetic Acid (XIIb).—Following the above procedure, 100 g (0.36 mol) of perfluorocyclohexanone (Vb) was allowed to react with 83.2 g (0.8 mol) of malonic acid in 240 ml of pyridine. A total of 91 g (83% yield) of colorless crystals, mp 122–125°, was obtained.

Anal. Calcd for $C_8H_4O_3F_{10}$: C, 28.4; H, 1.19; F, 56.2. Found: C, 28.22; H, 1.16; F, 56.07.

The infrared spectrum (KBr) showed absorptions at 2.9 (OH), 3.3, and 5.86 μ (CO_2H).

Ethyl (Perfluorocyclohexylidenyl)acetate (XIII).—Perfluorocyclohexanone (Vb) (10 g, 0.036 mol), carbethoxymethylene triphenylphosphorane (5.2 g, 0.015 mol) and ethyl ether (10 ml) were placed in an aerosol compatibility tube and heated for 3 hr at 70–80°. After cooling to ambient temperature, the mixture was filtered to remove the by-product, triphenylphosphine oxide (3.2 g). Ether was distilled from the filtrate to leave a liquid residue; this was purified by glpc separation to provide 3.0 g (57% yield) of a water-white liquid.

Anal. Calcd for $C_{10}H_8O_2F_{10}$: C, 34.5; H, 1.7; F, 54.6. Found: C, 34.4; H, 1.62; F, 54.6.

The infrared spectrum exhibited absorption bands at 5.72 (ester C=O) and 5.95 μ (C=C stretching).

1-Hydroperfluorocyclohexyl Acrylate (XIVb).—Acrylyl chloride (30 g, 0.33 mol) was rapidly added to 44 g (0.16 mol) of 1-hydroperfluorocyclohexanol containing 0.1 g of hydroquinone. The temperature was raised to 75° and maintained for 10 hr. Hydrogen chloride was evolved during the reaction. Fractionation of the resultant mixture gave 29 g (55%) of 1-hydroperfluorocyclohexyl acrylate (XIVd), bp 51–53° (35 mm), and 17 g (29%) of 1-hydroperfluorocyclohexyl-β-chloropropionate, bp 68° (10 mm).

The infrared spectrum of XIVb showed a C=O band at 5.8 and C=C band at 6.1 μ.

Anal. Calcd for $C_9F_{10}H_4O_2$: F, 56.89; H, 1.20. Found: F, 58.0; H, 1.40.

1-Hydroperfluorocyclopentyl Acrylate (XIVa).—1-Hydroperfluorocyclopentanol, treated as in the previous experiment, gave the acrylate XIVa (32%), bp 57–61° (10 mm).

Anal. Calcd for $C_8F_8H_4O_2$: C, 33.80; F, 53.52; H, 1.48. Found: C, 33.62; F, 53.61; H, 1.52.

The infrared spectrum showed a C=O absorption at 5.8 and a C=C band at 6.1 μ.

Perfluorocyclohexyl Acrylate (XIVd).—Perfluorocyclohexanone (45 g, 0.19 mol) was added to a slurry of 9.3 g (0.16 mol) of KF in 45 g of acetonitrile. The mixture was heated to 50° for 1 hr and then cooled to 20°. Acrylyl chloride (14.5 g, 0.16 mol) was added while the reaction temperature was maintained at 25°. The flask contents were washed with water. The lower layer was dried and distilled to give 36 g (53%) of perfluorocyclohexyl acrylate (XIVd), bp 64° (37 mm). The infrared spectrum showed a C=C band at 5.5 and a C=C band at 6.12 μ.

Anal. Calcd for $C_9F_{11}H_3O_2$: F, 59.37; H, 0.85. Found: F, 58.0; H, 0.90.

Perfluorocyclopentyl Acrylate (XIVc).—Perfluorocyclopentanone treated as in the previous experiment gave the acrylate XIVc (58%), bp 59–61° (58 mm). The infrared spectrum showed a C=O band at 5.5 and a C=C band at 6.1 μ.

Anal. Calcd for $C_8F_9H_3O_2$: F, 56.92; H, 0.99. Found: F, 57.5; H, 1.1.

Preparation of Polyacrylates (XVa–d).—Polymers of the various acrylates were prepared by polymerization of the acrylate ester monomers in aqueous media. In a typical polymerization reaction, 100 g of acrylate ester monomer (XVa), 480 g of deionized water, 3.0 g of sodium lauryl sulfate, and 0.5 g of potassium persulfate were charged to a 1-l., three-necked flask. The mixture was purged by bubbling nitrogen through it, stirred to induce emulsification, and heated to 55° for 6 hr. A latex was obtained containing 21% by weight of solids.

(1-Hydroxyperfluorocyclohexyl)acetyl Chloride (XVIb).—A mixture of 3.0 g (0.01 mol) of (1-hydroxyperfluorocyclohexyl)-acetic acid (XIIb), 1.92 g (0.016 mol) of thionyl chloride and two drops of pyridine was heated for 7 hr while the temperature was raised from 26 to 41°. Infrared analysis of the mixture indicated that most of the starting hydroxy acid had been converted into the hydroxy acid chloride. Attempts to isolate a pure sample of the acid by glpc were unsuccessful; the material eliminated hydrogen chloride on the chromatographic column to give predominantly the corresponding lactone (XVII) (*vide infra*). A portion of the reaction mixture was then added to carbon tetrachloride; refrigeration of this solution caused unreacted hydroxy acid to deposit leaving the acid chloride in the supernatant liquid. The infrared spectrum of this solution exhibited a hydroxyl absorption band at 2.83 and a band corresponding to the acid chloride function at 5.6 μ; no acid or lactone bands were present. Further heating of the orginal reaction mixture for 6 hr at 75° caused about 30% of the hydroxy acid chloride to be converted into the lactone (*vide infra*).

(1-Hydroxyperfluorocyclopentyl)acetyl Chloride (XVIa).—A mixture of 15.3 g (0.05 mol) of (1-hydroxyperfluorocyclopentyl) acetic acid (XIIa), 10.7 g (0.09 mol) of thionyl chloride, and 4 drops of pyridine was heated for 5 hr at 60°. Infrared analysis indicated that the conversion of the hydroxy acid into the hydroxy acid chloride was essentially complete at that time. Further heating for 6 hr at 75° resulted in the formation of some secondary products. However, gas chromatographic analysis showed that approximately 75% of the reaction mixture still consisted of the hydroxy acid chloride. An analytical sample, which was a colorless liquid, was obtained by glpc.

Anal. Calcd for $C_7H_3ClO_2F_8$: H, 0.99; F, 49.6. Found: H, 0.95; F, 50.7.

The infrared spectrum exhibited bands at 2.85 (hydroxyl) and 5.65 (acid chloride C=O) μ.

(1-Hydroxyperfluorocyclohexyl)acetic Acid β-Lactone (XVII).—An intimate mixture of 5.0 g (0.015 mol) of (1-hydroxyperfluorocyclohexyl)acetic acid (XIIb) and 4.26 g (0.03 mol) of phosphorus pentoxide was heated in a micro distillation apparatus until 3.9 g of distillate, boiling range of *ca.* 135–145°, was collected. Glpc analysis showed this to be 95% pure (77% yield). An analytical sample was obtained by glpc separation.

Anal. Calcd for $C_8H_2O_2F_{10}$: H, 0.63; F, 59.4. Found: H, 0.66; F, 58.92.

The lactone carbonyl absorption occurs at 5.3 with a shoulder at 5.23 μ.

(Perfluorocyclohexylidenyl)acetic Acid (XVIII).—(1-Hydroxyperfluorocyclohexyl)acetic acid (XIIb) (23.5 g, 0.70 mol) was mixed with 35.2 g of 100% sulfuric acid and heated until 22 g of distillate (bp 190–205°) had been collected. This material, which solidified upon cooling to ambient temperature, was recrystallized from petroleum ether (bp 65–110°). A total of 19.9 g (89% yield) of colorless crystals was obtained. An analytical sample, mp 66–67°, was prepared by further recrystallization from petroleum ether.

Anal. Calcd for $C_8H_2O_2F_{10}$: H, 0.63; F, 59.4. Found: H, 0.65; F, 58.94.

The infrared spectrum displays bands at 5.77 (shoulder at 5.65) and 5.94 μ corresponding to the acid and olefinic functions, respectively.

(Perfluorocyclohexylidenyl)acetyl Fluoride (XIX).—(Perfluorocyclohexylidenyl)acetic acid (5.0 g, 0.02 mol), 2.38 g (0.02 mol) of thionyl chloride, and 1 drop of pyridine were mixed and the temperature slowly was raised to 80°. After 30 min, the temperature was increased and 2.7 g of colorless liquid (bp *ca.* 120°) was distilled from the mixture. Glpc and infrared analysis indicated that 93% of this distillate was the acid fluoride (47% yield). An analytical sample was obtained by glpc separation.

Anal. Calcd for C_8HOF_{11}: C, 29.8; H, 0.31. Found: C, 29.8; H, 0.35.

The infrared spectrum showed bands at 5.39 and 5.95 μ corresponding to the acid fluoride and olefinic functions, respectively.

Upon standing in an open vessel the acid fluoride hydrolyzed to the corresponding acid, XVIII, identified by comparison of its melting point and infrared spectrum with those of an authentic sample (*vide ultra*).

Treatment of the acid fluoride with warm ethanol converted it into the ethyl ester XIII, identified by comparison of its infrared spectrum with that of an authentic sample (*vide ultra*).

(Perfluorocyclohexylidenyl)acetyl Chloride (XX).—(Perfluorocyclohexylidenyl)acetic acid (XVIII) (37.0 g, 0.12 mol) and benzotrichloride (35.2 g, 0.18 mol) were mixed and heated in a spinning-band distillation apparatus. The resulting acid chloride was distilled from the reaction mixture, bp 130–140°. Redistillation gave 32.6 g, of colorless liquid, bp 141–142°. Glpc analysis showed this to be 96% pure (78% yield). An analytical sample was purified by glpc separation.

Anal. Calcd for C_8HClOF_{10}: C, 28.4; H, 0.3; Cl, 10.5. Found: C, 26.4; H, 0.26; Cl, 10.4.

Absorption bands for C=O (acid chloride) and C=C stretching appear at 5.52 and 5.93 μ, respectively.

A sample of the acid chloride hydrolyzed upon standing in an open vessel to the parent acid (XVIII) identified by comparison of its melting point with that of an authentic sample (*vide ultra*).

Warming the acid chloride with ethanol produced the ethyl ester (XIII) identified by comparison of its infrared spectrum with that of an authentic sample (*vide ultra*).

Registry No.—IIa, 336-34-5; IIb, 4641-72-9; IIIa, 10363-97-0; IIIb, 10363-96-9; IIIc, 10363-98-1; IIId, 10363-93-6; IIIe, 10363-94-7; IIIf, 10363-95-8; IVa, 5561-34-2; IVb, 5561-36-4; Va, 376-66-9; Vb, 1898-91-5; VIa, 13394-65-5; VIb, 16621-77-5; VII, 16621-78-6; VIIIa, 10534-21-1; VIIIb, 5364-93-2; IXa, 16621-81-1; IXb, 16621-82-2; IXc, 16621-83-3; IXd, 16621-84-4; Xa, 16621-85-5; Xb, 16621-86-6; Xc, 16621-87-7; Xd, 16621-88-8; XIb, 16621-89-9; XIIa, 16621-90-2; XIIb, 16621-91-3; XIII, 16622-02-9; XIVa, 16621-92-4; XIVb, 16621-93-5; XIVc, 16621-94-6; XIVd, 16621-95-7; XVIa, 16621-96-8; XVII, 16621-97-9; XVIII, 16621-98-0; XIX, 16621-99-1; XX, 16622-00-7; 1-hydroxyperfluorocyclohexyl-β-chloropropionate, 16622-01-8.

Acknowledgments.—We are indebted to Mr. C. J. Piasecki for technical assistance.

Perchloric Acid Isomerization of Oleic Acid

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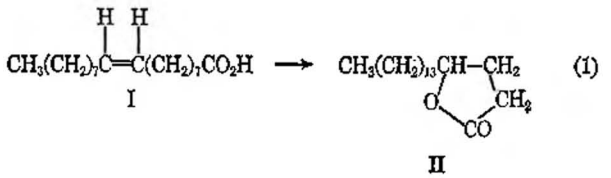
Received September 1, 1967

γ-Stearolactone was prepared from oleic acid using 70% perchloric acid in place of the concentrated sulfuric acid customarily used. Improved yields were obtained and the crude reaction product was easier to purify. Isomerization, addition, and polymerization reactions were all found to be important in this process. The procedure is applicable to other olefinic acids, monohydroxy acids, and the methyl esters of olefinic acids. δ-Stearolactone and di- and triestolides were the important intermediates in the production of γ-stearolactone. Other compounds isolated from the final product were the cyclic ketones, 2-tridecyl-2-cyclopentenone and 2-dodecyl-2-cyclohexenone, methyl branched C_{18} γ-lactones, produced by isomerization of the hydrocarbon chain prior to lactone formation, and δ-stearolactone.

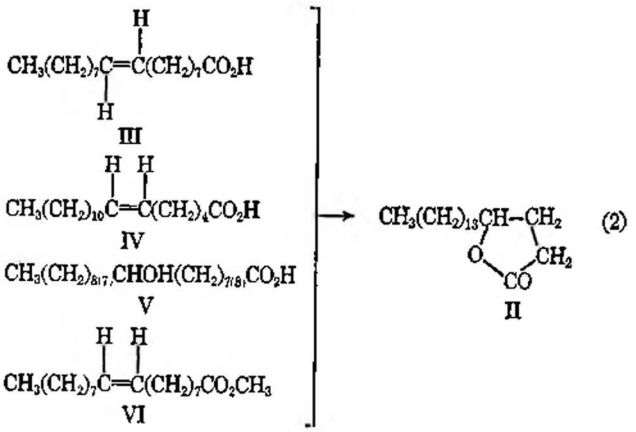
The sulfuric acid catalyzed isomerization of oleic acid, I, to 4-tetradecyl-5-butyrolactone (γ-stearolactone), II, shown in eq 1 was first discovered by Zhukov and



(1)

Shestakov in 1903,[2a] and was later studied in 1924.[2b] Although the yield is low and the isolation procedure laborious, this has remained the simplest and most direct route to γ-stearolactone. More recently, the reaction, using shorter chain monounsaturated acids as starting materials, has been restudied by Ansell and Palmer.[3,4]

Our studies show that 70% perchloric acid is superior to sulfuric and methanesulfonic acids in the isomerization of oleic acid; higher yields of γ-stearolactone are obtained and the recovery of the pure γ-lactone from the crude reaction product is much easier. Preliminary studies indicate that other C_{18}-monounsaturated acids can be readily converted into γ-lactone. Examples are elaidic acid (III) and petroselinic acid (IV, *cis*-6-octadecenoic acid). The hydration product of oleic acid, 9(10)-monohydroxystearic acid (V), yields the lactone smoothly, as does methyl oleate (VI) (eq 2). Yields of



(2)

γ-stearolactone under optimum isomerization conditions are essentially identical for elaidic, petroselinic, and 9(10)-monohydroxystearic acid; the yield from methyl oleate is lower because of the slow hydrolysis of the methyl ester under the reaction conditions.

Perchloric acid–oleic acid mixtures were heterogeneous under all the conditions studied in this work. Optimum conditions for the production of γ-stearolactone were determined by studying the reaction variables: temperature, perchloric acid–oleic acid mole ratio, perchloric acid concentration, rate of stirring, and reaction time.

Effect of Temperature.—At 30° (24 hr, 1:1 perchloric–oleic acid mole ratio), little γ-lactone (0.8%) was formed; the crude reaction product consisted essentially of estolides. The effect of varying the temperature (24 hr, 1:1 perchloric–oleic acid mole ratio) is illustrated in Figure 1. L, E, and A in Figure 1 stand, respectively, for the characteristic γ-lactone band at 1780, ester band at 1740, and acid band at 1710 cm^{-1}.[5] Figure 1 illustrates the decrease in γ-lactone yield with increasing temperature, the γ-lactone having essentially disappeared at 115°. The highest yield of γ-lactone was obtained at 85°, the order being 85 > 100 > 115°.

Effect of Reaction Time.—Maximum yields (decreasing order for 1:1 perchloric–oleic acid mole ratio) are 85°, 10 hr; 100°, 3 hr; 115°, 1 hr. The yield of γ-stearolactone as a function of the reaction time is shown in Figure 2.

Effect of Perchloric Acid–Oleic Acid Mole Ratio.—In the reaction mixture, the organic and inorganic layers are saturated with respect to one another. A 1:1 mole ratio of perchloric acid to oleic acid was found suitable for studies of the optimum synthetic conditions. The importance of the perchloric acid–oleic acid mole ratio is illustrated in Figure 3.

The 1:100 mole ratio produces estolide but no γ-lactone; with the 1:10 ratio, γ-lactone is produced and the intermediate estolide decreases. In the 1:1 mole ratio the estolide completely disappears and degradation reactions now become important. Since the 1:1 mole ratio gives acceptable yields, it was felt that use of higher mole ratios needlessly increases the potential hazard inherent in the use of perchloric acid. Safety shields should be used even at the 1:1 mole ratio.[6]

Effect of Stirring.—Because oleic acid and aqueous 70% perchloric acid are immiscible throughout the

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(2) (a) A. A. Zhukov and P. I. Shestakov, *J. Russ. Phys. Chem. Soc.*, **35**, 1 (1903); *ibid.*, **40**, 830 (1908); (b) P. W. Clutterbuck, *J. Chem. Soc.*, **125**, 2330 (1924).

(3) M. F. Ansell and M. H. Palmer, *J. Chem. Soc.*, 2640 (1963).

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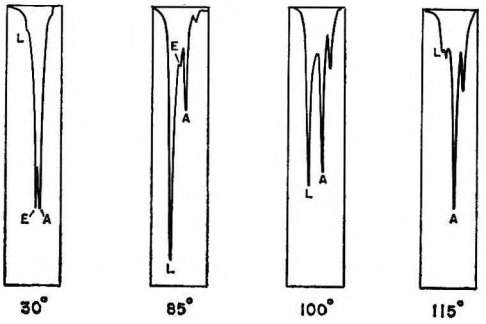


Figure 1.—The effect of temperature on the yield of γ-stearolactone in a 24-hr, 1:1 mole ratio reaction.

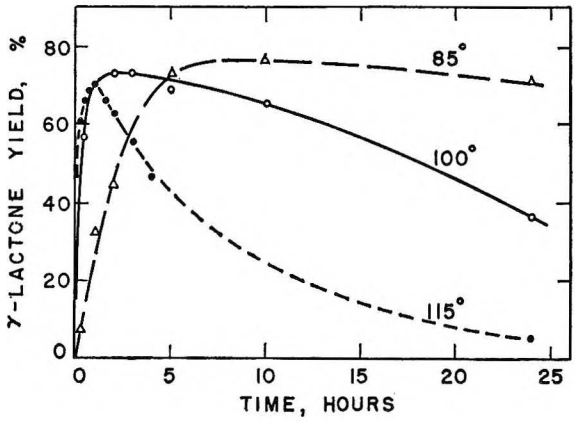


Figure 2.—The effect of reaction time on the yield of γ-stearolactone at three temperatures (1:1 mole ratio).

range of $HClO_4$–oleic acid mole ratios from 1:1 to 1:100, the rate of reaction will be influenced by the rate of stirring. The difference in behavior (85°, 5 hr, 1:1 mole ratio) between the stirred and nonstirred system is shown in Figure 4. The difference indicates that the extent of reaction is limited by the rate of diffusion of a reactant across the interface to the bulk of one of the two phases and does not occur principally at the interface, or reaction is occurring at the interface but does not have adequate surface area.

To distinguish between these possibilities, the reaction was carried out with the more intense mixing provided by a Vibromixer. No increase either in rate or yield was observed over that stirred with a magnetic stirrer. This strongly suggests that the reaction occurs in the bulk of one of the two phases. Furthermore, a reaction mixture containing only a catalytic amount of $HClO_4$ (1:100 mole ratio, 5 hr, 85°), mixed by the Vibromixer, showed substantially no reaction.

These facts, along with the knowledge that the extent of the reaction is influenced by the perchloric acid–oleic acid mole ratio, indicate that the principal reaction occurs in the perchloric acid phase; the reaction at the interface does not make any significant contribution.

Interactions of Variables.—Experimental conditions chosen finally as most satisfactory for a laboratory procedure represented a compromise among all the possible interactions. These are 100° for 3 hr with a 1:1 perchloric–oleic acid mole ratio.

Intermediates.—The intermediates in the perchloric acid catalyzed isomerization were studied by isolating and identifying the products formed during a 1-hr reaction at 85° with a 1:1 perchloric acid–oleic acid mole ratio; this reaction time is considerably less than

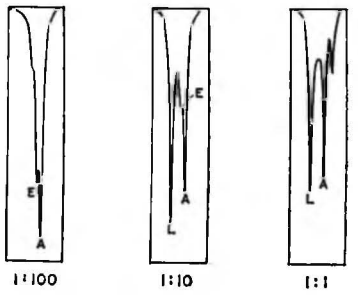


Figure 3.—The effect of perchloric–oleic acid mole ratio in 24-hr reactions at 100°.

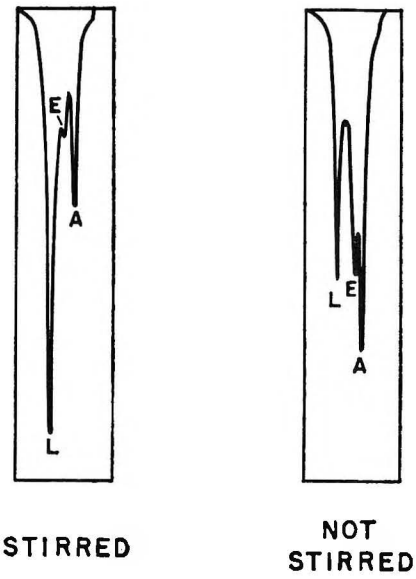


Figure 4.—The effect of stirring on γ-stearolactone yield in 5-hr, 1:1 mole ratio reactions at 85°.

required for maximum conversion to γ-stearolactone. The analytical data (expressed in milliequivalents per gram) show the extent of reaction at 1 and at 10 hr, respectively: acid equivalent 1.38 and 0.56; hydrogenation equivalent 1.13 and 0.39; ester equivalent 1.70 and 3.48.[7]

The relatively large ester value after 10 hr, coupled with the extensive consumption of carboxyl and olefin functions, indicates a high conversion into lactone. In the 1-hr reaction, however, the ester value is lower, and the acid and hydrogenation values higher, indicating only a partial conversion into final product, γ-lactone. The infrared spectrum of the 1-hr reaction product has a characteristic absorption at 968 cm^{-1} due to *trans*-1,2-disubstituted olefins.

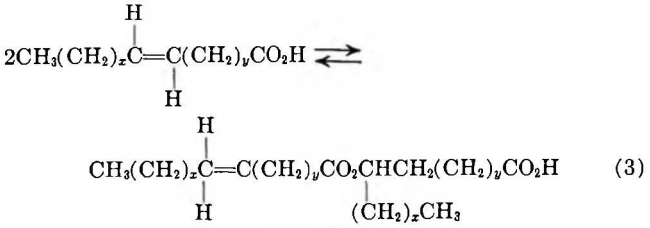
The 1-hr reaction product was methylated with freshly prepared diazomethane and separated into five major components, by partitioning in a Craig countercurrent distribution apparatus; a total of 700 transfers was performed by the single withdrawal procedure. Figure 5 shows a plot of weight against transfer number for the distribution.

Compounds corresponding to peaks A, C, D, and E are methyl esters of carboxylic acids present in the original reaction mixture; peak B corresponds to neutral materials.

Fraction A (1.1%) is a complex mixture of methyl esters of monomeric and polymeric monohydroxycar-

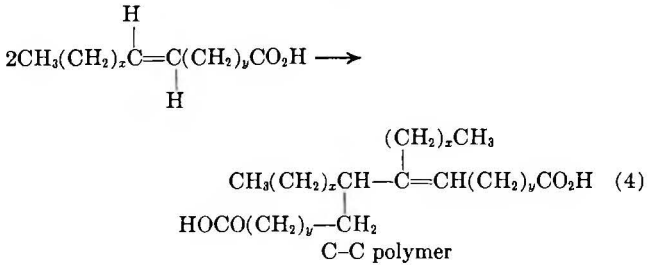
(7) J. S. Showell, *J. Amer. Oil Chemists' Soc.*, **36**, 343 (1959).

boxylic acids. Fraction C (20.2%) is a complex mixture of geometrical and positional isomers of octadecenoic acid. The double bond of the octadeceonic acids was located from $\Delta^{4,5}$ to $\Delta^{15,16}$ with a slightly higher proportion of isomers with the double bond at the center of the chain. Fractions D (33.7%) and E (5.9%) are dimers and trimers, respectively, of 9-octadecenoic acid. Detailed studies show that these exist as two distinct types "C–O polymer" and the "C–C polymer." The former class, the C–O polymers (eq 3),



(3)

C–O polymer



(4)

C–C polymer

are esters that are formed by the intermolecular addition of the carboxyl of one octadecenoic acid molecule to the double bond of another, with the formation of a C–O–C linkage of the typical ester (estolide). The latter class, the C–C polymers (eq 4), is formed by the addition of a carbonium ion (or its functional equivalent) to a double bond of another molecule, producing a C–C linkage forming a branched carbon skeleton double the original chain length. The C–O polymers are reversibly formed while C–C polymers are irreversibly formed in the reaction mixture. Other studies have shown that as the reaction time is increased the per cent of C–C polymer increases and forms an irreversible drain of the material from the pool of reactive intermediates in the reaction. The dimer fraction (peak D) could be partially converted into γ-lactone under the conditions of the isomerization procedure but could not be completely converted because of C–C polymer.

The neutral fraction B (nonacidic in the original crude reaction mixture) is a mixture of γ-stearolactone (74.7%) (infrared, 1780 cm^{-1}) and δ-stearolactone (25.3%) (1740 cm^{-1}). No other C=O bands were observed nor were conjugated carbonyl groups detected in the ultraviolet spectrum. Only one molecular ion peak at *m/e* 282 was observed under conditions of low ionization in a mass spectrometer. The mass spectrum of the mixture had its two most intense peaks at *m/e* 85 and 99 which correspond, respectively, to lactone ring fragments resulting from the cleavage of the side chains from a γ- and δ-lactone. Studies with the pure γ- and δ-lactones confirmed these observations.[8]

A low-intensity peak was observed at *m/e* 113, corresponding to a ring fragment remaining when the side chain was cleaved from an ε-lactone. However, the

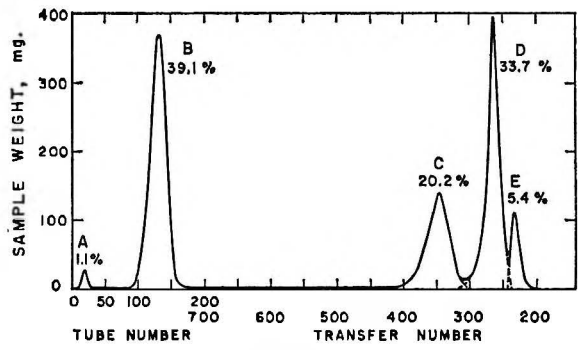


Figure 5.—Countercurrent distribution of the esterified reaction product (85°, 1 hr, 1:1 mole ratio).

extreme weakness of this peak plus a failure to detect any compound by glpc and tlc make the existence of the ε-stearolactone questionable. The δ-lactone is probably an intermediate in the production of the γ-lactone as is shown by the fact that the proportion of the δ- to γ-lactone (25.3:74.7) is much higher in fraction B than in a reaction carried out under the preparative conditions (1.8:98.2).

Competing Reactions.—The method of isolation permitted the essentially quantitative (≥99%) recovery of the organic material from the reaction mixture. The neutral fraction was shown to consist of the normal chain γ-stearolactone, branched chain C_{18} γ-lactones, δ-stearolactone, 2-tridecyl-2-cyclopentenone, and 2-dodecyl-2-cyclohexenone, representing 74.7% of the original crude product; the balance of the crude product consisted of the acidic fraction (isomeric octadecenoic acids, dimers, and trimers). The normal chain γ-lactone is 64.5% of the total crude product, while the branched chain γ-lactones are 6.6%. The δ-stearolactone represents 1.2% while the substituted cyclopentenone and substituted cyclohexenone are 2.3 and 1.7%, respectively.

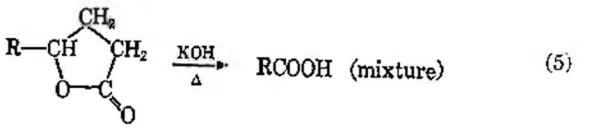
Crystallization of the original crude neutral fraction from acetone cleanly produces a solid precipitate consisting of the normal chain γ-lactone and a small amount of δ-lactone as the principal impurity; the liquid filtrate contains little normal chain γ-lactone. Two recrystallizations of the precipitate yield a solid whose physical properties are essentially identical with the material in the filtrate from the final crystallization.

The branched chain γ-lactones are an isomeric mixture resulting from the replacement of the normal tetradecyl side chain of the γ-stearolactone by a methyl tridecyl side chain. The branched chain γ-lactones show a relatively broad peak of shorter retention time than the normal γ-lactone in the glpc. This decrease in retention time is characteristic of branched chain compounds compared to normal chain isomers,[9] the breadth of the curve reflects the multiplicity of branched isomers present.

Integration of the nmr spectra indicates that the average number of methyl groups is two per molecule. Fusion of the branched γ-lactones with the molten KOH leads to the production of a mixture of branched acids *via* the dehydrogenation of the hydroxy acids to keto acids and the subsequent base-catalyzed cleavage of the

(8) W. H. McFadden, E. A. Day, and M. J. Diamond, *Anal. Chem.*, **37**, 89 (1965).

(9) J. W. Farquhar, W. Insull, Jr., P. Rosen, W. Stoffel, and E. H. Ahrens, Jr., *Nutr. Rev. Suppl.*, **17**, 1 (1959).



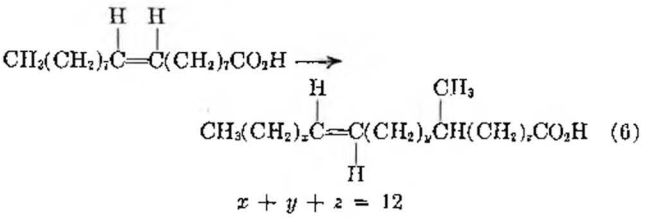
(5)

keto acids (eq 5). Glpc of the methyl esters of the acids revealed at least seven compounds with retention times greater than undecanoate and less than pentadecanoate, corresponding to none of the normal chain methyl esters. The straight chain γ-lactone produced only the straight chain pentadecanoic acid under identical conditions.[10] This behavior is to be expected when a single methyl group is randomly distributed on the chain. The mass spectra of the branched γ-lactones exhibit fragmentation patterns which differ principally from the normal chain isomer in having two series of peaks corresponding to $P - (15 + 14N)$ and $P - [15 + 14(N - 2)]$, where $N = 5$–12. This is the pattern of behavior expected for the random distribution of a single methyl group in the tridecyl side chain.[11] Under the preparative conditions the ratio of the normal chain γ-lactone (64.5%) to the branched chain lactones (6.6%) is approximately 10:1. There was no evidence for a methyl group located on the γ-lactone ring.

The δ-stearolactone, XI, was isolated in small yield and showed the characteristic ester carbonyl band at 1740 cm^{-1} in the ir region. Fusion of the δ-stearolactone with molten KOH caused cleavage of the δ-lactone analogous to that shown in eq 5. Glpc of the methyl ester of the fusion product showed only the tetradecanoic acid corresponding to normal chain δ-lactone.

The small amounts of substituted cyclic ketones, XVIIa and XVIIb, were characterized principally by means of their spectral properties. 2-Dodecyl-2-cyclohexenone, XVIIb, showed an infrared band at 1680 cm^{-1} and an ultraviolet band at 230 mμ characteristic of an α,β-conjugated cyclohexenone.[12,13] 2-Tridecyl-2-cyclopentenone, XVIIa, showed infrared bands at 1710 and 1640 cm^{-1}, characteristic of an α,β-unsaturated carbonyl group and a conjugated double bond, respectively.[5] The ultraviolet spectrum had a maximum at 223 mμ.[13,14] No attempt was made to show that the alkyl group of XVIIa and XVIIb were branched.

The reactions leading to the formation of the materials in both the neutral and acidic fractions can be formally broken into three classes: addition (inter- and intramolecular), isomerization, and polymerization. Hydration of the double bond to form hydroxy acids corresponds to intermolecular and cyclization to γ- and δ-lactones and to the cyclic ketones corresponds to intramolecular addition. Isomerization reactions are represented by three classes: *cis–trans* and positional isomerization of the double bond, and the chain branching reaction (eq 6) leading to the formation of the methyl side chains. The polymers formed are of two types: C–O polymers which contain an olefinic double bond, an ester, and a carboxyl function (eq 3); C–C polymers which contain an olefinic double bond and two carboxyl groups (eq 4).



(6)

From the nature of the reagents that form the γ-lactone (perchloric acid, sulfuric acid, methanesulfonic acid, microreticular resins), a carbonium ion intermediate must be formed. The variety of products and the types of reaction (addition, isomerization, and polymerization) are characteristic of carbonium ion reactions in general.

Occurrence of the principal reaction in the perchloric acid phase is consistent with the formation of a charged intermediate. The reaction of oleic acid (I) with a proton occurs *via* the rearrangement into a carbonium ion (VII) of the complex of the partially hydrated oxonium ion with the π electrons of the double bond. The resulting carbonium ion (VII) can then undergo a variety of reactions. These are represented schematically in Figure 6. *cis–trans* isomerization results from loss of the proton from the original addition point after rotation about the new single bond. A carbonium ion can accept an anion (or the formal equivalent, an electron pair) to form a neutral adduct such as a hydroxy acid. Thus it was found that 9(10)-monohydroxystearic acid (V) readily forms γ-stearolactone under the reaction conditions. This indicates that the reverse process, the protonation of the hydroxyl and the subsequent loss of water, is also a rapid, easily reversible one. The carbonium ion can undergo polymerization reactions whose easy reversibility to form a γ-lactone was demonstrated. On the other hand, the carbonium ion can alkylate the octadecenoic acid (II or IX) to form a C–C polymer (eq 4). This reaction, however, is an irreversible process under the reaction conditions. The carbonium ion (VII), the product of the protonation of the original double bond of oleic acid, can lose a proton to form VIII, an isomeric octadecenoic acid which by a repetitive sequence of proton addition and elimination reactions can form a mixture of isomeric octadecenoic acids, IX. Protonation of the octadecenoic acids, of general structure IX, will lead to the general carbonium ion X.

Although the rearrangement of the initial carbonium ion (VII) is visualized in Figure 6 as occurring through sequence of repetitive addition and proton elimination reactions, it is possible that the reactions occur by an intramolecular path. The present work provides no evidence on this point. Unpublished work strongly suggests the existence of both inter- and intramolecular paths.[15] The carbonium ion X is written in such a manner as to suggest that intramolecular processes can occur when x and y have suitable values. The work has quite clearly shown that δ-stearolactone XI ($x = 12, y = 2$) is formed in the reaction and probably acts as an intermediate in the subsequent formation of γ-stearolactone, II ($x = 13, y = 1$). The γ-stearolactone (II) forms a small amount of the isomeric octadecenoic acids (IX) under the conditions of the isomerization reaction. The isomerization of the carbon skeleton to

(10) R. G. Ackman, P. Linstead, B. J. Wakefield, and B. C. L. Weedon, *Tetrahedron*, **8**, 221 (1960).

(11) K. Biemann, "Mass Spectrometry; Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(12) H. Born, R. Pappo, and J. Szmuszkovicz, *J. Chem. Soc.*, 1779 (1953).

(13) M. F. Ansell and S. S. Brown, *ibid.*, 2955 (1958).

(14) H. S. French, *J. Amer. Chem. Soc.*, **74**, 514 (1952).

(15) J. S. Showell and I. S. Shepherd, unpublished work.

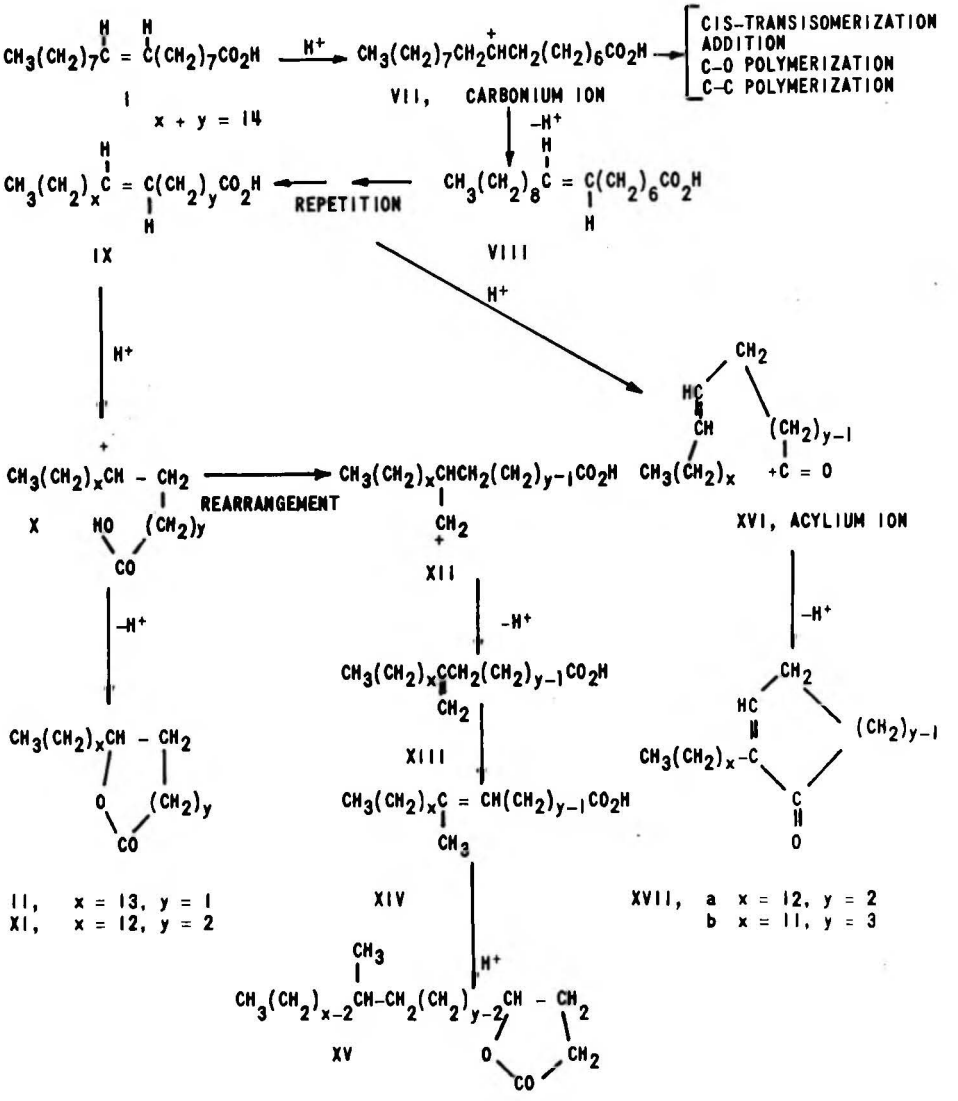


Figure 6.—Schematic representation of the reaction path.

the methyl branched γ-lactone is an irreversible process. This is visualized as taking place *via* carbonium ion X which rearranges from a secondary to a primary carbonium ion XII; carbonium ion XII can then undergo proton elimination to give the branched olefinic acid XIII; this would isomerize under the reaction conditions to the more stable isomer XIV. This branched octadecenoic acid (XIV) could then isomerize to a methyl branched γ-lactone (XV) by a process paralleling the formation of the straight chain γ-lactone. However, it is surprising that the branching reaction is as efficient as it appears to be. The observed ratio of the unbranched γ-lactone to the branched chain γ-lactone is approximately 10. The rearrangement of the secondary to the primary carbonium ion is energetically running up hill by at least 26 kcal mol.[16] The existence of such a large energy difference strongly suggests that another path may be an important one. The reaction path for the branched γ-lactone may be *via* an insertion reaction to form a cyclopropane which can be visualized as rearranging under these conditions,[17] or *via* a protonated cyclopropane intermediate of the type visualized in the protonation of the cyclopropane.[18a] Unpublished work from this laboratory has shown that a cyclopropane acid under these conditions will lead to γ-lactone.[18b]

The formation of the substituted cyclic ketones XVIIa ($x = 12, y = 2$) and XVIIb ($x = 11, y = 3$) is a different reaction involving protonation of the carboxyl group of the octadecenoic acid IX to form an acylium XVI which then undergoes an intramolecular cyclization.

Other acids beside perchloric acid were also investigated as reagents for the isomerization but none was as effective. These were sulfuric acid (96.5%), methanesulfonic acid, glacial phosphoric acid (84.2% H_3PO_4), and the sulfonic acid resin, Amberlyst 15.[19]

Sulfuric acid gave lower yields of γ-lactone and the work-up was complicated. Methanesulfonic acid caused isomerization but subsequent condensation reactions were significant and the resulting yield of lactone was poor. Glacial phosphoric acid was without action on oleic acid under extreme conditions of temper-

(16) F. H. Field and J. L. Franklin, "Electron Impact Phenomena and the Properties of Gaseous Ions," Academic Press Inc., New York, N. Y., 1957.

(17) J. Bayless, L. Friedman, J. A. Smith, F. B. Cook, and H. Shechter, *J. Amer. Chem. Soc.*, **87**, 661 (1965).

(18) (a) R. L. Baird and A. A. Aboderin, *ibid.*, **86**, 252 (1964); (b) J. S. Showell and W. R. Noble, unpublished work.

(19) Mention of products or companies does not constitute an endorsement by the Department of Agriculture over others of a similar nature not mentioned.

ature and time (130°, 24 hr). The sulfonic acid resin, Amberlyst 15, gave low yields of lactone; polymerization seemed to be the predominating reaction.

Other long chain monoolefinic acids were also investigated briefly. Undecylenic acid (10-hendecenoic acid) and erucic acid (13-docosenoic acid) were also isomerized under the optimum conditions used for oleic acid. Under these conditions γ-undecalactone was obtained in 48% yield as a colorless liquid, while γ-erucalactone was obtained in 46% yield as a white solid (mp 63°).

Experimental Section

General Procedure for Perchloric Acid Isomerization Reactions.—Oleic acid (99.5 mol %, 2.00 g, 7.08 mmol) and a quantity of 70% perchloric acid (exact $HClO_4$ content determined by titration) chosen to give the required $HClO_4$–oleic mole ratio were allowed to react in a jacketed flask concentrated to a constant-temperature bath. Maintainance of a positive nitrogen pressure prevented autoxidation by atmospheric oxygen; intimate mixing of the two phases was ensured by magnetic stirring. After a specified time interval, the reaction was quenched by pouring the hot mixture into cold water contained in a liquid-liquid extractor. Any residue remaining in the reaction flask was rinsed into the extractor with hydrocarbon solvent. The organic material was quantitatively recovered by extracting with distilled hexane. The γ-stearolactone content of the crude reaction product recovered from the hydrocarbon extract was estimated from the intensity of the infrared absorption at 1780 cm^{-1} (5 g/l., CS_2 solution).

Pure γ-stearolactone was treated with an equimolar amount of perchloric acid (70.0%) at 100° for 3 hr, the large-scale preparative conditions. The reaction mixture was worked up according to the standard procedure and the recovery of organic material was essentially quantitative. The crude residue consisted of 91% γ-lactone and the balance consisted principally of unsaturated polymeric acids. In studies at 85° for 10 hr and at 115° for 1.5 hr, recovery of the γ-lactone was 93 and 77%, respectively.

Large-Scale Preparation of γ-Stearolactone.—Large quantities of γ-stearolactone were prepared using the same procedure but with 200-g charges of oleic acid (99.2 mol %). They were a mole ratio of 1:1, steam-bath temperature, and a reaction time of 3 hr.

The crude reaction product isolated by liquid–liquid extraction was purified by chromatography and crystallization. The first purification step consisted of column chromatography, eluting with benzene on a short wide column of Florisil (6 g of adsorbent/g of sample). This step removed all acidic materials and the more highly colored impurities. The material recovered from the benzene eluate was crystallized at −32° from acetone (10 ml/g). Most of the impurities were removed by the first crystallization from which a liquid filtrate fraction (amounting to 12.6% of the quantity crystallized) was obtained. The principal impurity in the solid was the isomeric δ-lactone; two more crystallizations yielded pure γ-lactone. All subsequent filtrate fractions amounted to only 1% and were solids. The yield of pure γ-stearolactone (mp 51–52°) was 60–65%.

Countercurrent Distribution Studies.—Reaction conditions were chosen to give relatively low conversion to γ-stearolactone and a relatively high conversion to intermediates in the reaction: 85°, 1:1 mole ratio of oleic acid to perchloric acid, and a 1-hr reaction time (maximum yield is obtained at 10 hr). The reaction and extraction procedures were identical with those described in preceding sections; however, to ensure a sample as free of autoxidation products as possible, the extraction was performed under a nitrogen atmosphere using water and hexane which had been saturated with nitrogen. The crude reaction product was esterified with diazomethane.

The sample (28 g) was divided into five parts and placed in the first five tubes of a 200-tube Craig countercurrent distribution apparatus. It was then partitioned between acetonitrile (40 ml) and *n*-hexane (10 ml). The apparatus was allowed to run for 700 transfers while a single withdrawal procedure was followed.[20] A fundamental weight curve (Figure 5) was drawn of the material remaining in the apparatus and the single withdrawal fractions.

Each fraction was subjected to analysis by gas–liquid partition and thin layer chromatography and infrared spectroscopy. In addition, fraction B (the lactone fraction) was analyzed by mass spectrometry (Consolidated Electrodynamics Corp. 103-C mass spectrometer), ionization voltage 80 eV.

The glpc data were obtained at 214° with an 8 ft × 0.25 in. i.d. column packed with 20% ethylene glycol succinate on 60–80 mesh Chromosorb W. Infrared spectra were obtained with a Perkin-Elmer Infracord Model 137 using CS_2 solutions (5 g/l.). Thin layer chromatography data were obtained from silica gel G plates developed with petroleum ether (bp 80–90)–diethyl ether–glacial acetic acid (180:20:4).

Fraction A, 1.1% of the charge, was not characterized. The glpc data (long retention times), tlc data (R_f = 0), and the location in the countercurrent distribution (partition coefficient, 0.011) suggest a very polar material. The infrared spectrum showed a typical hydroxyl envelope at 3300–3500 cm^{-1}.

Fraction B (Lactones).—Fraction B, 39.1% of the charge and partition coefficient, 0.91, was analyzed by mass spectrometry. A molecular ion peak was observed at *m/e* 282, while strong fragment ion peaks were observed at *m/e* 85 and 99.[8,21] The infrared spectrum had two carbonyl absorptions: 1780 (γ-lactone) and 1740 cm^{-1} (δ-lactone). Two glpc peaks were observed, one with the same retention time as γ-stearolactone; the other, with a longer retention time, was δ-stearolactone. The relative amounts of the two lactones, determined by integration of the glpc curve, were γ-stearolactone (74.7%) and δ-stearolactone (25.3%).

Two spots were observed on a tlc plate, one with an R_f value identical with that of pure γ-stearolactone; the other spot, with a smaller R_f value, was δ-stearolactone.

Anal. Calcd for $C_{18}H_{34}O_2$: ester equiv, 282.5. Found: ester equiv, 280.6.

Fraction C (Methyl Octadecenoates).—Fraction C, 20.2% of the charge and partition coefficient, 5.5, on glpc yielded one large peak with the same retention time as methyl oleate. A number of much smaller peaks were observed but not identified. *trans* double bond absorption at 968 cm^{-1} in the infrared spectrum was observed. Positional isomerization was determined by oxidative cleavage.[22] The cleavage products were esterified with BF_3–CH_3OH and compared by glpc to standard methyl ester mixtures ranging from C_8 to C_{15}. The results showed that the double bond was distributed from $\Delta^{4,5}$ to $\Delta^{15,16}$ with slightly more double bond at the center of the chain.

Anal. Calcd for $C_{19}H_{36}O_2$: ester equiv, 296.5; hydrogen no., 296.5; mol wt, 296.5. Found: ester equiv, 329; hydrogen no., 318; mol wt, 296 (mass spectrometry).

Fraction D (Methyl Ester Dimer).—Fraction D, 33.7% of the charge and partition coefficient, 17, had an ester carbonyl absorption at 1730 cm^{-1} and a *trans* double bond absorption at 968 cm^{-1}. The sample was completely retained when injected on either polyester or silicone rubber glpc columns.

Anal. Calcd for $C_{37}H_{70}O_4$: mol wt, 579. Found: mol wt, 647.

Fraction E (Methyl Ester Trimer).—Fraction E, 5.9% of the charge and partition coefficient, 33, also had an ester carbonyl absorption at 1730 cm^{-1} and a *trans* double bond absorption at 968 cm^{-1} (less intense than fraction D). This sample was also completely retained by glpc columns.

Anal. Calcd for $C_{55}H_{104}O_6$: mol wt, 861. Found: mol wt, 826.

Conversion of the Dimer Fraction (Fraction D) into γ-Stearolactone.—The dimer fraction was allowed to react with 70% perchloric acid; mole ratio of $HClO_4$ to methyl ester dimer was 2:1 at 85° for 24 hr. The infrared spectrum of the crude reaction product showed that although some of the ester configuration has been retained most (67%) of the dimer had been converted into γ-lactone. This indicates that part of the dimer is in a reversible pool leading to γ-lactone.

Isolation of Polymeric Compounds from a Typical Reaction Product.—A reaction product (85°, 24 hr, 1:1 perchloric acid–oleic acid mole ratio), typical of those with a high γ-stearolactone

(20) L. C. Craig and D. Craig in "Technique of Organic Chemistry," Vol. III, Part 1, A. Weissberger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1956, p 149.

(21) E. Honkanen, T. Moisio, and P. Karvonen, *Acta. Chem. Scand.*, **19**, 370 (1965).

(22) M. R. Subbaram, and C. G. Youngs, *J. Amer. Oil Chemists' Soc.*, **41**, 150 (1964).

yield, was chromatographed on 100 mesh reagent grade silicic acid. The first fractions, all monomeric, were eluted from the column with 4% diethyl ether in redistilled hexane. They were, in order, octadecenoic acids and C_{18} γ- and δ-lactones. The octadecenoic acids (6.0%) had a typical fatty acid envelope and a *trans* double bond absorption at 968 cm^{-1}. The γ-lactones amounted to 71.0% of the reaction product. The δ-lactones were not obtained in sufficient purity to estimate their precentage accurately. The last fractions, eluted from the column with increasing percentages of ether, were polymeric. With one exception, the polymeric fractions had two carbonyl absorption bands in he infrared spectrum. One fraction, corresponding to the C–O type of polymer, had ester (1740 cm^{-1}) and acid (1710 cm^{-1}) carbonyl absorptions. Polymers of the C–C type were represented by two fractions: one with only an acid (1710 cm^{-1}) carbonyl absorption, the other with acid and γ-lactone (1780 cm^{-1}) carbonyl absorptions. Tlc definitely showed that the fractions with two carbonyl absorptions were not physical mixtures of two different, monomeric, carbonyl-containing compounds. When these fractions were spotted, developed, and visualized on a tlc plate, only one spot was observed per fraction. The R_f values were less than those of the monomeric C_{18} compounds eluted earlier in the chromatography, *e.g.*, the octadecenoic acids and the γ- and δ-lactones. The exception already noted, the fraction with only an acid carbonyl band in the infrared spectrum, was also considered polymeric. When analyzed by tlc, only one spot was observed with an R_f value much lower than that of the octadecenoic acids.

Isolation and Characterization of By-products from the Oleic Acid Isomerization.—Essentially all of the by-products were isolated from the first filtrate fraction in the purification of a large-scale γ-stearolactone preparation.

The filtrate fraction was chromatographed on a column (21 × 2.5 in.) packed with silicic acid (325 mesh, reagent grade). Development was started with redistilled hexane. Nothing was eluted with hexane. The remainder of the chromatography was performed with 4% diethyl ether in hexane except for the last fractions which were eluted with increasing amounts of diethyl ether. Four types of compounds were eluted from the column in the following order: a substituted cyclohexenone, a substituted cyclopentenone, C_{18} branched chain γ-lactones (all eluted with 4% ether), and δ-stearolactone. None of these compounds was isolated completely pure.

A. 2-Dodecyl-2-cyclohexenone Fraction.—This fraction was rechromatographed on silicic acid using benzene–hexane. The substituted cyclohexenone was eluted with 4–6% benzene. Following the chromatography, the ketone was distilled twice under vacuum. After purification, infrared analysis showed one large peak at 1680 cm^{-1} due to the carbonyl absorption of the conjugated cyclohexenone, with shoulders at 1640 and at 1710 cm^{-1} due to the conjugated double bond and carbonyl, respectively, of the conjugated cyclopentenone. Glpc data (silicone gum rubber column) paralleled the ir spectrum; there was one large peak and two smaller peaks. The rechromatography and distillations, while not completely purifying the sample, removed all lactonic material and substantially reduced the amount of the isomeric cyclopentenone.

Anal. Calcd for $C_{18}H_{32}O$: C, 81.75; H, 12.20; mol wt, 264. Found: C, 81.12; H, 11.99; mol wt, 260.

The $\nu_{max}^{CS_2}$ 1680 cm^{-1} (carbonyl) and the ultraviolet peak at 230 mμ (log ε 3.99, isooctane) are consistent with literature values for 2-alkyl-2-cyclohexenones.[6,12,13]

B. 2-Tridecyl-2-cyclopentenone Fraction.—This fraction was twice distilled in a microstill. The distillate still contained a substantial amount of the isomeric cyclohexenone both by the ir band at 1680 cm^{-1} and by glpc. The intense characteristic ir band of the α,β-unsaturated carbonyl group at 1710 cm^{-1} and the conjugated double bond at 1640 cm^{-1} are typical of a conjugated cyclopentenone.[5] The ultraviolet spectra showed a maximum at 223 mμ (isooctane) (log ε 3.98).[13,14]

Anal. Calcd for $C_{18}H_{32}O$; C, 81.75; H, 12.20; mol wt, 264. Found: C, 80.63; H, 12.05; mol wt, 256.

C. Branched γ-Lactones Fractions.—The lactone fraction was fractionally distilled under reduced pressure, yielding four fractions which had strong ir absorption bands of γ-lactones at 1780 cm^{-1} and very weak shoulders at 1740–1750 and 1710–1720 cm^{-1} owing to traces of the substituted cyclic ketones. Glpc curves substantiated these conclusions.

Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13; ester equiv, 282. Found for fraction I: C, 76.52; H, 12.06; ester equiv, 283. Found for fraction II: C, 76.73; H, 12.03; ester equiv, 280. Found for fraction III: C, 76.55; H, 12.03; ester equiv, 281. Found for fraction IV: C, 76.47; H, 12.03; ester equiv, 282.

The mass spectra of the four fractions were quite similar and the glpc curves were also similar but differed in relative shape. Both the mass and the glpc spectra were different from those of the normal chain γ-stearolactone, the latter showing a less complex fragmentation pattern and having a greater retention time. The mass spectra of the branched chain lactones, like that of the straight chain isomer, had their most intense peak at *m/e* 85, the fragment corresponding empirically to the lactone ring.

The integrated nmr spectra (Varian HR-60) of the branched γ-lactones indicated 1.83 ± 0.11 methyl groups per molecule.

A sample of branched γ-lactones was fused with molten KOH for 1 hr at 320° in a nickel pot fitted with a nickel stirrer and nitrogen inlet and outlet tubes for maintainance of an inert atmosphere.[10] The fusion reaction was stopped by immersing the pot in cold water. Cleavage products and excess KOH were washed from the pot and acidified with concentrated sulfuric acid. The products were recovered by ether extraction, washed to remove mineral acid, dried, and esterified with BF_3–CH_3OH. The methyl esters were then analyzed by glpc.

D. δ-Lactone Fraction.—The δ-lactone was vacuum distilled from the polymer and then saponified. The basic solution was extracted with hexane to remove unsaponifiables and treated with decolorizing carbon after acidification. Two successive uses of preparative thin layer chromatography with silica gel G (250-μ layer), developed with petroleum ether–diethyl ether–glacial acetic acid (140:60:4), enabled the δ-lactone to be purified. It showed a characteristic carbonyl band at 1740 cm^{-1} and a moderately intense band at 1240 cm^{-1}.

Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13; ester equiv, 282. Found: C, 76.50; H, 12.03; ester equiv, 285.

The alkali fusion technique was also applied to the purified δ-stearolactone. Glpc of the esterified cleavage products showed two peaks. The first peak had the same retention time as methyl tetradecanoate, the normal cleavage product of 5-hydroxyoctadecanoic acid. The second peak, which did not have a retention time equal to any normal straight chain ester, probably was methyl 3-methylhexadecanoate. Under similar conditions, Dytham and Weedon reported that 3-methylpentadecanoic acid was a major rearrangement product of 5-oxoheptadecanoic acid and that the cleavage products of keto and hydroxy acids are identical.[23]

γ-Erucalactone.—Erucic acid (2.47 g, 7.29 mmol) and perchloric acid (70.2%, 1.04 g 6.96 mmol) were heated at 85° for 10 hr. The work-up procedure was identical with that for oleic acid except that crystallization from acetone (20 ml/g, −30°) was preceded by treatment with decolorizing carbon to yield an easily crystallizable product. The erucalactone (1.13 g, 46% yield) had mp 62.5–63.5° and an ir band at $\nu_{max}^{CS_2}$ 1780 cm^{-1} (carbonyl).

Anal. Calcd for $C_{22}H_{42}O_2$: C, 78.04; H, 12.15; ester equiv, 339. Found: C, 78.18; H, 12.44; ester equiv, 342.

4-Hydroxyoctadecanoic Acid.—γ-Stearolactone (1.50 g, 5.32 mmol) and KOH (85.3%, 0.32 g, 13.0 mmol) were refluxed in 50% aqueous ethanol (100 ml) for 4 hr. The free acid was obtained by dropwise addition of the soap solution to a stirred mixture of dilute HCl (10% excess) and ice, followed by ether extraction. The ether extract was washed with aqueous Na_2SO_4 until neutral and dried over anhydrous Na_2SO_4. The ether was removed in a stream of N_2 and the residue recrystallized from tetrahydrofuran (15 ml) at −25°. The resulting 4-hydroxyoctadecanoic acid melted at 86.2–87.2°.[24]

Anal. Calcd for $C_{18}H_{36}O_3$: C, 71.95; H, 11.99. Found: C, 72.32; H, 12.08.

Reaction between Perchloric Acid and Octadecenoic Acid Derivatives.—The reaction between equimolar quantities of perchloric acid (70.6%) and 9(10)-monohydroxystearic acid was carried out using the optimum conditions for oleic acid (85°, 10 hr; 100°, 3 hr; 115°, 1 hr) and a similar work-up procedure.

The reaction between equimolar quantities of perchloric acid and petroselinic acid (*cis*-6-octadecenoic acid) was carried out using the optimum conditions for oleic acid and the standard work-up procedure. Yields were 10% higher than those from

(23) R. A. Dytham and B. C. L. Weedon, *Tetrahedron*, **8**, 246 (1960).

(24) S. Bergström, G. Aulin-Erdtman, B. Rolander, E. Stenhagen, and S. Ostling, *Acta Chem. Scand.*, **6**, 1157 (1952).

oleic acid, the side reactions being less important. Reaction of elaidic acid under the optimum conditions was essentially similar to that of oleic acid.

Reaction between Perchloric Acid and Undecylenic Acid.—Undecylenic acid (49.3 g, 268 mmol) and perchloric acid (70.2%, 37.9 g, 261 mmol) were heated at 100° for 3 hr and worked up using procedures similar to those for oleic acid. The acid fraction of the reaction product was polymeric, as indicated by its complete retention on glpc columns. The total residue contained 2.8% of α,β-conjugated carbonyl-containing compounds (λ_{max} at 230 mμ), 2-alkyl-substituted 2-cyclopentenone and 2-cyclohexenone. Fractional distillation of the neutral residue through a spinning-band column gave the colorless γ-undecalactone (bp 146° at 4.5 mm) in 48% yield.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.43; H, 10.76.

Registry No.—I, 112-80-1; II, 502-26-1; XI, 16317-08-1; γ-erucalactone, 16317-09-2; 4-hydroxyoctadecanoic acid, 2858-39-1; γ-undecalactone, 104-67-6; perchloric acid, 7616-81-1.

The Electrochemical Oxidation of Epimeric β-Hydroxycycloalkylacetic Acids[1]

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Received January 11, 1968

Chemical and spectral evidence for the configurations of the epimeric Reformatsky products from *trans*-2-decalone and cholestanone is presented. Electrochemical oxidation–decarboxylation of each of the epimeric β-hydroxycarboxylic acids derived from *trans*-2-decalone gave products *via* both radical and carbonium ion intermediates. No significant product differences attributable to the different configurations of the acids were found. Methyl substitution α to the carboxyl led to no specific bond migration in the rearrangement of the carbonium ion leading to homologated ketones.

In order to ascertain the possible effect of configurational differences on product distribution in the Kolbe electrosynthesis reaction, a study of the electrooxidation of epimeric β-hydroxycycloalkylacetic acids was undertaken. This reaction, which gives rise to ring homologated ketones *via* carbonium ion intermediates, was briefly described by Corey and his coworkers[2] in 1960. It seemed reasonable that steric differences might bear upon the electrode absorptivity requirements for the electrode processes leading to intermediates and possibly to the products as well. This report deals with the preparation and characterization of isomeric Reformatsky products from *trans*-2-decalone and cholestanone and the electrolysis of the pair of epimeric acids derived from the former.

Results and Discussion

The Reformatsky reaction of *trans*-2-decalone with ethyl bromoacetate and zinc in tetrahydrofuran gave a 61% yield of the two epimeric hydroxy esters, IIa and IIIa, in a 1:1 ratio after column chromatography (eq 1). The isomer that was eluted first (IIa) was assigned the axial (β) hydroxyl configuration. Chemical evidence for the hydroxyl configurations was obtained by dehydration of the hydroxy esters with pyridine–phosphoryl chloride.[3] The α isomer (IIIa), with an equatorial hydroxyl, gave as the major product an exocyclic olefin (V), while the β isomer gave an endocyclic olefin (IV).

The nmr spectra of the two epimers in dimethyl sulfoxide showed a chemical-shift difference of 0.23 ppm for the hydroxyl protons, the equatorial OH in IIIa resonating at a lower field in agreement with the observations of Chapman and King[4] (Table I).

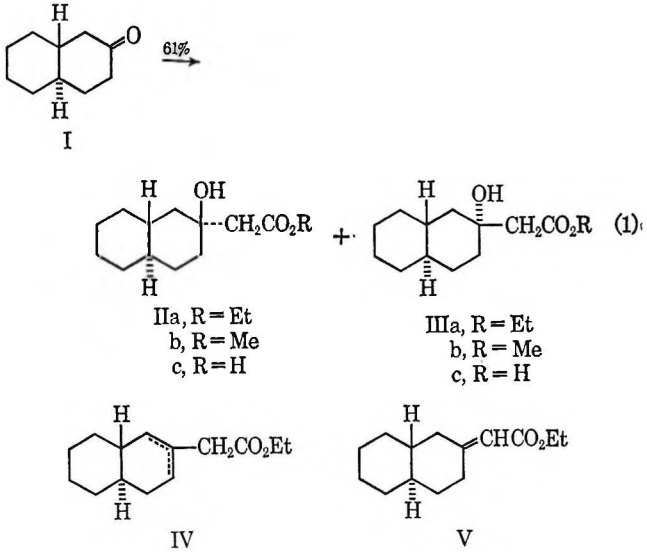


TABLE I

NMR SPECTRA (δ) OF EPIMERS IIa AND IIIa (IN PARENTHESES)[a]

DMSO-d_6	$CDCl_3$	Benzene	Pyridine
1.09 (1.10)	1.27 (1.30)	0.34 (0.34)	0.57 (0.46) (ester CH_3, three protons, T, J = 7 cps)
2.25 (2.37)	2.40 (2.59)	1.68 (1.89)	1.90 (2.06) (–CH_2CO–, two protons, S)
4.13 (4.36)	3.62 (3.16)	2.73	4.36 (4.65) (OH, one proton)
3.99 (3.99)	4.16 (4.22)	3.34 (3.37)	3.48 (3.50) (–OCH_2–, two protons, Q, J = 7 cps)

[a] T = triplet; S = singlet; Q = quartet.

The nmr spectra of these epimeric esters exhibited two interesting features. One was the singlet resonance of the geminal methylene protons of the acetic ester side chain instead of an AB quartet, even though the adjacent ring carbon is asymmetric. The other feature was that the axial methylene in IIIa resonated at a lower field than the equatorial one although one might expect the reverse because of C–C bond anisotropies. Surprisingly, these methylene resonances were reversed in the nmr spectra of the corresponding car-

(1) (a) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967. (b) Supported by the Michigan Cancer Foundation.

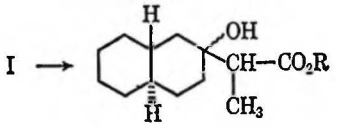
(2) E. J. Corey, N. L. Bauld, R. T. LaLonde, and J. Casanova, Jr., *J. Amer. Chem. Soc.*, **82**, 2645 (1960).

(3) D. H. R. Barton, A. da S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956); J. L. Beton, T. G. Halsak, E. R. H. Jones, and P. C. Phillips, *ibid.*, 753 (1957).

(4) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 125 (1964).

boxylic acids in which the axial methylene resonated at a higher field. Comparison of the nmr spectra of the esters in $CDCl_3$ and in benzene did not reveal any differences, the axial and equatorial methylenes both having nearly equal upfield shifts of *ca.* 0.7 ppm which indicates similar geometries for the collision complexes. Pyridine also caused equal upfield shifts of *ca.* 0.5 ppm. The ester methyl and methylene protons also showed large upfield shifts in both of these solvents.

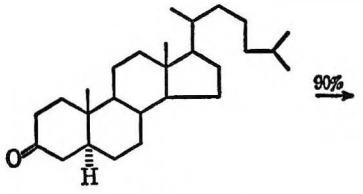
To determine the effect on the electrolytic behavior of an alkyl group α to the carboxyl, the Reformatsky product of *trans*-2-decalone and ethyl α-bromopropionate was prepared. Hydrolysis of the ester followed by fractional recrystallization of the resulting acid mixture yielded one of the isomers (VIc) whose configuration was not determined (eq 2).



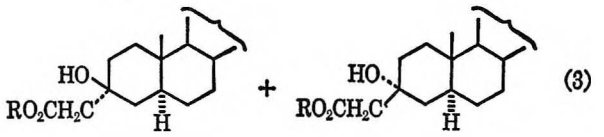
(2)

VIa, R = Et
b, R = Me
c, R = H

The Reformatsky reaction of cholestanone with ethyl bromoacetate, which was studied earlier by Campos-Neves,[5] was repeated. The *cis*- and *trans*-hydroxy esters VIIIa and IXa, in a 3:2 ratio, were obtained in 90% yield after column chromatography (eq 3). The *trans*



VII



(3)

VIIIa, R = Et
b, R = H

IXa, R = Et
b, R = H

isomer which was eluted first was the higher melting and the more sparingly soluble of the two. As was found with the hydroxy esters derived from *trans*-2-decalone, the axial and equatorial methylenes of the acetic ester side chain had an appreciable chemical-shift difference, the former resonating at a lower field as a singlet. Because of the insolubility of the esters in DMSO, the nmr spectra were taken in pyridine[6] in which solvent the hydroxyl resonances had a chemical-shift difference of 0.48 ppm; the equatorial hydroxyl (VIIIa) resonating at a lower field (see Table II).

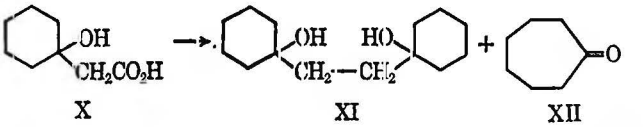
TABLE II
CHEMICAL SHIFTS AND MULTIPLICITY[a] OF SOME ALCOHOLS IN PYRIDINE

Compound	Chemical shift (δ)	Multiplicity	Coupling constant, J, cps
Methanol	4.7	Q	5.5
2-Hexanol	4.73	D	5
Allyl alcohol	5.7	T	5
Benzyl alcohol	5.92	T	5.5
1,3,5-Triisopropyl-benzyl alcohol	5.25	T	4.5
Cholesterol	4.77	D (partially resolved)	4.5

[a] Q = quartet; T = triplet; D = doublet.

Electrolysis Studies

Electrolysis of 1-Hydroxycyclohexylacetic Acid.[2,7]—To gain an insight into the reaction, an attempt was made to optimize the yield of cycloheptanone but yields greater than *ca.* 50% could not be realized. Electrolysis at lower temperatures were carried out at a carbon anode[8] which appeared to avoid the surface coating problems encountered with a platinum anode. While no dimer was obtained with the solvents acetonitrile, dimethylformamide, or 10% water in pyridine using a carbon anode, substantial dimer XI formation was observed with N-methylformamide as the solvent (eq 4).



X XI XII

(4)

Dimer formation could not be suppressed even at −40° in methanol. At 0° the yield of dimer had trebled while the yield of cycloheptanone was not changed appreciably (Table III).

Electrolysis of (2β-Hydroxy-2-*trans*-decalyl)acetic Acid (IIc) and the Epimeric Acid (IIIc).—Electrolysis of the β-hydroxy acid (IIc) in DMF using a carbon anode gave 76% CO_2, 56% a mixture of the two possible homodecalones XIII and XIV (75% in N-methylformamide as solvent), 2% dimer XVa, 15% an hydroxy ester probably of the structure XVIa, and 2.9% a nitrogen-containing substance assigned the structure XVII. The 2,4-dinitrophenylhydrazone of the homodecalone mixture had a wide melting point range, but neither this derivative nor the ketonic mixture could be resolved by chromatographic techniques. Structure assignment to the nitrogen-containing substance (XVII) was based on the ir and nmr spectra supported by the mass spectrum. The nmr spectrum in DMSO showed the tertiary nature of the hydroxyl by its singlet resonance at δ 4.65, a doublet for the N-methyl group coupled with the NH proton, a higher field singlet for the side-chain methylene attached to the amide carbonyl, and a broad lowfield signal for the NH proton. The mass spectrum exhibited a

(5) A. da S. Campos-Neves, *Bol. Escola. Farm. Univ. Coimbra*, 19–20, 207 (1959–1960); *Chem. Abstr.*, 56, 4821 (1962).

(6) R. T. Oulette [*J. Amer. Chem. Soc.*, 86, 4378 (1964)] has observed the chemical-shift difference of hydroxyls in *cis*- and *trans*-4-*t*-butylcyclohexanols in pyridine, but no mention was made of any observation of spin–spin coupling of the hydroxyl proton and the proton on the carbon bearing the hydroxyl.

Primary, secondary, and tertiary alcohols can be differentiated by observing the multiplicity of the hydroxyl resonance in the nmr spectra in dry pyridine (10% solution). Some values for hydroxyl peaks are shown in Table II. Where comparisons had been made with DMSO as solvent it was seen that the hydroxyl resonances occur farther downfield in pyridine than in DMSO, possibly indicating the formation of stronger H bonds with pyridine.

(7) Triethylamine was used in all the electrolyses to effect partial neutralization.

(8) J. Koehl, Jr., *J. Amer. Chem. Soc.*, 86, 4686 (1964).

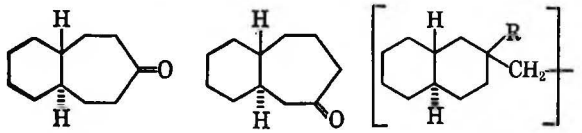
TABLE III

ELECTROLYSIS OF 1-HYDROXYCYCLOHEXYLACETIC ACID

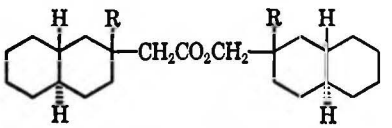
Amount, g (mol)	Solvent (ml)	NEt_3, ml (mol)	Anode	Applied voltage, V	Temp, °C	Current, mA	CO_2, %	% yield Dimer XI	% yield Ketone XII
3.16 (0.02)	DMF (35)	0.6 (0.004)	Pt	100	60–70	400	91	18–20	9
3.16 (0.02)	DMF (40)	0.6 (0.004)	Pt	150	100–110	1000	90	40	5
3.16 (0.02)	CH_3CN (18)	0.9 (0.006)	C	54–130	10	400	55	0	50
4.0 (0.025)	CH_3CN (15)	1.8 (0.012)	C	40–140	10–15	500	54	0	47
4.0 (0.025)	DMF (15)	0.9 (0.006)	C	50–120	10–15	450	55	0	50
3.0 (0.019)	10% H_2O in pyridine	1 (0.0066)	C	70–140	15–20	300	...	0	55
3.0 (0.019)	N-Methylformamide	1 (0.0066)	C	30–90	10–15	450	82	14	50
10 (0.063)	CH_3OH (30)	5.4 (0.036)	C	45–120	−40	450	...	8.3	27
10 (0.063)	CH_3OH (30)	2.7 (0.018)	C	24–60	0	470	70	23.3	30

molecular ion at *m/e* 225 and intense peaks at M − 18, M − 153, M − 195, etc. The M − 153 peak may be the result of a simple β cleavage of the N-methylacetamido group not accompanied by H rearrangement. The intense peak at *m/e* 30 (M − 195) is attributed to the species $(NH_2{=}CH_2)^+$ characteristic of many secondary amide spectra.[9]

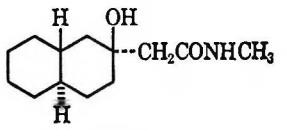
Electrolysis of the α-hydroxy acid (IIIc) under conditions similar to those employed for the epimeric acid (IIc) gave 72% CO_2, 50% the mixture of homodecalones (XIII and XIV), 2% dimer XVb, and 12% an hydroxy ester probably of the structure XVIb.



XIII XIV XVa, R = β-OH b, R = α-OH



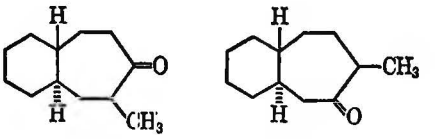
XVIa, R = β-OH b, R = α-OH



XVII

The 2,4-dinitrophenylhydrazone of this homodecalone mixture had a large melting point range similar to that of the homodecalone mixture obtained from the β-hydroxy acid (IIc), and from which information the similar composition was judged. Except for the somewhat lower yields of the ketonic product from the α epimer there did not appear to be any significant differences in the electrolytic behavior of these epimeric acids based on the equal distribution of dimeric, ketonic, and ester products.

Electrolysis of α-(2-Hydroxy-2-*trans*-decalyl)propionic Acid (VIc).—In order to determine the effect of α-alkyl substitution on the product distribution the α-methylhydroxy acid (VIc) was electrolyzed under conditions similar to those described above. No dimeric or ester products could be isolated but the two possible α-methylhomodecalones were obtained in 58% yield in a 1:1 ratio based on the integrated nmr spectrum in which the two methyls showed distinct doublets.



XVIII XIX

Attempted Electrolysis of 3-Carboxymethylcholestan-3-ol.—The hydroxy acids VIIIb and IXb were quite sparingly soluble in the preferred solvents such as DMF, acetonitrile, and pyridine. Hexamethylphosphoramide was the best solvent found for these acids but at the low temperatures employed (10–15°) during electrolysis the solution viscosity was high and current density low. In methanol–hexamethylphosphoramide mixtures as solvent, electrolysis could be carried out but only quite low yields of dimeric product could be isolated and the reaction was not investigated further.

Experimental Section

The nmr spectra were recorded downfield relative to TMS at 0 ppm as an external standard using a Varian A-60A spectrometer. Multiplicity of the signals is denoted by S = singlet, D = doublet, T = triplet, and Q = quartet. The ir spectra were obtained with a Beckman IR-5 spectrophotometer. Mass spectra were obtained using a CEC Model 110-B mass spectrometer. Melting points are uncorrected. The petroleum ether used had bp 30–45°.

Reformatsky Reaction of *trans*-2-Decalone.—To a gently refluxing, stirred solution of 55 g (0.36 mol) of *trans*-2-decalone and 67 g (0.4 mol) of freshly distilled ethyl bromoacetate in 500 ml of dry tetrahydrofuran was added 36 g (0.55 mol) of activated zinc[10] in three lots, the first addition being followed by a crystal of iodine. The reaction mixture was refluxed for 2 hr, cooled to 5°, acidified with 2 l. of 5% H_2SO_4 at 5° and worked up by ether extraction. Removal of solvent gave 84 g of yellow viscous liquid which was chromatographed in two lots on two 1-kg portions of alumina, elution being carried out initially with 5% ethyl acetate in benzene and finally with ethyl acetate. A total of 22.1 g of hydroxy ester IIa, mp 32–35°, 25.6 g of hydroxy ester IIIa, mp 40–43°, and 5.8 g of a mixture of these two were obtained. Total yield was 53.5 g (61%). The nmr spectra of the epimers IIa and IIIa are given in Table I. Each ester was saponified with a fourfold excess of 20% NaOH solution at 70–80° for 6 hr, cooled to 5°, and acidified with 5% H_2SO_4. The acid was filtered, washed, dried in a vacuum desiccator, and recrystallized from anhydrous ether.

(2β-Hydroxy-2-*trans*-decalyl)acetic acid (IIc) exhibited the following characteristics: mp 118–119°; $\nu_{max}^{CHCl_3}$ 3546–3175 (broad, OH and carboxylic OH) and 1709 cm^{-1} (carboxylic C=O); nmr ($CDCl_3$), δ 2.65 ($-CH_2CO-$, two protons, S) and 7.54 (OH and CO_2H, two protons, disappeared upon addition of D_2O).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.93; H, 9.63. Found: C, 68.25; H, 9.30.

(9) J. A. Gilpin, *Anal. Chem.*, **31**, 935 (1959); H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, 1964, Chapter 4.

(10) L. F. Fieser and W. S. Johnson, *J. Amer. Chem. Soc.*, **62**, 575 (1940).

(2α-Hydroxy-2-*trans*-decalyl)acetic acid (IIIc) exhibited the following characteristics: mp 143–144°; $\nu_{max}^{CHCl_3}$ 3546–3175 (broad, OH and carboxylic OH) and 1709 cm^{-1} (carboxylic C=O); nmr ($CDCl_3$), δ 2.49 ($-CH_2CO-$, two protons, S) and 7.16 (OH and CO_2H, two protons, disappeared upon addition of D_2O).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.93; H, 9.63. Found: C, 68.17; H, 9.49.

The methyl esters were prepared by reaction with diazomethane and recrystallized from petroleum ether.

Methyl (2β-hydroxy-2-*trans*-decalyl)acetate (IIb) exhibited the following characteristics: mp 47.5–48.5°; nmr (DMSO-d_6), δ 2.36 ($-CH_2CO-$, two protons, S), 3.59 (OCH_3, three protons, S), and 4.17 (OH, one proton, S).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.03; H, 9.73. Found: C, 69.29; H, 9.84.

Methyl (2α-hydroxy-2-*trans*-decalyl)acetate (IIIb) exhibited the following characteristics: mp 75.5–76.0°; nmr (DMSO-d_6), δ 2.46 ($-CH_2CO-$, two protons, S), 3.59 (OCH_3, three protons, S), and 4.4 (OH, one proton, S).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.03; H, 9.73. Found: C, 69.43; H, 9.34.

Pyridine–Phosphoryl Chloride Dehydrations.—A solution of 0.52 g of ethyl (2α-hydroxy-2-*trans*-decalyl)acetate (IIIa) in 20 ml of dry pyridine was treated in the cold with 5 ml of freshly distilled phosphoryl chloride and allowed to stand overnight at room temperature. The solution was added to ice-cold water and worked up by ether extraction to give 0.54 g of a liquid with no OH absorption in the ir spectrum. Distillation at 120° (0.1 mm) in a short-path distillation tube gave a colorless liquid which was predominantly the exocyclic olefin (V) contaminated with *ca.* 20% of the endocyclic isomer (IV): ν_{max}^{film} 1712 (ester C=O) and 1645 cm^{-1} (strong C=CH); nmr ($CDCl_3$), δ 1.3 (ester methyl, T, J = 7 cps), 4.19 ($-OCH_2-$, Q, J = 7 cps), and 5.65 (=CH, S).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.67; H, 9.97. Found: C, 75.62; H, 10.10.

A solution of 0.5 g of ethyl (2β-hydroxy-2-*trans*-decalyl)acetate (IIa) in 20 ml of pyridine was similarly dehydrated with 5 ml of phosphoryl chloride. The crude product was distilled at 120° (0.1 mm) to give predominantly the endocyclic olefin (IV) contaminated with *ca.* 20% of the exocyclic isomer: ν_{max}^{film} 1730 (ester C=O) and 6.08 (medium, C=CH); nmr ($CDCl_3$), δ 1.29 (ester methyl, T, J = 7 cps), 2.98 (CH_2 flanked by a double bond and an ester C=O, S), 4.19 ($-OCH_2-$, Q, J = 7 cps), and 5.59 (C=CH, broad).

α-(2-Hydroxy-2-*trans*-decalyl)propionic acid (VIc).—The Reformatsky reaction was carried out essentially as described above with 22 g of *trans*-2-decalone, 27 g of ethyl α-bromopropionate in 200 ml of tetrahydrofuran, and 10 g of activated zinc. The reaction product (36 g) was chromatographed on 1 kg of basic alumina. The eluate (27 g) from 5% MeOH–EtOAc and 20% MeOH–EtOAc was saponified with 150 ml of 10% NaOH solution at 70–80° with stirring for 6 hr, cooled, and acidified with 2% H_2SO_4 at 5–10°. Work-up by ether extraction gave 19.8 g of a brown viscous liquid. Crystallization from petroleum ether–dry ether gave 8 g of a white crystalline material, mp 155–158°. Recrystallization from petroleum ether gave VIc as white needles: mp 157–158°; $\nu_{max}^{CHCl_3}$ 3448 (OH and CO_2H, broad) and 1709 cm^{-1} (carboxylic C=O), addition of 2 drops of triethylamine shifted the carbonyl band to 1597 cm^{-1}; nmr ($CDCl_3$ + 1 drop of pyridine), δ 1.22 (CH_3, three protons, D, J = 7 cps) and 2.46 (CH_2CH-, one proton, Q, J = 7 cps).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.03; H, 9.73. Found: C, 69.38; H, 9.88.

The methyl ester prepared by reaction with diazomethane was crystallized from petroleum ether to give methyl α-(2-hydroxy-2-*trans*-decalyl)propionate (VIb) as white needles, mp 64.5–65.5°.

Anal. Calcd for $C_{14}H_{24}O_3$: C, 70.88; H, 10.24. Found: C, 70.38; H, 9.99.

Reformatsky Reaction with Cholestanone.—The Reformatsky reaction of 33 g of cholestanone [dried at 132° (2 mm) for 4 hr] was carried out as described above for *trans*-2-decalone, using 18 g of ethyl bromoacetate and 12 g of activated zinc to give 40 g of the crude reaction product. Chromatography of 35 g on 900 g basic alumina gave 13.2 g of the *trans*-hydroxy ester (IXa), mp 95–98° (from 3 l. of 10% EtOAc in benzene), 0.27 g of a mixture, and 18.3 g of the *cis* isomer (VIIIa), mp 70–73° (from 2.5 l. of EtOAc). Both the epimers were recrystallized from absolute methanol.

3-Carboethoxymethylcholestan-3α-ol (IXa) exhibited the following characteristics: white flakes; mp 96.5–97.5° (lit.[5] mp 98.5–99°); $\nu_{max}^{CCl_4}$ 3546 (OH) and 1724 cm^{-1} (ester C=O); nmr ($CDCl_3$), δ 1.38 (ester methyl, T, J = 7 cps), 2.42 ($-CH_2CO-$, two protons, S), 4.18 ($-OCH_2-$, two protons, Q, J = 7 cps), and 2.97 (OH, broad); nmr (pyridine), δ 4.52 (OH one proton, S) and 1.98 ($-CH_2CO-$, two protons, S).

Anal. Calcd for $C_{31}H_{54}O_3$: C, 78.47; H, 11.39. Found: C, 78.70; H, 11.39.

3-Carboethoxymethylcholestan-3β-ol (VIIIa) exhibited the following characteristics: mp 72.5–73.5°; $\nu_{max}^{CCl_4}$ 3546 (OH) and 1727 cm^{-1} (ester C=O); nmr ($CDCl_3$), δ 1.25 (ester methyl, T, J = 7 cps), 2.58 ($-CH_2CO-$, two protons, S), 4.18 ($-OCH_2-$, two protons, Q, J = 7 cps; nmr (pyridine), δ 5.0 (OH, one proton, S) and 2.12 ($-CH_2CO-$, two protons, S).

Anal. Calcd for $C_{31}H_{54}O_3$: C, 78.47; H, 11.39. Found: C, 78.67; H, 11.85.

Saponification with 10% alcoholic KOH gave the *trans* acid (IXb), mp 198–200° (lit.[5] mp 198.5–200°), and the *cis* acid (VIIIb), mp 219–220° (lit.[5] mp 219–220°).

Electrochemical Oxidation Experiments.—Ascarite bulbs were used to trap CO_2 liberated during the electrolysis. The electrolytic cell has been described previously.[11] A coolant at −15° was run through the outer jacket of the cell. The carbon anode when used, was a rod 3 mm in diameter and protruding 2 cm from a glass sleeve. The platinum electrodes employed circular Pt foil 1 cm in diameter. The electrodes were separated by a distance of 5 mm. The yields of dimeric, ketonic, and ester products in the electrolyses were calculated based on the starting hydroxy acid.

Electrolysis of 1-Hydroxycyclohexylacetic Acid (X).—A solution of the hydroxy acid was partially neutralized with triethylamine and then electrolyzed between Pt electrodes or a carbon anode and a Pt cathode. The various conditions are shown in Table III. When the neutral product from the electrolysis was warmed with petroleum ether the dimer separated out as a white powder. The residue from the mother liquors was treated with excess 2,4-dinitrophenylhydrazine reagent to afford the cycloheptanone derivative. Recrystallization from petroleum ether–ethyl acetate gave yellow needles, mp 150–151°, mixture melting point with an authentic sample undepressed. The dimer was recrystallized from a large volume of ether to give 1,2-bis(1-hydroxy-1-cyclohexyl)ethane (XI) as colorless, fine needles, mp 132–133° (lit.[12a] mp 129°, 130–131°[12b]). The mass spectrum showed M^+ at m/e 226.

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.33; H, 11.57. Found: C, 74.61; H, 11.55.

Electrolysis of (2β-Hydroxy-2-*trans*-decalyl)acetic Acid (IIc).—A solution of 2.96 g of the hydroxy acid in 11 ml of DMF (dried over Linde 5A Molecular Sieves) containing 1 ml of triethylamine was electroyzed using a carbon anode at an initial applied voltage of 54 V and at 15°. To maintain the current at *ca.* 300 mA the applied voltage was increased slowly to 140 V during 5 hr; electrolysis was continued for 19 hr. The dark electrolysate was poured into ice-cold water and extracted thoroughly with ether, and the ether extract was successively washed with ice-cold 3 *N* HCl, 5% NaOH solution, and brine, dried ($MgSO_4$), and distilled to give 2.3 g of a brown liquid. On dilution with petroleum ether, 50 mg of a crystalline solid separated out. Repeated recrystallization from absolute methanol gave 1,2-bis(2β-hydroxy-2-*trans*-decalyl)ethane (XVa) as white flakes: mp 207–207.5°; ν_{max}^{KBr} 3333 cm^{-1} (OH); M^+ in the mass spectrum at m/e 334.

Anal. Calcd for $C_{22}H_{38}O_2$: C, 79.04; H, 11.38. Found: C, 79.44; H, 11.48.

The mother liquors were concentrated and chromatographed on 70 g of neutral alumina. Elution with 400 ml of benzene gave 1.32 g of a mixture of *trans*-bicyclo[5.4.0]undecan-3-one (XIII) and *trans*-bicyclo[5.4.0]undecan-4-one (XIV) of uncertain proportion. The 2,4-dinitrophenylhydrazone of this mixture was recrystallized from 95% ethanol: mp 114–135°; M^+ in the mass spectrum was at m/e 346

Anal. Calcd for $C_{17}H_{22}N_4O_4$: C, 58.95; H, 6.36; N, 16.19. Found: C, 59.36; H, 6.44; N, 16.15.

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(11) L. Rand and A. F. Mohar, *J. Org. Chem.*, **30**, 3156, 3885 (1965).

(12) (a) C. D. Nenitzescu and I. Necsoiu, *J. Amer. Chem. Soc.*, **72**, 3483 (1950); (b) A. S. Bailey, D. G. M. Diaper, and M. V. H. Schwemin, *Can. J. Chem.*, **39**, 1147 (1961).

The eluate (0.35 g) from 500 ml of ethyl acetate, a brown viscous gum, was warmed in petroleum ether from which 15 mg of a white powder and 90 mg of a hard crystalline substance separated. Recrystallization of the larger fraction from petroleum ether–ether gave white needles of 2-(N-methylacetamido)-*trans*-decalin-2β-ol (XVII): mp 109.5–110°; ν_{max}^{KBr} 3497, 3289 and 3125 (OH and NH) and 1639 cm^{-1} (amide C=O); nmr ($CDCl_3$), δ 2.26 (–CH_2CO–, two protons, S), 2.8 (CH_3, three protons, D, J = 5 cps) and 4.34 (OH, one proton, disappeared upon addition of D_2O); nmr (DMSO-d_6), δ 2.16 (–CH_2CO–, two protons, S), 2.59 (CH_3, three protons, D, J = 5 cps), 4.65 (OH, one proton, S), and 7.76 (NH, one proton, broad); M^+ in the mass spectrum at m/e 225, intense peaks at M − 18, M − 17, M − 70, M − 71, M − 89, M − 153, M − 166, and M − 195.

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.25; H, 10.31; N, 6.21. Found: C, 69.56; H, 10.32; N, 6.27.

The smaller fraction accompanying the above compound was shown to be the dimer (XVa) by mixture melting point and ir spectra.

Elution with 400 ml of 50% ethyl acetate in benzene gave 0.47 g of a viscous liquid, considered to be the hydroxy ester (XVIa): ν_{max}^{film} 3448 (OH) and 1724 cm^{-1} (ester C=O). This material decomposed on attempted distillation under high vacuum.

Similar electrolysis of 3 g of the hydroxy acid (IIc) in 10 ml of N-methylformamide containing 1.1 ml of triethylamine for 32 hr at 10° gave, after chromatography, a 75% yield of a mixture of homodecalones XIII and XIV. The 2,4-dinitrophenylhydrazone, after recrystallization, melted at 110–132°.

Electrolysis of (2α-Hydroxy-*trans*-2-decalyl)acetic Acid (IIIc).—A total of 15 g of the hydroxy acid was electrolyzed in five 3-g lots, each in DMF containing triethylamine, and under conditions similar to those for the epimeric acid (IIc). The neutral fraction which was obtained was chromatographed on 250 g of neutral alumina. Elution with 1 l. of 1:1 benzene–ether gave 5.8 g of a mixture of the homodecalones XIII and XIV. The 2,4-dinitrophenylhydrazone melted, after recrystallization from 95% ethanol, at 113–128°. Its mass spectrum exhibited M^+ at m/e 346.

Anal. Calcd for $C_{17}H_{22}N_4O_4$: C, 58.95; H, 6.36; N, 16.19. Found: C, 59.21; H, 6.33; N, 16.07.

Elution with ether gave 1.8 g of an hydroxy ester fraction XVIb which could not be purified: ν_{max}^{film} 3448 (OH) and 1724 cm^{-1} (ester C=O).

Elution with 10% methanol in ethyl acetate gave 3.2 g of a viscous liquid. This was dissolved in warm petroleum ether and allowed to stand overnight to afford two crystalline forms (140 and 90 mg). Both showed similar ir spectra and were considered to be polymorphic forms of the dimer. Recrystallization of the larger fraction from absolute methanol gave transparent peaks of 1,2-bis(2α-hydroxy-2-*trans*-decalyl)ethane (XVb): mp 215–216.5°; ν_{max}^{KBr} 3448 cm^{-1} (OH); M^+ in the mass spectrum at m/e 334. The smaller fraction on recrystallization from absolute methanol gave feathery needles of the dimer (XVb): mp 152.5–153.5°; ν_{max}^{KBr} 3333 cm^{-1} (OH); M^+ in the mass spectrum at m/e 334.

Electrolysis of α-(2-Hydroxy-2-*trans*-decalyl)propionic Acid (VIc).—A solution of 3.19 g of the hydroxy acid in 15 ml of DMF containing 0.85 ml of triethylamine was electrolyzed at a C anode and the dark brown electrolysate was worked up as above. When 3.04 g of the neutral product was diluted with petroleum ether and allowed to stand overnight, a small amount of a dark solid separated out. The residue from the mother liquors was chromatographed on 100 g of basic alumina. Elution with 1:1 benzene–ether gave 1.5 g of a mixture of *trans*-4-methylbicyclo[5.4.0]undecan-3-one (XVIII) and *trans*-3-methylbicyclo[5.4.0]undecan-4-one (XIX). Distillation in a short-path distillation tube at 120° (0.1 mm) gave a colorless liquid with a strong band in the ir at 1695 cm^{-1}. The nmr spectrum ($CDCl_3$) showed two methyl doublets (J = 7 cps) at 1.08 and 1.11 with nearly equal integrated intensities.

Anal. Calcd for $C_{12}H_{20}O$: 80.00; H, 11.11. Found: C, 80.16; H, 11.57.

The 2,4-dinitrophenylhydrazone was chromatographed on basic alumina and crystallized from petroleum ether, mp 72.5–76°.

Anal. Calcd for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.56. Found: C, 60.32; H, 6.85; N, 15.22.

Registry No.—IIa, 16666-51-6; IIb, 16666-52-7; IIc, 16666-53-8; IIIa, 16666-54-9; IIIb, 16666-55-0; IIIc, 16666-56-1; V, 16666-57-2; VIb, 16666-58-3; VIc, 16666-59-4; VIIIa, 16666-60-7; IXa, 16666-61-8; 2,4-dinitrophenylhydrazone of XIII, 16666-66-3; 2,4-dinitrophenylhydrazone of XIV, 16666-67-4; XVa, 16666-62-9; XVb, 16666-63-0; XVII, 16666-64-1; XVIII, 16666-65-2; 2,4-dinitrophenylhydrazone of XVIII, 16666-36-7; XIX, 16666-37-8; 2,4-dinitrophenylhydrazone of XIX, 16666-38-9.

The Preparation of *cis*-β-Acetylacrylic Acid[1]

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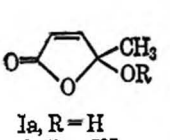
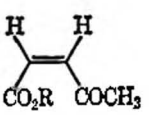
Received October 2, 1967

Kinetic studies have been carried out to determine the best conditions for the hydrolysis of the pseudo-ethyl ester of *cis*-β-acetylacrylic acid leading to the *cis* acid without the concurrent formation of the *trans* acid. *cis*-β-Acetylacrylic acid has been isolated in crystalline form. Nmr, uv, and ir spectra indicate that the *cis* acid is cyclic but that the anion exists in open form.

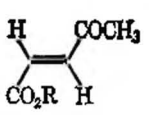
In connection with studies of *cis–trans*-catalyzed isomerizations[2] it became necessary to synthesize *cis*-β-acetylacrylic acid. An examination of the literature indicated that there still was some doubt in the structural assignment for the β-acetylacrylic acid isomer (mp 125–126°) that Wolff[3] had prepared more than 75 years ago by the dehydrobromination of bromolevulinic acid. Shaw[4] prepared the acid by Wolff's method but, because of its ultraviolet maximum at 220 mμ, he suggested the pseudo-acid structure, Ia, for Wolff's compound rather than IIa or IIIa. By treatment with diazomethane, Shaw isolated a methyl ester which he assigned as Ib on the basis of the similarity of its ultraviolet absorption to that for Ia. The ester Ib appears to be different from the ester derived from partial catalytic reduction of methyl acetylpropiolate obtained



Ia, R = H
b, R = CH_3
c, R = C_2H_5



IIa, R = H
b, R = CH_3



IIIa, R = H
b, R = CH_3

(1) Research performed under the auspices of the U. S. Atomic Energy Commission.

(2) K. D. Stevens, and S. Seltzer, to be published.

(3) L. Wolff, *Ann.*, **264**, 229 (1891).

(4) E. Shaw, *J. Amer. Chem. Soc.*, **68**, 2510 (1946).

by Shen and Whiting.[5] The latter authors assigned structure IIb to their compound on the basis of the propensity for *cis* addition in catalytic reduction. By selenium dioxide dehydrogenation of methyl levulinate, Raymond[6] obtained a methyl ester identical in its properties with that prepared by Shaw and identical with the product of dehydrohalogenation of methyl bromolevulinate.[7] Structure Ib for Shaw's methyl ester was thus ruled out and, in view of Shen and Whiting's work, the ester probably has the *trans* configuration (IIIb). One might infer at this point that the starting acid (mp 125°) possesses the same configuration.

Pseudo-esters having the same basic skeleton as I have been prepared by the photosensitized 1,4 addition of oxygen to 2-methylfuran in alcoholic solution[8] and presumably could be formed by the addition, to that same molecule, of singlet oxygen, generated by the combination of sodium hypochlorite and hydrogen peroxide.[9] On acid hydrolysis of Ic, however, Schenck obtained the free acid that melted at 125° and assigned it the *trans* structure (IIIa);[10] alkaline hydrolysis of the pseudo-ethyl ester (Ic) led to polymer.[8] Milder alkaline hydrolysis of the pseudo-methyl ester (Ib), however, was claimed to lead to a mixture of the *cis* (Ia) and *trans* (IIIa) isomers although the *cis* acid was not isolated.[11] The authors report here the preparation, isolation, and properties of the *cis* acid.

Results and Discussion

β-Acetylacrylic acid was prepared by the method of Wolff;[3] the *trans* configuration is indicated by its nmr spectrum. In acetone-d_6 the spectrum consists of a singlet at τ 7.63 (methyl), an AB quartet (vinyl protons) with centers at τ 3.33 and 3.05 (J_{AB} = 16 cps), and a broad singlet (carboxyl proton) at τ 2.0 but its position varied with concentration. The areas of the three groups were in the ratio of 3:2:1. That this is the *trans* acid is shown by the large vinyl coupling constant.[12]

The ethyl pseudo-ester of β-acetylacrylic ester was prepared by Schenck's method and purified by vapor phase chromatography. In carbon tetrachloride, its nmr spectrum exhibited a triplet at τ 8.85 (methyl), a singlet at 8.38 (methyl), a quartet at 6.57 (methylene), and an AB quartet (vinyl protons) with centers at 3.80 and 2.59 (J_{AB} = 5.7 cps) with areas in the ratio of 3:3:2:1:1.

It is apparent from the previous studies[8,11] that, under normal conditions of hydrolysis of the pseudo-ester, rapid *cis–trans* isomerization ensues. Levisalles, however, reported that very gentle acid hydrolysis of 2,5-dimethoxy-2,5-dimethyldihydrofuran leads successfully to *cis*-3-hexene-2,5-dione which easily isomerizes to the *trans* isomer under more vigorous conditions.[13] Examination of the nmr spectrum of the mixture resulting from the partial acid-catalyzed hydrolysis of the ethyl pseudo-ester of β-acetylacrylic acid, indicated the appearance of a new methyl and vinyl absorption in addition to those due to presence of pseudo-ester and *trans* acid. These new peaks were tentatively assigned to the *cis* acid and will be discussed later. In addition, shifted upfield from the methyl peak of the *trans* acid by about 0.18 ppm, was another singlet with an intensity somewhat smaller than the *trans* acid methyl peak together with a multiplet at about τ 7.05. Examination of the conditions that led to the presence of these leads us to believe that they are due to hydrated β-acetylacrylic acid (*i.e.*, α- and/or β-hydroxylevulinic acid). Support for these assignments was gained by examination of the solution after longer reaction times. By the time the ester was almost completely hydrolyzed the *cis* acid was almost completely absent; the *trans* acid and hydrate only remained.

An attempt was made to obtain approximate kinetic data in order to determine the best conditions for preparing the pure *cis* acid. A change in the concentration of the acid catalyst would not be expected to improve the ratio of *cis* to *trans* acid since both the hydrolysis and isomerization are probably first order in hydrogen ion.[14] If the activation energies for hydrolysis, hydration, and *cis–trans* isomerization were to be different, it might be possible to increase the fraction of the *cis* product by a suitable change in temperature. The approximate product distributions, obtained from the areas of the methyl nmr peaks due to ester, *cis*, *trans*, and hydrated acids, at two temperatures of hydrolysis, are shown in Table I. It appears that for similar large extents of hydrolysis the ratio of products is relatively insensitive to temperature.

Table I

Distribution of Products from Acid Hydrolysis of the Ethyl Pseudo-Ester of *cis*-β-Acetylacrylic Acid at Different Temperatures[a]

Temp, °C	Reaction time	% hydrolysis	β-Acetylacrylic acid [cis]/[trans]	[cis acid]/[trans + hydrated acid]
49	2.5 hr	76	7.4	6.4
49	4 hr	89	3.9	3.6
49	39 hr	98	0.12	0.096
98	2 min	63	12	12
98	4 min	85	4.6	4.3
98	8 min	93	0.81	0.77
98	23 min	99	0.087	0.078

[a] The initial reaction mixture was a 1:1 (v/v) ester–0.138 *M* hydrochloric acid mixture. The two phases initially present became completely miscible before the first nmr spectrum was recorded. The quantities shown here are from integration of nmr signals.

Additional experiments revealed that the *cis/trans* ratio could be increased by increasing the initial ratio of acid solution to ester. The results of these studies are shown in Table II. The hydrolysis reaction is rapidly reversible and in the presence of a high concentration of ethanol, as in the case where equal volumes of ester and aqueous acid are mixed initially, the hy-

(5) T. Y. Shen and M. C. Whiting, *J. Chem. Soc.*, 1772 (1950).
(6) S. Raymond, *J. Amer. Chem. Soc.*, **72**, 4304 (1950).
(7) H. Pauly, R. Gilmour, and G. Will, *Ann.*, **403**, 119 (1914).
(8) G. O. Schenck, *ibid.*, **584**, 156 (1953); K. Gollnick and G. O. Schenck in "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press Inc., New York, N. Y., 1967, p 255.
(9) C. Foote and S. Wexler, *J. Amer. Chem. Soc.*, **86**, 3879 (1964).
(10) There appears to be no discussion in ref 8 for the basis of this assignment.
(11) G. Fuchs and N. Hellstrom, *Lantbrukshogskol. Ann.*, **30**, 615 (1964).
(12) J. W. Emsley, J. Feeney, and J. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press Inc., New York, N. Y., 1966, pp 710–730.
(13) J. Levisalles, *Bull. Soc. Chim. Fr.*, 997 (1957).
(14) See, *e.g.*, K. Nozaki and R. A. Ogg, Jr., *J. Amer. Chem. Soc.*, **62**, 2583 (1941); A. J. Deyrup, *ibid.*, **56**, 60 (1934); R. P. Bell and A. D. Norris, *J. Chem. Soc.*, 118 (1941).

drolysis is retarded with respect to the isomerization. By decreasing the available ethanol, the hydrolysis proceeds to a greater extent before substantial isomerization takes place. The preparative method follows from these results. After incomplete hydrolysis, the unhydrolyzed ester is extracted from the neutral aqueous solution and the *cis* acid extracted from the remaining acidified aqueous solution. The small amount of hydrated acid is apparently extracted at a much slower rate. The crystalline *cis* isomer melts almost 100° lower than the *trans* acid.

TABLE II

DISTRIBUTION OF PRODUCTS FROM ACID HYDROLYSIS OF THE ETHYL PSEUDO-ESTER OF *cis*-β-ACETYLACRYLIC ACID[a]

Aqueous acid/ester (v/v)	Reaction time, min	% hydrolysis	β-Acetylacrylic acid [*cis*]/[*trans*]	[*cis* acid]/[*trans* + hydrated acid]
1	30	72	30	13
1	50	89	9.2	4.0
1	125	94	1.8	0.88
5[b]	8	66	86	26
5[b]	12	86	85	28
5[b]	16	93	74	20
5[b]	20	97	49	13
10[b]	8	80	>300	>150
10[b]	12	94	55	20
10[b]	16	96	54	14

[a] All hydrolyses were carried out at 98°. Concentrations shown here are from integration of nmr signals. [b] The aqueous acid solution was 1.0×10^{-3} *M* hydrochloric acid; all others were 1.5×10^{-3} *M*.

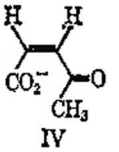
The nmr spectrum of *cis*-β-acetylacrylic acid is decidely different from that of the *trans* acid, but in some respects similar to the spectrum of the pseudo-ester. The *cis* acid in chloroform-*d* exhibits a singlet at τ 8.30 (methyl), an AB quartet with centers at 3.88 and 2.56 (vinyl protons, J_{AB} = 5.6 cps), and broad singlet at 3.88 (hydroxyl). The areas are in the ratio of 3:2:1. That this is the *cis* isomer is shown by the small vinyl proton coupling constant.[12] The nmr spectrum is consistent with the *cis* acid existing in the cyclic form (Ia). Support for this structure comes from the examination of the chemical shift of the methyl peak and the vinyl proton coupling constant.

It has been shown that conversion of a carbonyl group into a *gem*-diol (*i.e.*, hydration) is accompanied by an upfield shift of the protons α to the original carbonyl group.[15] α protons of hydrated aldehydes and ketones are shifted +0.7 to +0.9 ppm relative to their unhydrated forms.[15,16] Smaller effects are observed for β protons. In the *trans* acid the methyl group appears at τ 7.63. If the acid were the open *cis* acid (IIa) the position of the methyl group would not be expected to differ substantially from that for the *trans* compound. As will be shown below, the anion, a derivative of the hypothetical open *cis* acid, exhibits a methyl peak only 0.08 ppm away from that of the methyl peak of the *trans* acid. Cyclization as in Ia, however, alters the magnetic anisotropy of the carbonyl group in a way exactly analogous to the hydration of the carbonyl group. The position of the methyl peak in the *cis* acid, τ 8.30, is in line with the expected shift.

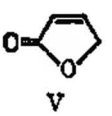
(15) E. Lombardi and P. G. Sogo, *J. Chem. Phys.*, **32**, 635 (1960).
(16) P. Greenzaid, Z. Luz, and D. Samuel, *J. Amer. Chem. Soc.*, **89**, 749 (1967).

The magnitude of coupling constants of *cis*-olefinic protons incorporated in a ring show a marked dependence on the size of the ring.[17] For five-membered cyclic olefins and unsaturated ketones, the coupling constant was found to be between 5.4 and 7.0 cps.[18] The coupling constant increases with increased ring size; for six-membered rings the constant is found to be between 9.9 and 10.5 cps. It should be recalled that the vinyl coupling constant of the ethyl pseudo-ester is 5.7 cps which fits well within the predicted range. The *cis* acid's vinyl coupling constant is essentially the same as in the pseudo-ester, and it too must have a cyclic pseudo-acid structure. It is interesting that this structure is maintained in aqueous solution as shown by the presence of the same coupling constant.

The pK_a of the pseudo-acid was found[2] to be 4.48. This is to be contrasted with a pK_a of 3.24 for the *trans* acid.[19] It was of interest to examine the nmr spectrum of the conjugate base. In aqueous bicarbonate solution an interesting change takes place. The methyl peak moves downfield 0.59 ppm toward the position where the methyl peak of the *trans* acid anion can be found. Moreover, the vinyl proton coupling constant changes to 12.2 cps. From the previous discussion both of these changes are consistent with an open structure (IV) for the conjugate base of the *cis* acid. Cyclization is reversible upon reacidification as shown by the return of the methyl peak and vinyl coupling constant to previous values for the *cis* acid.


IV

The ultraviolet spectra of the *cis* acid and its conjugate base and the *trans* acid were recorded in aqueous solution and shown in Figure 1. As reported previously[4] an aqueous solution of the *trans* acid exhibits a maximum at 220 mμ. The *cis* acid in acidic solution (pH <2.5), however, exhibits a maximum at 195 mμ. The ultraviolet spectra of the pseudo-ester and *cis* acid are similar as they should be if both have a cyclic structure; in aqueous solution the ester has a maximum at 195 mμ. In 95% ethanol the single maximum of the pseudo-ester moves to 200 mμ. The rules that are used to preduct ultraviolet maxima for α,β-unsaturated compounds are well known.[20] Application of these rules to the ester and *cis* acid suggests that the skeletal structure (V), the γ-lactone of 4-hydroxycrotonic acid,


V

should exhibit a maximum at 202 mμ in ethanol. Only partial vertification of this predicted maximum exists; it appears to be somewhere below 210 mμ (log ε >3.8).[21] Further substitution on the γ carbon

(17) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 53, 54.
(18) O. L. Chapman, *J. Amer. Chem. Soc.*, **85**, 2014 (1963).
(19) M. Sanesi, *Ann. Chim.* (Rome), **50**, 997 (1960).
(20) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold Ltd., London, 1955, pp 90–92.
(21) R. J. D. Smith and R. N. Jones, *Can. J. Chem.*, **37**, 2092 (1959).

in V, as to produce the ester and acid, would not expect to change appreciably the position of the maximum.

An almost neutral aqueous solution (pH >5.5) of the *cis* acid results in the appearance of a new maximum at 240 mμ and a shift of the low-wavelength peak to 198 mμ. The spectrum of the cyclic pseudo-acid reappears upon reacidification of the neutral solution. The behavior of *cis*-β-acetylacrylic acid in neutral and acidic media parallels that of β-formylacrylic acid.[22] The latter compound also develops a maximum at 240 mμ with increasing pH where the change has been suggested to involve ring opening.[23]

The infrared spectra of the cyclic ester and *cis* acid are given in the Experimental Section. They exhibit strong carbonyl absorption at 5.61 and 5.63 μ, respectively. γ-Lactones characteristically absorb at about 5.64 μ. α,βunsaturation generally increases this to about 5.70 μ.[24] The low-wavelength carbonyl band in the *cis* acid also supports the cyclic acid structure. In summary the nmr, uv, and ir spectra are in accord with a cyclic *cis* acid but with an open carboxylate anion.

Experimental Section

All ultraviolet spectra were obtained on a Cary Model 14 spectrophotometer. Nmr spectra were obtained on a Varian A-60 spectrometer. Infrared spectra were obtained on a Perkin-Elmer Infracord. Elemental analyses were performed by the Schwarzkopf Microanalytical Laboratory.

trans-β-Acetylacrylic acid was prepared from bromolevulinic acid by the method of Wolff.[3] The product was recrystallized from petroleum ether (bp 30–60°)–benzene, mp 125–126°.

Anal. Calcd for $C_5H_6O_3$: C, 52.63; H, 5.30. Found: C, 52.47; H, 5.37.

Pseudo-ethyl ester of *cis*-β-acetylacrylic acid was prepared from 2-methylfuran by the method reported by Schneck[8] with some modification. 2-Methylfuran (42 g, 0.513 mol), eosin Y (0.635 g), vanadium pentoxide (0.135 g), and 2.35 l. of absolute ethanol were mixed and placed in a water-cooled photoreactor connected to a 3.5-l. gas buret containing oxygen. The light source was a 100-W 20-V unfrosted incandescent lamp (GE No. 100T8/1DC) which was cooled by a rapid stream of air. In addition, the solution was stirred during reaction. After about 65% of the required oxygen had been consumed, the fluorescence due to the eosin Y diminished considerably, and the rate of oxygen consumption was reduced significantly. At this point another 0.62 g of eosin Y was added, and the reaction was allowed to continue until, after 3 days, a total of 11.60 l. (STP) (0.518 mol) of oxygen had been consumed. Five-hundred-milliliter aliquots of the ethanolic solution and 500 ml of saturated aqueous ferrous sulfate were shaken and allowed to remain in contact for 30 min to destroy any remaining peroxides. The resulting mixture was further diluted with 500 ml of water, and then the whole solution was extracted with one 300-ml plus three 100-ml portions of ether. The combined ether extracts were dried over magnesium sulfate. After filtering and removal of the ether, the dark orange residue was distilled: bp 55° (0.5 mm); yield 30 g, 41%. The distillate was purified further by gas chromatography on an Aerograph A-700 instrument (Carbowax 20M column, 0.375 in. × 10 ft; injector, 205°; column, 165°; detector, 205°; collector, 170°; helium flow, 275 cc/min). The material collected was light yellow and showed no impurities by nmr; $n^{25}D$ 1.4432 (reported 1.4360,[8] 1.4460[11]). The purified ester exhibited strong bands at 3.36, 3.40, 3.47, 5.61, 7.90, 8.45, 9.10 (doublet), 9.50 (doublet), and 10.90 μ (doublet).

(22) G. O. Schenck and R. Appel, *Naturwissenschaften*, **33**, 122 (1946).
(23) N. Hellstrom, *Nature*, **187**, 146 (1960).
(24) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1959, p 186.

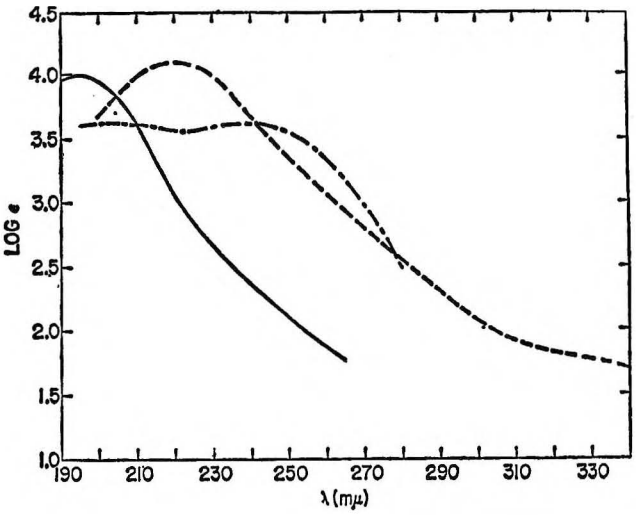


Figure 1.—The ultraviolet spectrum of *cis*-β-acetylacrylic acid (solid line), *trans*-β-acetylacrylic acid (dashed line), and the carboxylate anion of *cis*-β-acetylacrylic acid (dash–dot line).

The nmr and uv spectra are discussed in the Results and Discussion.

Pseudo-*cis*-acetylacrylic Acid.—Hydrochloric acid (50 ml, 1.0×10^{-3} *M*) was heated in a boiling-water bath. Pseudo-ester (3 ml) was added to the stirred acid solution. Heating and stirring was continued for 8 min after which time the flask was removed and placed in crushed ice and the sitrring continued. After the solution was cool, the pH was adjusted to 7 with sodium carbonate solution and the reaction mixture extracted with three 30-ml portions of ether. The pH was then adjusted to 2.5 with hydrochloric acid and extracted continuously for 18 hr with ether. The ether layer was dried over anhydrous sodium sulfate overnight and filtered. Evaporation of the filtered solvent left a pale yellow liquid which was dried for 3 days over phosphorus pentoxide under vacuum. The pale yellow liquid was molecularly distilled at room temperature. The acid is very hydroscopic and therefore all transfers from this point on were made in a drybox. The distillate was a clear water white liquid. Upon refrigeration in the presence of a drying agent, it crystallized to a white solid. Four successive room temperature sublimations were carried out. It was noticed that after the earlier sublimations a very small yellow liquid residue, probably polymer, remained. This was almost completely absent when the sublimations were carried out in the dark. Integration of nmr methyl signals indicated that the *cis* acid was at least 99% pure. The large melting point range, 33.8–36.4° (sealed tube under nitrogen), is thought to be due to some thermal polymerization of the neat material during heating.

Anal. Calcd for $C_5H_6O_3$: C, 52.63; H, 5.30. Found: C, 52.51, 53.03; Y, 5.30, 5.57.

The nmr and uv spectra are given in the Results and Discussion. The following strong infrared bands were observed: 2.96 (broad, associated hydroxyl), 5.63 (carbonyl), 7.90, 8.35, 9.09, 10.92 μ (doublet).

Kinetic studies were performed with small quantities of ester and acid solution contained in sealed nmr tubes. After mixing the two components, the sealed nmr tube was placed in a refluxing cyclopentane bath (49°) or boiling-water bath (98°) for a specified time. The reaction was quenched by cooling in ice, and the nmr integrals for the methyl peaks of the ester, *trans* acid, and hydrated acid were determined with the aid of a CAT-1024. After satisfactory analyses were obtained the same tube was returned to the bath for an additional reaction period and the process repeated several times until the ester was essentially completely hydrolyzed.

Registry No.—Ia, 14300-71-1; Ic, 2833-26-3; IIa, 2833-21-8; IIIa, 2833-28-5; carboxylate anion of IIa, 16504-49-7.

Cyclopropylcarbinyl *p*-Toluenesulfonate Solvolysis. III. 1-*p*-Anisyl Substituent Effect[1]

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Received February 21, 1968

Solvolysis rates of 1-*p*-anisylcyclopropylcarbinyl tosylate (6) have been determined in a series of solvents of varying ionizing strength. The solvolysis of 6 relative to cyclopropylcarbinyl tosylate (1) is only slightly accelerated. The solvolytic reactivity of allylcarbinyl tosylate, the homoallylic isomer of 1, demonstrates a similar insensitivity to substitution at the 3 position. In addition, both the cyclopropylcarbinyl and allylcarbinyl series yield the same cyclobutyl solvolysis products. The implications of this solvolytic behavior are discussed in terms of similar neighboring-group participation in the transition state. An analysis of the partitioning of the activation parameters lends further support to the transition-state speculation.

The work reported in this series of papers[2] has clearly established that cyclopropylcarbinyl tosylate (1) suffers solvolysis without responding to 1-ring substitution. Various explanations have been advanced to explain this unpredicted result.[3] These explanations tend to rationalize the apparent insensitivity of a phenyl substituent to charge development on a neighboring carbon in terms of a balance between the rate accelerating conjugative effect and the rate-retarding inductive effect. More specifically, it has been argued that (1) the geometry of the reacting molecular orbitals in the transition state is unfavorable to maximization of the phenyl ring conjugative effect while the inductive effect is stereoelectronically independent and (2) the orbitals involved in the cationic portion of the transition state structure promote a bonding intermediate between σ and π types resulting in a near balance of the phenyl group electron-donating effect (conjugatively *via* π interaction) and the electron-withdrawing effect (inductively *via* σ interaction).

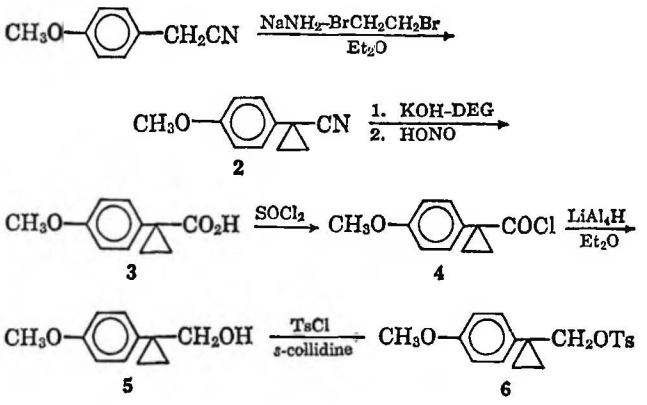
A related explanation[2a,b] was also advanced where it was suggested that extension of the delocalized charge structure to include both the phenyl π bond and the cyclopropane τ bond network was prohibited because of unfavorable orbital geometry. It was further suggested, based principally upon product structure and to a lesser extent upon solvent effect studies, that a transition-state structure was favored where the charge was localized at the methinyl carbon.

As a further test of these explanations, the solvolytic reactivity of 1-*p*-anisylcyclopropylcarbinyl tosylate was investigated. The greatly enhanced ability of a *p*-anisyl group to assist ionization is well established;[4-6] therefore, it is to be expected that the *p*-anisyl substituent would be a significantly more sensitive probe for charge distribution in the transition state than the phenyl substituent.

Synthetic Procedures and Experimental Results

The synthesis of 1-*p*-anisylcyclopropylcarbinyl tosylate was accomplished as shown in Scheme I. The

SCHEME I



preparation of 2 by the method employed for the synthesis of 1-phenylcyclopropylcarbonitrile was attended with difficulty; only trace quantities of 1-*p*-anisylcyclopropylcarbonitrile were obtained. Modification of the reaction conditions, based upon the extensive alkylation work of Hauser, *et al.*,[7] gave 2 in 45% yield. The remaining compounds, 3–6, were obtained in high yield by the procedure[2a] developed for the preparation of 1-phenylcyclopropylcarbinyl tosylate.

The kinetic data are summarized in Table I. Each of these esters was allowed to solvolyze in the indicated solvent and the course of reaction was followed by titrating the liberated *p*-toluenesulfonic acid. All reactions were strictly first order in *p*-toluenesulfonate up to at least 80% conversion and furnished, within experimental error,[8] 100% of the theoretical amount of acid present. That 1-ring-substituted cyclopropylcarbinyl tosylates solvolyze by a SN1-type mechanism has been well established[2b] and evidence[9] has also been presented in support of a SN1 mechanism for the formolysis of allylcarbinyl tosylate (7). The use of formic acid, 0.08 *N* in lithium formate, should introduce less than 5% SN2 reaction of the tosylate with formate ion, based on the study of Roberts.[9]

(1) This work was supported in part by the Petroleum Research Fund of the American Chemical Society. This support is gratefully acknowledged.

(2) (a) D. D. Roberts, *J. Org. Chem.*, **29**, 294 (1964); (b) D. D. Roberts, *ibid.*, **30**, 23 (1965); (c) D. D. Roberts, *ibid.*, **31**, 2000 (1966).

(3) (a) R. Breslow in "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 4; (b) K. L. Servis and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 1331 (1965); (c) P. von R. Schleyer and G. W. Van Dine, *ibid.*, **88**, 2321 (1966); (d) M. Nikoletic, S. Borcic, and D. E. Sunko, *Tetrahedron*, **23**, 649 (1967); (e) Z. Majerski, M. Nikoletic, S. Borcic, and D. E. Sunko, *ibid.*, **23**, 661 (1967); (f) C. D. Ritchie in "Carbonium Ions," G. A. Olah and P. R. Schleyer, Ed., Interscience Publishers, Inc., New York, N. Y.

(4) For example *p*-methoxyneophyl tosylate suffers acetolysis 118 times faster than neophyl tosylate[5] and 2-*p*-anisyl-2-propyl chloride undergoes solvolysis about 3400 times faster than 2-phenyl-2-propyl chloride.[6]

(5) S. G. Smith, A. H. Fainberg, and S. Winstein, *J. Amer. Chem. Soc.*, **83**, 618 (1961).

(6) H. C. Brown, and Y. Okamoto, *ibid.*, **79**, 1914 (1957).

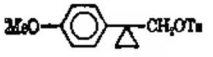
(7) For example, see C. R. Hauser and W. R. Bracken, *J. Amer. Chem. Soc.*, **78**, 494 (1956).

(8) The solvolysis of 3-phenyl-3-buten-1-yl tosylate at 80° liberated 87% of theoretical amount of acid after 20 half-lives. The *p*-toluenesulfonic acid catalyzed addition of solvent to the disubstituted alkene bond[3b] would lead to the less reactive saturated ester.

(9) K. L. Servis and J. D. Roberts, *ibid.*, **86**, 3773 (1964).

TABLE I

SUMMARY OF SOLVOLYSIS RATES FOR ORGANIC TOSYLATES

Compound	Solvent	Temp, °C	k_1,[a] 10^5 sec^{-1}	ΔH^*, kcal/mol	ΔS^*, eu
	AcOH	15.0	18	19.9	−6.3
		20.0	33		
		25.0	62		
		30.0	106		
	Sulfolane[b]	30.0	8.3	19.5	−13.1
		40.0	22		
		50.0	68		
	EtOH	20.0	8.0	22.0	−2.1
		30.0	29		
		40.0	95		
	DMSO[c]	20.0	20	17.9	−14.5
		30.0	59		
		40.0	147		
CH_2=$CHCH_2CH_2OTs$	HCO_2H[d]	50.0	0.35	23.2	−11.9
		60.0	1.00		
		70.0	3.20		
		80.0	8.00		
CH_2=$CPhCH_2CH_2OTs$	HCO_2H[d]	50.0	2.0	20.8	−15.9
		60.0	5.8		
		70.0	14.0		
		80.0	20.0[e]		

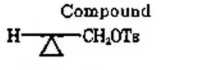
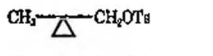
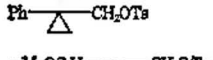
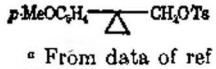
[a] The uncertainties varied from 0.6 to 1.6 standard deviation units from the mean. [b] Tetramethylene sulfone. [c] Dimethyl sulfoxide. [d] Contained 0.08 *N* HCO_2Li. [e] Value not included in activation parameter calculations.

Discussion

Table II compares the relative rates of several selected tosylates in carboxylic acid solvents. It is readily apparent that *p*-anisyl substitution at the 1-ring position has substantially no greater influence than

TABLE II

RELATIVE ACETOLYSIS RATES AT 30°[a]

Compound	AcOH	Sulfolane[b]	EtOH	DMSO[c]
	1.0	1.0	1.0	1.0
	4.9		4.0	
	2.0	8.5	0.8	1.1
	3.1	13.7	2.5	3.0

[a] From data of ref 2. [b] Tetramethylene sulfone. [c] Dimethyl sulfoxide.

phenyl on the solvolytic reactivity of cyclopropylcarbinyl tosylate. The finding is even more marked when one notes the small variation of the relative rates over the range of solvents. This result clearly rules out any significant localization of charge at the methinyl carbon in the transition state and implies that the transition state must have little resemblance to the 1-arylcyclobutyl cationic intermediate suggested by the exclusive formation of ring-expanded products.

Furthermore, in view of the near insensitivity of the solvolysis rate to effects of substituents varying over a wide range of charge stabilizing ability,[10-12] to argue that the absence of substituent effect for all three groups is due to a balance in the rate-retarding and rate-accelerating interaction mechanisms would seem to be too coincidental.

For the limiting type of solvolysis reactions of unsubstituted cyclopropylcarbinyl derivatives, a single transition-state structure, similar to the bicyclobutonium ion, accounts for both the kinetic and product distribution data.[13] On the other hand, with substituted cyclopropylcarbinyl derivatives, the kinetic and product distribution data[2,3b-e] support considerable structural reorganization between the transition state and the cationic intermediate eventually captured by solvent.

In this connection, it is interesting to examine the influence of substitution on the solvolytic reactivity of allylcarbinyl tosylate. The small rate-accelerating effect of a γ-methyl group (see Table III) relative to a δ-methyl group, as noted by Roberts and Servis,[3b] implies less charge development at the γ position in the transition state,[14] and is compatible with a homoallyl-like[15] transition-state structure. Consistent with this proposed transition state is the finding of this study that a γ-phenyl substituent compared to a δ-phenyl substituent exerts a similar small rate-accelerating effect on the solvolytic reactivity of allylcarbinyl tosylate.

TABLE III

RELATIVE FORMOLYSIS RATES AT 50°

Compound	$k_1 \times 10^4$, sec^{-1}	k_{rel}
CH_2=$CHCH_2CH_2OTs$	0.035	1.0
	0.031[a]	
	0.014[b]	
CH_2=$C(Me)CH_2CH_2OTs$	0.043[b]	3.3
CH_3CH=$CHCH_2CH_2OTs$	0.61[b]	45
CH_2=$C(Ph)CH_2CH_2OTs$	0.20	5.7
$PhCH$=$CHCH_2CH_2OTs$	2.1[a]	96

[a] Taken from data in ref 3b, determined in 98% formic acid. [b] Taken from data in ref 3b, determined in 98% formic acid containing 10% pyridine.

Although the homoallyl-like transition state satisfactorily accommodates the kinetic data, the almost exclusively ring-expanded products from the formolysis of both 3-methyl and 3-phenyl-3-buten-1-yl tosylates (see Table IV) demand that the cationic intermediate, captured by the solvent, involve appreciable 1,4 interaction with concomitant localization of charge at the methinyl carbon. These structural requirements are conveniently illustrated by Figure 1. The intervening intermediate(s) I represents a structural reorganization continuum varying from predominantly 1,3 interaction (T_1) to predominantly 1,4 interaction (T_2).

Failure of the solvent to capture effectively an intermediate with 1,3-interaction geometry supports the presence of the currently recognized,[16] stepwise

$$ROTs \rightleftharpoons \underset{a}{R^+OTs^-} \rightleftharpoons \underset{b}{R^+ + OTs^-}$$

ionization mechanism. With bridged ions, the back side of the initially formed ion pair, a, is protected, in addition to the front side; consequently, to the extent that poorly dissociated ionic intermediates intervene between the two transition states, progress along the reaction coordinate to T_2 is more favorable than reaction with solvent.

(10) The relative solvolysis rates of primary tosylates[5,11] $R(Me)_2CCH_2OTs$ for the R groups are Me (1.0), Ph (460), *p*-anisyl (54,000); and for the related tertiary series,[5,12] $R(Me)_2CCl$, are Me (1.0), Ph (620), *p*-anisyl 2 × 10^6.

(11) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Amer. Chem. Soc.*, **74**, 113 (1952).

(12) E. Grunwald and S. Winstein, *ibid.*, **70**, 846 (1948).

(13) For a review, see ref 3f.

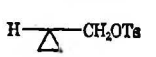
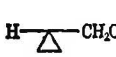
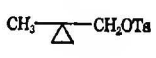
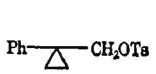
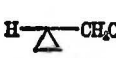
(14) However, see ref 3b and 3d for a discussion concerning the extension of substituent effects in classical ion formation to nonclassical ion formation.

(15) S. Winstein and E. M. Kosower, *J. Amer. Chem. Soc.*, **81**, 4399 (1959).

(16) S. Winstein, P. E. Klinedinst, Jr., and E. Clippinger, *ibid.*, **83**, 4986 (1961).

TABLE IV

SOLVOLYSIS PRODUCTS

Compound	Solvent	Products		
	AcOH[a]	 71%	 24%	CH_2=$CHCH_2CH_2OAc$ 8%
	AcOH[b]	 100%		
	AcOH[c]	 100%		
CH_2=$CHCH_2CH_2OTs$	HCO_2H[d,e]	 45%	 45%	CH_2=$CHCH_2CH_2OH$ 10%
CH_2=$C(Me)CH_2CH_2OTs$	HCO_2H[d,f]	 96.7%		CH_2=$C(Me)CH_2CH_2OH$ 2.3%
CH_2=$C(Ph)CH_2CH_2OTs$	HCO_2H[d]	 >97%		

[a] Taken from data in ref 2a. [b] Taken from data in ref 2c. [c] From data of ref 21. [d] Formate ester hydrolyzed to alcohol. [e] Taken from data of ref 9. [f] Taken from data of ref 3b.

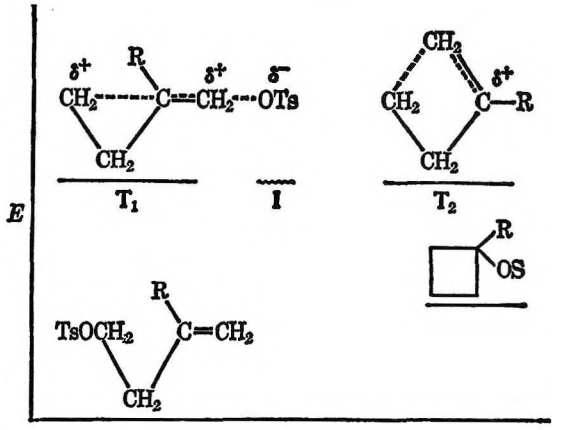
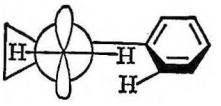


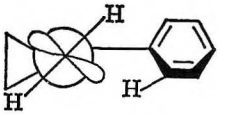
Figure 1.

The effects of 1-ring substitution in the cyclopropylcarbinyl series parallel the effects of similar structural change in the allylcarbinyl series. This correlation between the two series of homoallylic isomers suggests that the effects of 1-ring substitution in the cyclopropylcarbinyl tosylates may be explained by a reaction mechanism similar to that shown in Figure 1. Again, the transition-state structure is stabilized by homoallyl-like neighboring-group assistance. Then, further progress along the reaction coordinate with consequent greater structure reorganization and localization of charge at the methinyl carbon leads to the cationic intermediate eventually captured by solvent (see Table IV).

An examination of framework molecular orbital models of the 1-phenylcyclopropylcarbonium ion gives further support to the speculation that the character of the transition state is influenced by substitution. If the conformation with the phenyl plane bisecting the three-membered ring is energetically most favorable,[17] then symmetrical homoallylic interaction (8) is accompanied by nonbonded steric strain between an *o*-hydrogen and a σ-hydrogen bond. The nonbonded steric strain, however, is relieved with unsymmetrical homoallylic interaction (9).



8

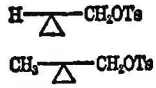
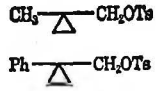
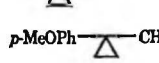


9

Finally, it is pointed out that, in a limiting type of solvolysis of cyclopropylcarbinyl tosylate, the partitioning of the activation parameters is greatly influenced by 1-ring substitution. The ΔS^* values for all of the 1-ring-substituted compounds recorded in Table V are within experimental error equal to -5.4 eu, contrasting with the -19-eu value for the unsubstituted compound. The fact that 1-ring substitution is distinguished from nonsubstitution by such an entropy change supports a transition state with significantly less molecular reorganization for the 1-ring-substituted compounds. The fact that the entropy value is not sensitive to the considerable steric bulk difference of the methyl and the *p*-anisyl group argues against the meaningful influence of steric hindrance to solvation.

TABLE V

SUMMARY OF ACTIVATION PARAMETERS FOR ACETOLYSIS REACTIONS OF ORGANIC TOSYLATES

Compound	ΔH^*, kcal/mol	ΔS^*, eu
	16.7	−19
	20.1	−5.2
	21.0	−4.2
	19.9	−6.3

Experimental Section

All boiling points are uncorrected for stem exposure. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer using sodium chloride optics. A F & M Model 700 gas

(17) (a) A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949); (b) G. L. Closs and H. B. Klinger, *J. Amer. Chem. Soc.*, **87**, 3265 (1965).

chromatographic instrument equipped with a hydrogen flame ionization detector was used for this work. All microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

1-*p*-Anisylcyclopropylcarbonitrile (2) was prepared several times. In a typical run, *p*-methoxyphenylacetonitrile (Aldrich Chem. Co., 14.7 g, 0.1 mol) was added all at once to a stirred suspension of sodium amide (8.6 g, 0.22 mol) in 200 ml of dry ether. After stirring for 2 hr at reflux temperature, 300 ml of dry ether was added followed by the rapid addition of ethylene bromide (18.8 g, 0.1 mol). The brown mixture was stirred at reflux temperature for 20 hr; then 200 ml of crushed ice was added. The flocculent precipitate was filtered out and the filtrate was washed twice with cold, dilute HCl (100-ml portions), three times with cold water (75-ml portions), dried (Na_2SO_4), concentrated, and distilled giving 8.0 g (45%) of the nitrile **2**: bp 112–113° (0.1 mm); $n^{25}D$ 1.5400; ir (neat) 950 cm^{-1} (cyclopropane ring[18]). The glpc retention times (GE SE-30 on Celite, 180°) of **2** and *p*-methoxyphenylacetonitrile were different.

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.41; N, 8.10. Found: C, 76.20; H, 6.40; N, 8.22.

1-*p*-Anisylcyclopropanecarboxylic Acid (3).—A solution of the nitrile, **2** (41 g, 0.24 mol), in 50 ml of diethylene glycol was added to a solution of potassium hydroxide (85%, 16.5 g, 0.25 mol) in 100 ml of diethylene glycol and refluxed for 3 days. After cooling, it was poured into cold, dilute HCl. The precipitated organic acid was separated by filtration and stirred with dilute HONO (generated by slow addition of aqueous NaONO to dilute HCl) for 1 hr. The resulting organic acid was collected by filtration, washed with water, and air dried to yield 40.0 g (87%) of crude acid (mp 120–124°). Four recrystallizations from 1:1 alcohol-water gave the analytical sample of the acid **3**, mp 129–130°.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.72; H, 6.30. Found: C, 68.78; H, 6.45.

1-*p*-Anisylcyclopropylcarbonyl Chloride (4).—A solution of **3** (40.0 g, 0.21 mol) and 100 ml of thionyl chloride was refluxed for 3 hours. Distillation yielded 39.1 g (88%) of the chloride **4**: bp 106–107° (0.2 mm); $n^{25}D$ 1.5475; ir (neat), 1775 (acid chloride C=O), 960 cm^{-1} (cyclopropane ring[18]).

Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.76; H, 5.22; Cl, 16.80. Found: C, 63.02; H, 5.32; Cl, 16.68.

1-*p*-Anisylcyclopropylcarbinol (5) was prepared in 95% yield by lithium aluminum hydride reduction of **4**. Recrystallization from hexane yielded the pure alcohol **5**: mp 40–41°; ir (CCl_4), 3300 (OH), 1026 cm^{-1} (primary alcohol C–O).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.18; H, 7.92. Found: C, 73.85; H, 7.81.

1-*p*-Anisylcyclopropylcarbinyl *p*-toluenesulfonate (6) was prepared several times. In a typical run, 3.5 g (17 mmol) of recrystallized *p*-toluenesulfonyl chloride was added in 10 min to a solution of **5** in 10 ml of purified *s*-collidine maintained at 0° by an ice–water bath. After standing 20 min at 0°, the tan paste was hydrolyzed by rapid addition of 40 ml of cold, dilute HCl. The resulting ester was collected by filtration and washed several times with cold, dilute HCl, followed by water, and recrystallized from petroleum ether (bp 39.7–57°)–ethyl acetate to give the tosylate **6**: mp 53° dec; ir (CCl_4), 1358 (νSO_2 asymmetric), 1172 cm^{-1} (ν^{SO_2}, symmetric). The purity calculated from infinity titers of the solvolyses was 100% of theoretical (the tosylate was too unstable for combustion analysis).

Allylcarbinyl *p*-Toluenesulfonate (7).—Lithium aluminum hydride reduction of 15.0 g of 3-butenoic acid gave 8.0 g (63%) of allylcarbinol, bp 112–113° (lit.[9] bp 110–113°). The reaction of 1.46 g of allylcarbinol with 4.2 g of *p*-toluenesulfonyl chloride in *s*-collidine gave 2.5 g of the tosylate **7**: bp 139–140° (1.0 mm) [lit.[9] bp 150° (~6 mm)]; ir (neat) 1610 (C=C), 1360 (ν^{SO_2}, asymmetric), 1175 (ν^{SO_2}, symmetric), 900 cm^{-1} (CH_2=).

3-Phenyl-3-buten-1-ol was prepared in 30% yield by published procedure:[19] bp 82° (0.1 mm); $n^{20}D$ 1.5580 [lit.[19] bp 130–131° (13 mm); $n^{20}D$ 1.5581]; ir (neat) 3330 (OH), 1630 (C=C), 1045 (RCH_2OH), 890 cm^{-1} (CH_2=). Analysis by glpc revealed the presence of only trace quantities of 3-phenyl-2-buten-1-ol.

3-Phenyl-3-buten-1-yl *p*-Toluenesulfonate.—To 2.96 g (20 mmol) of 3-phenyl-3-buten-1-ol in 15 ml of *s*-collidine cooled to 0° was added 4.19 g (22 mol) of *p*-toluenesulfonyl chloride. The mixture was allowed to stand at 3° for 1 day then hydrolyzed with 40 ml of cold, 3 *N* HCl. The precipitated oil was taken up in 40 ml of methylene chloride, washed twice with cold, dilute HCl (40-ml portions) and twice with cold water (40-ml portions), dried (Na_2SO_4–$NaHCO_3$), and concentrated to yield an oil. The crude ester was dissolved in hot petroleum ether (bp 39.7–57°) and cooled to −78°. The solvent was removed from the precipitated ester by decantation and flash distillation under reduced pressure (*ca.* 0.1 mm) to yield 5.0 of an oil. The purities, calculated from infinity titers of the formolyses, ranged from 93 to 96%. The infrared spectrum [ν^{SO_2} (asymmetric) 1360 cm^{-1} and ν^{SO_2} (symmetric) 1177 cm^{-1}] was consistent with the assigned structure.

Rate measurements were accomplished by the usual technique.[2] The titrating solutions were, for reaction in sulfolane, ethanol, and dimethyl sulfoxide, 0.020 *N* sodium hydroxide and, for acetolysis and formolysis, 0.050 *N* sodium acetate in acetic acid. The indicators used were bromthymol blue and bromphenol blue, respectively. The end point in the formolyses was improved by diluting a 2-ml aliquot with 5 ml of purified dioxane and titrating to a bromcresol green end point.

Solvents.—Sulfolane was purified by redistillation just prior to use. Dimethyl sulfoxide was purified by drying over calcium hydride and distillation. Absolute ethanol was prepared according to the method of Fieser.[20] Acetic acid solvent was prepared from 994.9 ml of glacial acetic acid (Matheson Scientific, 99.8%) and 5.1 ml of acetic anhydride. Formic acid solvent was dried over boric anhydride, decanted, and distilled from fresh anhydride.

Treatment of Kinetic Data.—The activation parameters were obtained by IBM 1620 computer regression analysis of ln (k/**T**) *vs.* 1/**T**.

Product Studies.—A solution (50 ml) of 3-phenyl-3-buten-1-yl tosylate (7 mmol) in formic acid containing lithium formate (12.5 mmol) was thermostated at 50° for 27 hr. The material was added to ice water (200 ml) and extracted three times with ether (50-ml portions). The ether extract was shaken with powdered sodium bicarbonate until neutral, dried (Na_2SO_4), and concentrated to yield 1.1 g (89%) of an oil. Analysis by glpc (6-ft sucrose acetate–isobutyrate column at 170°) revealed the presence of a single major peak accounting for more than 97% of the chromatogram area. The infrared spectrum had a strong carbonyl band at 1710 cm^{-1} and was transparent in the 1620–1650-cm^{-1} region. The formolysis product was hydrolyzed with dilute sodium hydroixde and extracted with ether. Analysis of the concentrated ether extract by glpc (sucrose acetate isobutyrate at 120°) revealed, other than trace peaks, a single product peak with a retention time identical with that of authentic 1-phenylcyclobutanol.[21]

Registry No.—**1**, 1015-45-8; **2**, 16728-00-0; **3**, 16728-01-1; **4**, 16728-02-2; **5**, 16728-03-3; **6**, 16728-4-4; **7**, 778-29-0; 3-phenyl-3-buten-1-yl *p*-toluenesulfonate, 16728-06-6.

(18) The characteristic cyclopropane ring absorption band at approximately 1025 cm^{-1} is obscured by a strong absorption band present in the spectrum of *p*-methoxyphenylacetonitrile. The latter compound is transparent in the 1000–850-cm^{-1} region.

(19) E. G. E. Hawkins and R. D. Thompson, *J. Chem. Soc.*, 370 (1961).

(20) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1957, p 285.

(21) J. W. Wilt and D. D. Roberts, *J. Org. Chem.*, **27**, 3430 (1962).

Electrochemical Reduction of Alkyl Esters of *p*-Toluenesulfonic Acid

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Received December 27, 1967

Reduction of alkyl tosylates has been studied at carbon and mercury electrodes in acetonitrile. The reaction results in the formation of alcohols, ethers, and toluene as major products. A reaction scheme, involving alkoxide and tolyl carbanions as intermediates, is suggested.

Although chemical reactions of tosylates have been studied in detail, relatively little attention has been paid to the electrochemical behavior of these compounds. Mairanovskii and Neiman[1] studied the polarographic behavior of tosylates in alcohol–water mixtures with tetraethylammonium iodide as supporting electrolyte. They observed a single two-electron step which they attributed to reduction of the ester to sulfonic acid. Reduction of thiosulfonic acid esters at the dropping mercury electrode was studied by Boldeyrev, *et al.*[2] They observed two-step waves, with the potential of the second step dependent upon the ester structure. Aromatic esters were reduced at higher potentials than were aliphatic esters.

Petrovich and Baizer[3] have examined the polarographic behavior of allyl and 2-carbethoxyallyl chlorides, bromides, and tosylates in aqueous ethanol, dimethyl sulfoxide, and dimethylformamide solutions. Allyl tosylate showed a single step which was attributed to a one-electron process producing the allyl radical which was immediately reduced at the same potential to the anion. The 2-carbethoxy derivative showed two waves, the first presumably due to a two-electron reduction to ethyl acrylate, the second to reduction of the ester. They observed that addition of phenol caused an increase in the wave height which was explained by assuming that the anionic product, in the absence of phenol, reacts with incoming tosylate to reduce the wave height. Phenol was thought to serve as a proton donor to the anion, thus blocking its reaction with the depolarizer.

We have studied the electrochemical reduction of five tosylates, observing their cyclic voltammetric behavior and recovering products of large-scale electrolyses for identification.

Our results substantiate the main point of the previous work, *i.e.*, that the initial cathodic reduction product formed would be capable of reacting with an allylic group; however, the reactions lead to products different from those envisioned by Petrovich and Baizer.

Results

Cyclic Voltammetry.—Cyclic voltammetric curves for methyl tosylate are shown in Figures 1, 2, and 3. Figure 1 shows only the tosylate. Figure 2 shows the same tosylate solution with methanol added. Figure 3 shows the same solution with both methanol and phenol added. These were obtained by cycling the microelectrode potential continuously within the indicated limits. Curves were recorded after a steady-state condition had been achieved.

Other compounds studied were ethyl tosylate, *n*-butyl tosylate, cyclohexyl tosylate, and neopentyl tosylate. Cyclic voltammetry curves for these were qualitatively similar to those for methyl tosylate. Differences will be discussed below. In all cases, the most cathodic reduction reaction, which corresponds to the single dc polarographic wave which these compunds produce will be designated the A peak. In Figure 1 it is the reduction peak about 1 cm from the right side of the illustration. The most cathodic oxidation peak, located about 0.5 cm to the right of center in Figure 1, will be referred to as the B peak. The second most cathodic reduction peak, which appears slightly more than 1 cm to the right of center in Figure 1, will be called the C peak.

All peaks other than the A peak are caused by reactions of the products of the A peak. That is, the microelectrode potential must have been the region of the A peak within about 15 sec if any of the other peaks is to be seen. If the sweep is operating just over the region of the A peak and is extended to the left, the other peaks appear as expected. However, if the sweep is operating only in the region of the B peak and is then extended to the right, nothing is observed until the A peak is seen, at which time the B peak, as well as those appearing to its left in Figure 1, appears. If the solution is stirred while a signal like that in Figure 1 is being observed, the A peak increases while the others decrease in height.

Potentials for the A, B, and C peaks of all compounds studied are shown in Table I. Results are averages of five replicate curves. Each of the three values for methyl tosylate is an average of five values with the three sets taken on separate days.

TABLE I

CYCLIC VOLTAMMETRIC PEAK POTENTIALS

Compound[a]	Registry no.	A peak[b]	B peak	C peak
Methyl tosylate	80-48-8	−2.61	−1.24	−1.45
		−2.64	−1.22	−1.46
		−2.60	−1.31	−1.50
		−2.58	−1.22	−1.43
Ethyl tosylate	80-40-0	−2.52	−1.21	−1.45
n-Butyl tosylate	778-28-9	−2.61	−1.24	−1.44
Neopentyl tosylate	2346-07-8	−2.52	−1.21	−1.45
Cyclohexyl tosylate	953-91-3	−2.57	−1.20	−1.45

[a] *Ca.* 5 m*M* in 0.10 *M* tetrapropylammonium perchlorate in acetonitrile. [b] Reference electrode, 0.10 *M* $AgNO_3$–Ag^0 in acetonitrile.

Constant Potential Electrolysis.—Large-scale reductions were carried out at glassy carbon and mercury electrodes. Acetonitrile was used as the solvent except

(1) S. G. Mairanovskii and M. B. Neiman, *Dokl. Akad. Nauk SSSR*, **87**, 805 (1952).

(2) B. G. Boldeyrev, M. A. Kovbuz, and T. A. Trofimova, *Zh. Obshch. Khim.*, **35**, 22 (1965).

(3) J. P. Petrovich and M. M. Baizer, *Electrochim. Acta*, **12**, 1249 (1967).

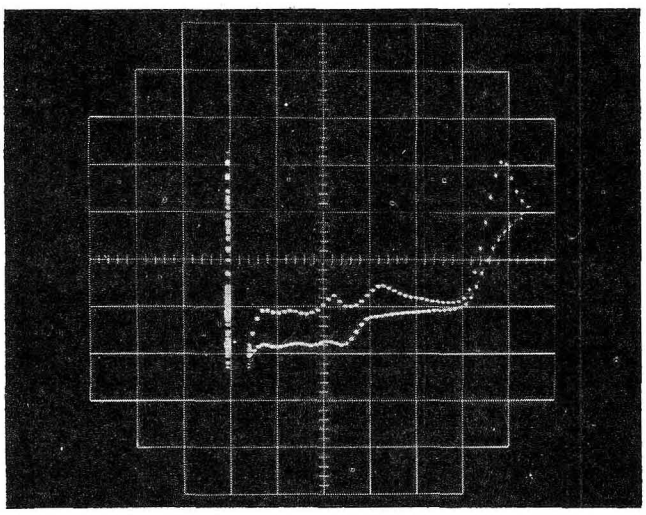


Figure 1.—Methyl tosylate: continuous sweep cyclic voltammetric curve for ~10 m*M* MeOTs in 0.10 *M* Pr_4NClO_4–MeCN. Signal oriented with reduction current (300 μA/cm) up and cathodic potential (0.5 V/cm) to the right. The irregular line 2 cm to the left of center denotes zero on the potential axis.

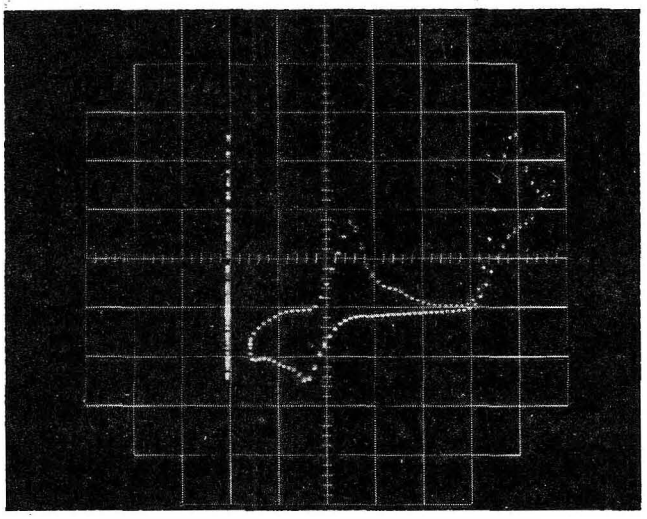


Figure 2.—Methyl tosylate with methanol: conditions as described in the caption of Figure 1.

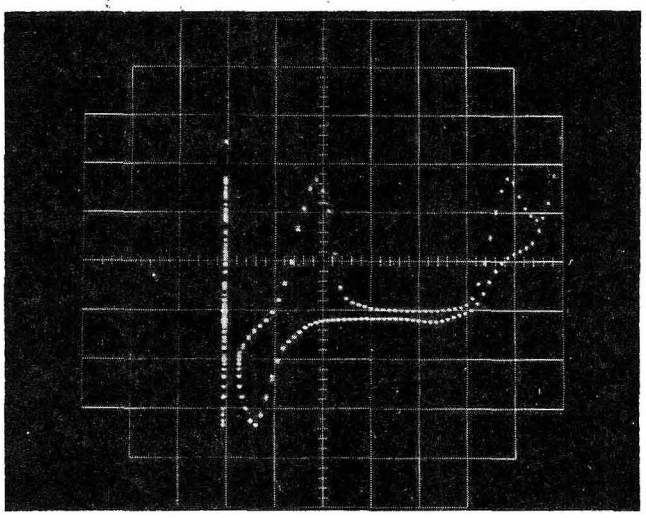


Figure 3.—Methyl tosylate with methanol and phenol: conditions as described in the caption of Figure 1.

in one experiment with dimethylformamide. Tetraethylammonium bromide, tetrapropylammonium iodide, and tetrapropylammonium perchlorate were used as supporting electrolytes. Coulometry and product analysis results are presented in Table II. With carbon electrode reductions, reaction current dropped continuously to the background. Initial currents were typically 25–30 mA, final currents typically 0.1–0.2 mA. With mercury cathodes, the initial current was about as indicated; however, instead of dropping continuously, the current went through a maximum, typically a few milliamperes above the starting value, a few minutes after the start of the reaction. It then fell rapidly to the background value.

TABLE II

CONSTANT POTENTIAL REDUCTION OF ALKYL TOSYLATES at −2.80 V *vs.* Ag–$AgNO_3$

Compound	Working electrode	Supporting electrolyte	n[a]	% ROH[b]	% ROR	% $PhCH_3$
Methyl	C	TPAP[c]	1.0	24	36	27
tosylate	Hg	TPAP	1.0	44	...	25
	Hg	TEAB[d]	1.0	42		
Ethyl	C	TPAP	1.1	32	35	30
tosylate						
n-Butyl	C	TPAP	1.0	62	18	26
tosylate	Hg	TPAP	1.1	58	...	28
Neopentyl	C	TPAP	1.2	68		34
tosylate	C	TPAI[e]	1.4	98	...	28
	Hg	TPAI	1.3	97	...	25
Cyclohexyl	C	TPAP	1.2	75[f]	...	4
tosylate	Hg	TPAP	0.91	60[g]	...	23
	C	TEAB	2.0	96	...	Trace
	Hg	TEAB	1.9	96	...	Trace

[a] Number of electrons per molecule of starting tosylate. [b] All yields mole % of starting tosylate. [c] Tetra-*n*-propylammonium perchlorate. [d] Tetraethylammonium bromide. [e] Tetra-*n*-propylammonium iodide. [f] Plus 4% cyclohexanone. [g] Plus 5% cyclohexanone.

In addition to the compounds indicated in Table II, others were identified, but not quantitatively determined, in the reaction mixture. Propylene and tripropylamine were identified as products of reactions for which tetrapropylammonium ion was used as supporting electrolyte. Alkanes corresponding to the alkyl group of the tosylate being examined were sought unsuccessfully.

Toluene and sulfinate anions were identified by ultraviolet absorption spectroscopy. The volatile fraction of the contents of the cathode compartment was removed at reduced pressure and trapped at liquid nitrogen temperature. The ultraviolet spectrum of the volatile fraction was identical with that of toluene. The residual solid was taken up in water. This solution showed absorption peaks at 220 and 260 mμ. After acidifying, the 220-mμ peak was changed, the 260-mμ peak was eliminated, and a more intense peak was observed at 240 mμ. The Sadtler Standard ultraviolet spectrum collection shows, for *p*-toluenesulfinate in methanol, peaks at 268, 263–265, and 222 mμ, with extinction coefficients of 999, 969, and 12,200, respectively. After acidifying, the peaks are shown at 241 and 222 mμ, with extinction coefficients of 3310 and 11,400, respectively. This behavior was observed for products of mercury cathode reduction of methyl, butyl, and cyclohexyl tosylates and for carbon electrode reduction of cyclohexyl tosylate. It is assumed that it would be observed in all cases and that it constitutes a qualitative indication of the presence of *p*-

toluenesulfinate anion in the products. *p*-Toluenesulfonate ion shows ultraviolet absorption at 221 mμ, unaffected by acid. Since this is at nearly the same wavelength as the similarly unaffected peak of *p*-toluenesulfinate ion, the presence of sulfonate cannot be proved or disproved on this basis.

There was no indication, by gas chromatography or ultraviolet spectroscopy, that any unidentified compounds in significant amounts were present.

Attempts were made to detect mercury in the reaction mixtures by atomic absorption spectroscopy. These were unsuccessful because of the large signal caused by the solvent. Volatile components of the product mixtures were removed under reduced pressure, and the determination was repeated on carbon tetrachloride extracts of the remaining solids. No mercury was detected. Standard sample determinations indicated that mercury in excess of 1 mol % of the starting tosylate should have been detected by this procedure; however, volatile compounds would not have been found.

Discussion

The electrolytic reduction of tosylates has been carried out at carbon and mercury electrodes. A scheme for the reaction at the carbon electrode is outlined in eq 1 through 7 below. It is suggested that the

$$\mathrm{ROTs} + e^- \longrightarrow \underset{\mathbf{1}}{p\text{-}\dot{C}H_3C_6H_4SO_2OR^-} \quad (1)$$

$$\mathbf{1} \longrightarrow \mathrm{ROSO_2^-} + \mathrm{CH_3}\text{–}C_6H_4\cdot \xrightarrow{e^-} \underset{\mathbf{2}}{\mathrm{CH_3}\text{–}C_6H_4^-} \quad (2)$$

$$\mathbf{1} \longrightarrow \mathrm{OR^-} + p\text{-}CH_3C_6H_4SO_2\cdot \xrightarrow{e^-} \underset{\mathbf{3}}{p\text{-}CH_3C_6H_4SO_2^-} \quad (3)$$

$$\mathbf{2} + \mathrm{H^+} \longrightarrow C_6H_5CH_3 \quad (4)$$

$$\mathrm{RO^-} + \mathrm{H^+} \longrightarrow \mathrm{ROH} \quad (5)$$

$$\mathrm{RO^-} + \mathrm{ROTs} \longrightarrow \mathrm{ROR} + \mathrm{OTs^-} \quad (6)$$

$$\mathrm{ROSO_2^-} + H_2O \longrightarrow \mathrm{ROH} + \mathrm{HSO_3^-}\cdot \quad (7)$$

initial step involves addition of one electron to the tosylate forming a very short-lived anion radical having the unpaired electron localized at the sulfur atom. This is based on our failure to observe any indication of reversibility, indicating radical lifetimes of less than a few milliseconds. This anion radical could decompose by scission of either a carbon–sulfur bond as in step 2 or a carbon–oxygen bond as in step 3. It is suggested that at the potential required for step 1, the *p*-tolyl radical produced by decomposition of **1** is immediately reduced to the *p*-tolyl carbanion, **2**. Protonation of **2** in step 4 would account for the appearance of toluene as a product.

Cleavage of a sulfur–oxygen bond in the decomposition of **1** yields alkoxide ions and *p*-toluenesulfinyl radicals which are presumably immediately reduced to sulfinate ions, as indicated in step 3. The formation of **3** is inferred from the ultraviolet data. Since only one reduction peak is observed in the cyclic voltammetric curve, immediate reduction of the radical seems indicated.

The recovery of substantial yields of alcohols reflects protonation of alkoxide during or after the electrolysis. Identification of propylene and of tripropylamine indicates that the supporting electrolyte is serving as at least a partial source of protons for steps 4 and 5. A possible reaction is shown in eq 8. Quantitative

$$\mathrm{R^-} + \mathrm{Pr_4N^+} \longrightarrow \mathrm{RH} + \mathrm{CH_3CH{=}CH_2} + \mathrm{Pr_3N} \quad (8)$$

studies in connection with other work show that an analogous reaction of tetraalkylammonium ions could account for only a part of the protons involved. The remainder were shown to come from the solvent, acetonitrile.[4] It is likely that the same is probably true in these experiments.

Isolation of substantial yields of ethers suggests the displacement reaction indicated in step 6. The reaction of alkoxides with tosylates has been studied and shown to involve an S$_N$2 displacement.[5] The yields of ethers indicated in Table II decrease in the order methyl > ethyl > butyl > neopentyl, as would be expected for an S$_N$2 reaction.

The results obtained for carbon cathode large-scale reductions are reasonably compatible with the reaction scheme proposed. The major discrepancy is failure to account for all of the alkyl groups of the starting tosylate sample in the reaction of neopentyl and cyclohexyl tosylates. It may be noted that use of halide salts, rather than perchlorates, resulted in a nearly quantitative recovery of alcohols in these cases.

Reactions at mercury cathodes differed from those at carbon cathodes in that no ethers were formed from methyl or butyl tosylates. This evidently indicates that alkoxide ions are prevented from coming in contact with unreacted tosylate, since it is known that ethers are formed under the conditions of these experiments. The possibility was considered that the absence of ethers simply indicates that, at mercury electrodes, step 3 is not occurring. Alcohol and toluene would be produced by steps 2, 4, and 7. This, however, would require the formation of equal amounts of alcohol and toluene. Since the yields of alcohols are much larger than yields of toluene, step 3 cannot be omitted. It may be possible that the composition of the electrical double layer at the mercury–solution interface, which would be expected to differ from the double layer at a carbon–solution interface, is responsible for this difference.

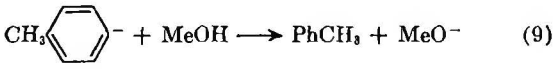
The possibility that formation of unreactive organomercury compounds may be responsible for failure to account for all of the alkyl groups in the reduction of low-molecular-weight tosylates at mercury cathodes was considered. An attempt was made to detect mercury in butyl tosylate reaction products by atomic absorption spectroscopy. Direct determination on the reaction mixture was unsuccessful because of the large background signal caused by the solvent. Removal of the solvent followed by analysis of extracts of the residual solids gave negative results. This does not eliminate the possibility of an unreactive volatile mercury compound having been formed.

(4) C. K. Mann, J. F. Webb, and H. M. Walborsky, *Tetrahedron Lett.*, 2249 (1966); additional data to be published.

(5) C. H. Snyder and A. R. Soto, *J. Org. Chem.*, **29**, 742 (1964).

Cyclic Voltammetry.—We suggest that the A voltammetric peak is caused by the electron-transfer reactions in steps 1, 2, and 3 of the proposed scheme for all compounds studied. This assignment is made because the constant potential reductions, carried out at the potential of the A peak, produced products which could be formed from these reactions and because only one reduction peak occurred at this potential.

It is evident from Figure 2 that addition of methanol eliminates the B–C pair and augments the pair immediately to the left. We attribute this to reaction 9 which forms methoxide.



Addition of potassium methoxide to a solution such as that being electrolyzed to obtain Figure 2 causes an increase in the peaks attributed to methoxide without causing other changes, except for the appearance of a pair of reversible peaks due to the potassium couple.

Addition of phenol to the solution illustrated in Figure 2 produces the solution electrolyzed to get Figure 3. The methoxide peaks are eliminated and a pair of peaks at more anodic potentials is generated. These coincide with phenoxide peak potentials. Presumably phenol is protonating methoxide.

These results show that, for methyl tosylate, methanol eliminates the B peak reactant and that, as expected from the pK_a values in Table III,[6] phenol removes both the B peak reactant and methoxide.

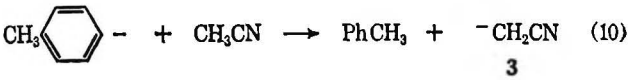
TABLE III[6]

Compound	pK_a
Phenol	10
Methanol	16
Ethanol	18
Acetonitrile	25
Benzene	37

It has been noted with amines that a correlation exists between base strength and ease of oxidation of the base. Values of pK_a[7] and cyclic voltammetric oxidation peak potentials[8] have both been shown to be correlated with polar substituent constants for substituents on the nitrogen atoms. Potentials can therefore be correlated with pK_a values. The stronger the base, the more easily it is oxidized. This would be anticipated considering the Lewis definition of a base.

We have observed that the order of increasing ease of oxidation of the conjugate bases of phenol, and the alcohols examined is phenoxide < methoxide < ethoxide < cyclohexoxide, with cyclohexoxide most easily oxidized. We base this on observations of the effect of successive addition of alkali alkoxides and alcohols to a solution while a voltammetric signal is being observed. This type of experiment is not suited to quantitative measurement of potentials, but as can be seen from Figures 2 and 3 does give unequivocal qualitative information. Again, the stronger the base, the more easily it is oxidized.

Regarding the identity of the reactant being oxidized at the B peak, one possibility is the tolyl carbanion 2 formed in step 2 of the reaction scheme. Another possibility is cyanomethylene carbanion 3 formed in eq 10.



From the pK_a values in Table III, it would be expected that step 10 would occur, if it is accepted that the pK_a of toluene for the loss of the *para* hydrogen would be about the same as that of benzene. The potentials given in Table I for the B peaks are, within experimental error, the same for all compounds examined. This would be the case for either alternative. We suggest that the correlation between bacisity and oxidation potential should be valid for carbanions as well as amines and alkoxides. If so, then the potential for oxidation of 2 would be more cathodic than for oxidation of 3 which would, in turn, be more cathodic than the methoxide oxidation peak.

On the basis of the data presently available, we cannot definitely distinguish between then two possibilities. We are inclined to believe that the B peak is caused by oxidation of 2 and that, although reaction 10 is occurring, we are seeing that fraction of 2 formed at peak A which survives the 0.2-sec period which elapses between peak A and peak B. This could be adsorbed on the microelectrode. As one indication that this may be true, we have seen, in other work,[4] peaks which can reasonably be ascribed to alkyl and aryl carbanions produced by electrochemical reduction of alkyl and aryl halides which occurred near but not at the potential of the B peaks. A peak which behaved like the B peak was observed on reduction of *m*-bromotoluene. If 2 is entirely eliminated in favor of 3, then presumably the same would be true for other carbanions, since they are, in general, substantially more basic than 3. It may be noted that the methoxide peaks in Figure 2 are substantially larger than the B peaks of Figure 1. This suggests that we are seeing in Figure 1 the oxidation peak of the surviving portion of 2, followed by the oxidation of the 3 formed and of methoxide. This results in the fairly substantial but varying current indicated to the left of the B peak in Figure 1. When methanol is added, it protonates all of 2 and 3, leaving a single much larger methoxide peak in Figure 2.

The cyclic voltammetry curve was obtained for methyl tosylate in dimethylformamide solutions. It was qualitatively similar to that obtained in acetonitrile. This observation is in accord with our supposition that the B peak is due to 2, since it leads us to expect that the solvent change should not eliminate the B peak. However, this does not prove the point either way since a reaction of 2 with dimethylformamide to form an oxidizable substance is possible.

The other tosylates studied are derivatives of more weakly acidic alcohols than methanol. This is reflected in a rather ill-defined B peak for ethyl and butyl tosylates, presumably because the alkoxide oxidation is occurring at only slightly less anodic potentials than are required for the B peak.

The case of cyclohexyl tosylate is different from the others in one respect. The B peak for this compound is large and well defined; however, investigation showed that this is caused by the coincidence of cyclo-

(6) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 1.
(7) H. K. Hall, *J. Amer. Chem. Soc.*, **79**, 5441 (1957).
(8) C. K. Mann, *Anal. Chem.*, **36**, 2424 (1964).

hexoxide being oxidized at very nearly the same potential as is required for 2 or 3. Addition of cyclohexanol to a solution of the tosylate did not eliminate the B peak, in contrast to the effect of methanol on the B peak of methyl tosylate. Instead, there was a very slight shift of peak potential in the anodic direction, indicative of the slightly less cathodic oxidation potential of cyclohexoxide as compared with that of 2 or 3. Addition of cyclohexoxide caused the B peak to increase without affecting the rest of the signal. Addition of methanol eliminated the cyclohexoxide peak, as expected.

The authors intend to investigate further the behavior of very easily oxidized anions. However, they expect to use a system other than tosylate because the mixture of products produced causes undesirable voltammetric complexity.

Experimental Section

Reagents.—Acetonitrile was prepared according to the procedure previously described.[9] Commercial tetraethylammonium bromide was recrystallized from methanol and dried under a vacuum at 80°. Tetrapropylammonium perchlorate was prepared from the iodide as previously described by Kolthoff.[10]

Methyl, ethyl, neopentyl, and cyclohexyl tosylates were prepared according to the procedure of Tipson.[11] Our experimental melting points agreed with literature values for the following: cyclohexyl tosylate, 44°: methyl tosylate, 28°; ethyl tosylate, 32°;[12] neopentyl tosylate, 48°.[13] *n*-Butyl tosylate was Eastman White Label.

Dicyclohexyl ether, with a boiling point of 244° (lit.[14] bp 239–240°), was prepared by a hydrogen–Raney nickel reduction of phenylcyclohexyl ether in cyclohexane solution at 175° and 30 atm. Other reagents were the best available grade, used without purification.

Cyclic Voltammetry.—Cyclic voltammetry curves were obtained on the apparatus previously described.[15] Sweep rates were 10 V/sec, with a 3-m/sec step width. The microelectrode was a mercury-plated platinum wire. A silver–0.10 *M* $AgNO_3$–acetonitrile reference electrode was used for all electrolyses. Voltammetric curves were recorded using unthermostated cells in a room having ambient temperature at 22°.

Constant Potential Electrolyses.—Electrolyses were performed with a conventional three-electrode potentiostat. All electrolysis cells were constructed to permit use of vacuum-line techniques for solution handling. Large-scale electrolyses were performed in H cells with either mercury pool or glassy carbon cathodes and silver or platinum anodes. Solutions were degassed by repeated freezing and pumping and were then stored under a nitrogen or a helium atmosphere.

Product Analyses.—Reaction vessels were fitted with septums which allowed direct sampling of cathode solution or head space by a syringe. Alcohols, ethers, tripropylamine, propylene, methane, ethane, butane, cyclohexane, neopentane, and toluene were determined or sought by gas chromatography, on appropriate columns, on samples taken directly from the cathode compartment. In all cases, valid samples of compounds of interest were chromatographed for comparison. This applies also to compounds sought but not found, *e.g.*, methane after methyl tosylate reduction; care was taken to ascertain that these would be seen, if present, considering the interferences present in the samples analyzed.

Toluene and *p*-toluenesulfinate ion were detected by ultraviolet absorption spectroscopy.

Mercury analyses were performed on reaction mixtures with a Perkin-Elmer Model 290 atomic absorption spectrometer.

Acknowledgment.—The authors wish to acknowledge financial support from the National Institutes of Health through Grant GM-10064.

(9) J. F. O'Donnell, J. T. Ayers, and C. K. Mann, *Anal. Chem.*, **37**, 1161 (1965).
(10) I. M. Kolthoff and J. F. Coetzee, *J. Amer. Chem. Soc.*, **79**, 870 (1957).
(11) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).
(12) R. S. Tipson, M. A. Clapp, and L. H. Cretchen, *ibid.*, **12**, 133 (1947).
(13) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Amer. Chem. Soc.*, **74**, 1113 (1952).
(14) H. Willstatler, *Chem. Ber.*, **45**, 1466 (1912).
(15) C. K. Mann, *Anal. Chem.*, **36**, 2424 (1964).

The Tetramers of Acetylenedicarboxylic Esters[1]

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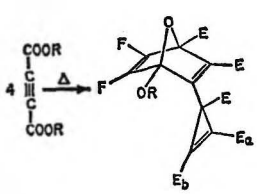
Received November 6, 1967

Dimethyl and diethyl acetylenedicarboxylate form thermal tetramers which have been characterized as cyclopropenyl derivatives of oxanorbornadiene **1a** and **1b**. Various degradative reactions verify this structural assignment. The hexadeuterated tetramer analog **1c** was synthesized by trapping the reactive cyclopropenylfuran **10a** with dimethyl acetylenedicarboxylate-d_6. The tetramer of the methyl ester undergoes photochemical reaction to form semibullvalene derivative **13**.

The dimethyl[2,3] and diethyl esters of acetylenedicarboxylic acid spontaneously react to form tetrameric products. From spectral studies Le Goff and LaCount have recently proposed the cyclopropenyloxanorbornadiene structure **1a** for the crystalline methyl ester **1a**.[3] The chemical and spectral studies here reported verify this assignment. The tetrameric ethyl ester which exhibits similar infrared and ultraviolet spectra is assigned analogous structure **1b**.

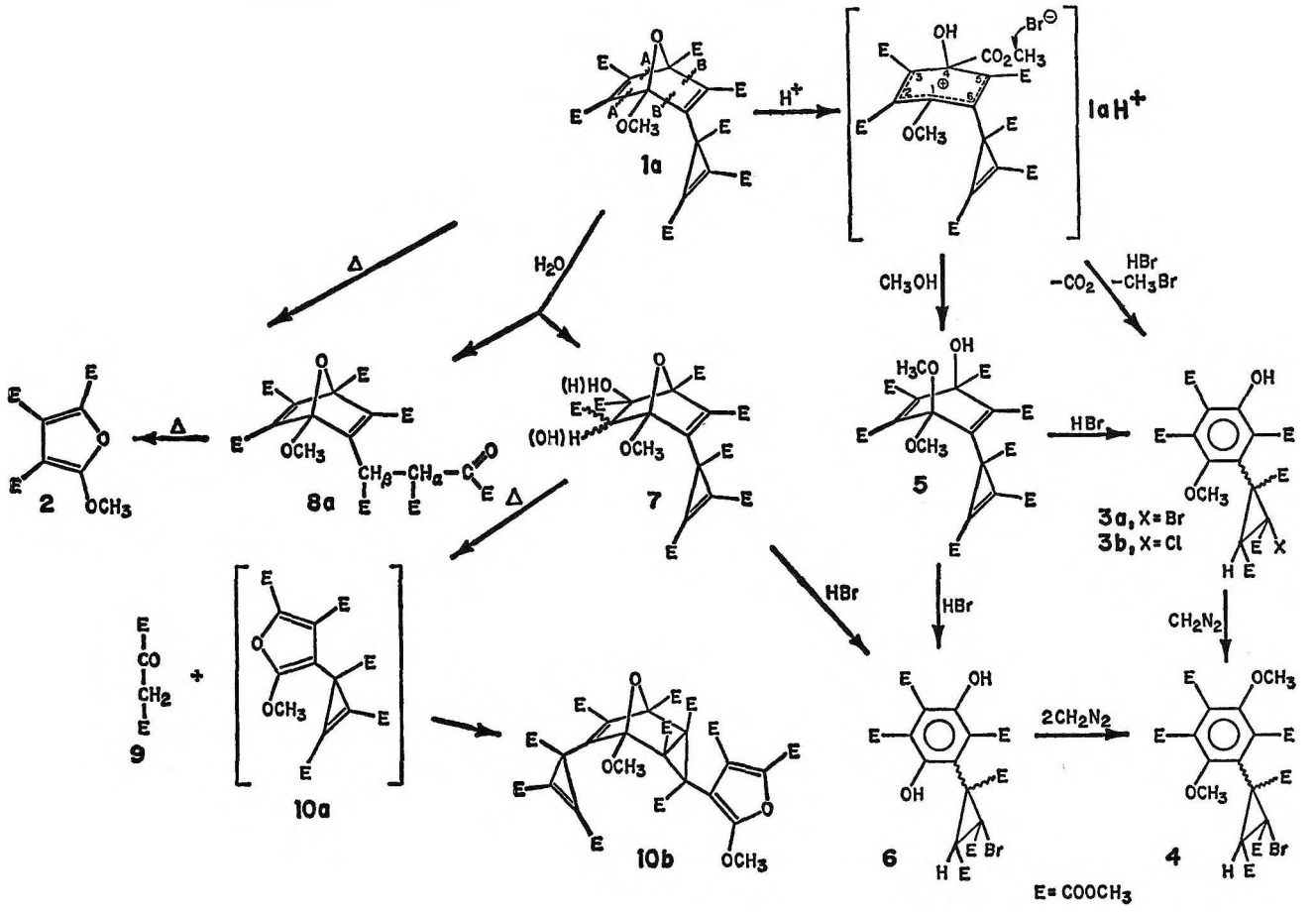


1a, E = F = $COOCH_3$; R = CH_3
b, E = F = $COOC_2H_5$; R = C_2H_5
c, E = $COOCH_3$; F = $COOCD_3$; R = CH_3

Spectral Features.—The tetramers and several of their derivatives described below exhibit medium intensity absorptions at 1870–1900 cm^{-1} in their infrared and Raman spectra. Absorptions in this region are characteristic of the highly substituted cyclopropene ring system,[4] although compounds containing conju-

(1) Presented in part at the Third Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1968.
(2) (a) M. J. Goldstein, private communication. (b) G. L. Thayer, Jr., Thesis, Cornell University, 1965, p 89 ff; *Dissertation Abstr.*, **26**, 104 (1965).
(3) E. Le Goff and R. B. LaCount, *Tetrahedron Lett.*, 2333 (1967).
(4) (a) G. L. Closs, *Advan. Alicyclic Chem.*, **1**, 74 (1966); (b) *ibid.*, **1**, 115 (1966).

SCHEME I
RING-OPENING REACTIONS OF THE TETRAMER OF DIMETHYL ACETYLENEDICARBOXYLATE



gated allenic[6] linkages, cyclopropanones,[6] or cyclopropenones[4b] also exhibit such absorptions.

The nmr spectrum of tetramer **1a** in acetone-d_6 exhibits eight distinct and equal methoxyl resonances. (The synthesis of the hexadeuterated analog **1c** described below permits the rational assignment of two of these peaks.) Somewhat poorer separation of the eight peaks is observed in acetonitrile-d_3 and benzonitrile, whereas in chloroform and bromoform two of the peaks coalesce to form a sharp singlet, leading to the seven-line spectrum reported by Le Goff and La Count.[3] When the bromoform solution is warmed to 135–150°, the peaks again separate, and a well-resolved eight-line spectrum is obtained.

At first glance, structure **1a** might be considered to be incompatible with the observed eight-line nmr spectrum. The cyclopropene ring is attached to an asymmetric system, however, and even with free rotation around the bond connecting it with the oxanorbornadiene moiety, the methoxycarbonyl groups E_a and E_b are at all times in different magnetic environments. Similar chemical-shift differences for *gem*-dimethyl (and other) groups adjacent to asymmetric systems have often been observed.[7]

Although the tetramers exhibit a strong, broad absorption "tail" in the ultraviolet region between 200 and 250 mμ, careful studies using either purified acetonitrile or isooctane solvent in a 1-mm cell indicate no absorption maximum above 200 mμ. A distinct shoulder at 225 mu (ε *ca.* 17,000) is observed, however, in both **1a** and **1b**.[8a] The absorption intensity at 205 mμ (ε 18,000) in acetonitrile is in reasonable agreement with the presence of three *cis*-1,2-bis(methoxycarbonyl)ethylene (or acrylic ester) chromophores in the tetramer molecule. By comparison, dimethyl maleate exhibits very similar end absorption in this region.[8b]

Chemical Properties of the Tetramer.—As Le Goff and LaCount[3] have pointed out, the tetramer is very sensitive to base, and attempts to hydrolyze the ester with aqueous base rapidly extinguish the cyclopropene absorption.[9]

Although the tetramer **1a** possesses three double bonds, attempts at direct bromination, even in the presence of bromide ion, were unsuccessful. Catalytic hydrogenation produced an ill-defined mixture of hydrogenation products which could not be separated. The dienophilic reactivity of the cyclopropene double bond in **1a** has been noted by other workers.[2,3]

Strong support for structure **1a** comes from the pyrolysis of the tetramer and from several ring-

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 62.

(6) See, for instance, N. J. Turro, W. B. Hammond, and P. A. Leermakers, *J. Amer. Chem. Soc.*, **87**, 2774 (1965).

(7) G. M. Whitesides, D. Holtz, and J. D. Roberts, *ibid.*, **86**, 2628 (1964).

(8) (a) Le Goff and LaCount[3] report λ_{max}^{EtOH} 220 mμ (ε 15,500), 232 shoulder (ε 12,600) for **1a**; Thayer[2b] reports no absorption maximum above 220 mμ. We prefer to avoid the use of hydroxylated solvents because of the reaction of **1a** with both water and methanol (see below). (b) R. F. Rekker, P. J. Brombacher, H. Hamann, and W. T. Nauta [*Rec. Trav. Chim.*, **73**, 410 (1954)] report for dimethyl maleate λ_{max}^{EtOH} 205 mμ (log ε 3.90). We find no real peak above 200 mμ in acetonitrile solvent; at λ^{CH_3CN} 205 mμ, ε = 7000.

(9) Careful treatment of the ester with 7 equiv of aqueous barium hydroxide at 25° produces a yellow barium salt. Acidification with the calculated amount of sulfuric acid produces a solid, water-soluble acid, which on treatment with diazomethane yields an intractable methyl ester having no cyclopropene absorption.

opening reactions which lead to easily crystallized products. These reactions are summarized in Scheme I.

Pyrolysis.—When the tetramer is heated to 180° under reduced pressure, some dimethyl acetylenedicarboxylate is obtained as well as 2-methoxy-3,4,5-tris(methoxycarbonyl)furan (2). The latter is identical in all its properties with the product recently reported by other laboratories.[2,10] This reaction provides strong evidence that a 7-oxanorbornene residue is present in the molecule; cleavage of the molecule (a reverse Diels–Alder reaction) at bonds B–B (Scheme I) would yield the furan whereas similar cleavage at A–A would produce dimethyl acetylenedicarboxylate. The other pyrolysis products were not characterized. This reverse Diels–Alder reaction to produce the furan **2** was found to be generally useful to verify the presence of the 7-oxanorbornadiene (or 7-oxanorbornene) moiety in the derivatives described below.

Reaction of the tetramer **1a** with anhydrous hydrogen bromide in benzene gives a phenolic monobromide **3a**. This can occur by protonation of the oxygen bridge of **1a** to produce the stabilized carbonium ion **1a**-H$^+$ (Scheme I). Attack by bromide ion at the methyl of the methoxycarbonyl group in the 4 position could lead to direct aromatization of the six-membered ring. Such displacements have precedence in solvents such as benzene, where bromide ion (or its solvates or complexes) is known to be very nucleophilic.[11] Addition of hydrogen bromide to the cyclopropene ring ultimately produces the cyclopropyl bromide **3a**, which reacts with 1 mol of diazomethane to give the dimethyl ether **4**.

The tetramer **1a** also reacts with hydrogen chloride to form the monochloride **3b**, whose infrared, ultraviolet, and nmr spectra are nearly superimposable on those of the bromide **3a**.

Methanolysis.—Tetramer **1a** reacts with methanol in the presence of a trace of hydrogen chloride to form the stable ketal **5** in 42% yield. Here again, protonation of the oxygen bridge can produce the carbonium ion **1a**-H$^+$ which is attacked by methanol at the 1-carbon atom. Cyclopropene (1880 cm^{-1}) and hydroxyl (3550 cm^{-1}) absorptions are prominent in the infrared spectrum of **5**, and the nmr spectrum shows one hydroxyl and nine methoxyl groups. Seven of the latter resonances occur between δ 3.65 and 3.86 ppm downfield from tetramethylsilane in acetone-d_6, typical positions for ester or vinyl methoxyl groups, and two occur at δ 3.10 and 3.18 ppm, typical of methoxyl groups attached to saturated carbon atoms. The ultraviolet spectrum of **5** suggests the presence of three *isolated* 1,2-bis(methoxycarbonyl)ethylene (or acrylic ester) chromophores[8b] and rules out structures having conjugated double bonds (*e.g.*, those resulting from attack by methanol on ion **1a**-H$^+$ at positions 3 or 5). The ketal **5** is cleaved by hydrogen bromide to form the methoxyphenol **3a**, as well as the corresponding hydroquinone **6**. The latter is converted by diazomethane into the dimethyl ether **4**, identical with that obtained from **3a**. As expected, pyrolysis of **5** at 180° did not give the furan **2**.

Hydration.—The tetramer reacts slowly in 50% aqueous dioxane to form approximately equal amounts of two hydrates, **7**, mp 126° (26%), and **8a**, mp 147° (25%). The reaction, which can be followed by thin layer chromatography, is virtually complete after 10 days at 25°.

The higher melting hydrate does not exhibit the typical cyclopropene absorption in the infrared region. Addition of water to the cyclopropene ring of **1a** followed by cleavage produces the partially enolized β-keto ester **8a**. On pyrolysis of **8a** at 170°, furan **2** was obtained, verifying the presence of the oxanorbornadiene ring system. The only peak in the uv spectrum of **8a** (λ_{max}^{EtOH} 260 mμ, ϵ 12,080) shows a bathochromic shift when sodium hydroxide is added to its ethanol solution (λ_{max}^{EtOH} 270 mμ, ϵ 14,000). The enolic nature of the product, suggested by its ready solubility in warm, aqueous potassium bicarbonate, is verified by its nmr spectrum in which both the keto and enol forms can be distinguished.

At 25° in chloroform-*d*, the proportion of the enol is about 70% as determined by the $H_{\beta E}$ and $H_{\beta K}$ resonances at δ 4.58 and 4.71 ppm, respectively. This assignment was verified by the synthesis of the deuterium analog **8b** by treatment of **1a** with deuterium oxide followed by exchange with water. The nmr spectrum of **8b** was essentially superimposable on that of **8a**, except that the resonances assigned to $H_{\beta K}$ and $H_{\beta E}$ were absent.

The lower melting hydrate has been assigned structure **7**, which arises from the addition of water to one of the oxanorbornadiene double bonds of **1a**. The presence of the intact cyclopropene ring is indicated by the infrared absorption at 1882 cm^{-1}. The nmr spectrum in acetone-d_6 exhibits eight well-resolved methoxyl resonances as well as a nonexchangeable single proton absorption assigned to tertiary C–H and an exchangeable hydroxyl resonance. The ultraviolet spectrum is similar to those of the parent tetramers **1a** and **1b**; however, the intensity of the absorption (at λ^{CH_3CN} 200 mμ, ϵ 10,900) suggests only two maleic or acrylic ester residues.[8b]

On treatment with hydrogen bromide, **7** is converted in good yield into the hydroquinone **6**. Pyrolysis of **7** at *ca.* 140° (0.3 μ) produces in good yield two fission products, dimethyl oxalacetate (**9**) and a crystalline solid dimer of the furan **10a** (the furan **2** was not detected). The formation of **9** indicates that the less hindered double bond of the oxanorbornadiene ring of **1a** is involved in the hydration reaction; however, the direction of the addition cannot be deduced from these results. Evidence for the intermediacy of the cyclopropenyl furan **10a** is described below. This furan is the intermediate which Le Goff and La Count[3] propose in the thermal tetramerization of dimethyl acetylenedicarboxylate.

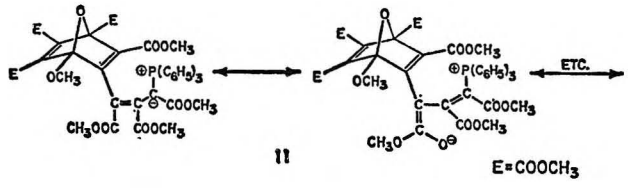
We tentatively assign structure **10b** to the dimer. The infrared spectrum indicates the presence of a cyclopropene moiety. Twelve methoxyl resonances appear in the nmr spectrum. One of these, far upfield, is assigned to the bridgehead methoxyl, and the other eleven

(10) This compound has been reported to be present among the products of the liquid phase pyrolysis[2,10c,b] and copper-catalyzed[10a] decomposition of dimethyl acetylenedicarboxylate. It seems probable that the tetramer **1a** is the actual intermediate which leads to this furan. (a) C. F. Huebner, E. Donoghue, L. Dorfman, F. A. Stuber, N. Danieli, and E. Wenkert, *Tetrahedron Lett.*, 1185 (1966). (b) T. Fukunaga, private communication. (c) E. Winterfeldt and G. Gieseler, *Angew. Chem.*, **78**, 588 (1966).

(11) I. V. Smirnov-Zamkov and G. A. Piskovitina, *Ukr. Khim. Zh.*, **30**, 1076 (1964); *Chem. Abstr.*, **62**, 5160e (1965). *Cf.* H. C. Brown and J. D. Brady, *J. Amer. Chem. Soc.*, **74**, 3570 (1952).

are grouped in the region in which ester, vinyl, or aryl methoxyls are normally observed.

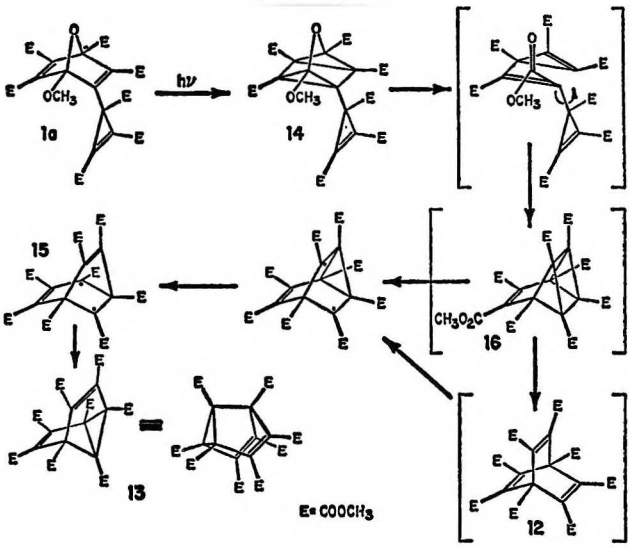
Reaction with Triphenylphosphine.—The aromatization of cyano-substituted oxanorbornadienes with triphenylphosphine has been reported by Weis.[12] In an attempt to employ this reaction to degrade the tetramers, ether or benzene solutions of **1a** and triphenylphosphine were mixed at room temperature, and a deep red color was immediately produced. When the solution was allowed to stand or was diluted with pentane, a red, crystalline 1:1 adduct, mp 213–214°, was obtained in high yield. The absence of the 1880–1900-cm^{-1} infrared absorption indicates that the cyclopropene ring has reacted, but the oxanorbornadiene ring appears to be intact, since the furan **2** is obtained on heating the red adduct above its melting point. Attack by triphenylphosphine to form the ylide **11** is suggested.



Delocalization of the charge over the long conjugated system could account for the deep color.[13]

Photochemistry.—Irradiation of **1a** in ether or tetrahydrofuran gives a photoisomer which melts at 163° and whose nmr spectrum in chloroform-*d* exhibits two methoxyl resonances in a ratio of 3:1. The larger peak is noticeably unsymmetrical and splits into two peaks in a ratio of 1:2 in acetone-d_6. The resulting three-peak 1:2:1 spectrum is clearly not consistent with the barrelene **12** tentatively suggested by other workers.[3] In addition, the ultraviolet spectrum of the photoisomer suggests the presence of only two bis(methoxycarbonyl)-ethylene residues.[8b] On these grounds we suggest the semibullvalene structure **13** for the photoisomer. The ultraviolet absorption maximum (225 mμ, ε 12,400) is at slightly longer wavelength than that of most maleic ester derivatives (195–212 mμ),[8b] indicating that the two chromophores may interact weakly with each other or with the cyclopropane ring.[14] Semibullvalenes have been reported to arise from the photolysis of barrelene and its derivatives.[15] By a minor modification of the reasonable mechanism suggested by Le Goff and LaCount[3] we can account for the formation of **13** (Scheme II). Irradiation of **1a** is expected to give the oxaquadricyclane **14**, a reaction which has been demonstrated recently for oxanorbornadienedicarboxylic

SCHEME II



ester derivatives.[16] Cleavage of **14**, perhaps photochemically, can ultimately lead to the diradical **15** by either of the pathways indicated. Zimmerman and coworkers[14b] have recently provided evidence for the intermediacy of such allylic diradicals in the formation of semibullvalene from barrelene. The barrelene **12** or its valence isomer **16** may be involved in the reaction; however, we have no evidence on this point.

In semibullvalene[15] and its derivatives reported to date, it has not been possible to "freeze out" the bond fluctuation A ⇋ B by cooling. When a solution of **13**



in acetone-d_6 was cooled to −90°, no broadening of the 1:2:1 proton nmr spectrum was detected. A 1:2:2:2:1 pattern would be expected if the A ⇋ B fluctuation became slow with respect to the nmr time scale.

Formation of the Tetramers of Acetylenedicarboxylic Ester.—Both the ethyl and methyl esters of acetylenedicarboxylic acid slowly undergo the tetramerization reaction at 25°. The rate of conversion is *ca.* 3% per year even when light is excluded. After several years, the solution of the methyl ester is supersaturated. Crystallization of **1a** can be induced by seeding, and two interconvertible crystalline modifications, mp *ca.* 105 and 115°, respectively, can be isolated. We did not succeed in crystallizing the ethyl analog **1b**, although it can be purified by column chromatography.

The reaction rate is greatly increased at elevated temperatures; however, **1** decomposes above its melting point. We find that, for a laboratory preparation of **1a**, a good compromise between rate and yield is reached at 85°. Under these conditions **1a** may be isolated in 20–25% conversion after 10–11 days merely by seeding the reaction mixture; the yield based on the dimethyl acetylenedicarboxylate is *ca.* 50%.

(12) C. D. Weis, *J. Org. Chem.*, **27**, 3520 (1962).

(13) A. N. Hughes and M. Woods [*Tetrahedron*, **23**, 2973 (1967)] report that 2-methoxy-3,4,5-tris(methoxycarbonyl)furan (**2**) reacts with triphenylphosphine in ether at room temperature to give a red 2:1 adduct ($C_{40}H_{39}O_{16}P$), mp 215–217°. We observe no reaction under their conditions between carefully purified furan (**2**) and triphenylphosphine. We do find that much **1a** is produced by both procedures which they describe for the preparation of **2**. Since their red adduct has nearly the same melting point, elemental composition, and uv and nmr spectra as **11** ($C_{42}H_{39}O_{16}P$), it seems probable that their product is identical with **11** and arises from contamination of their furan sample with **1a**.

(14) (a) Y. Yukawa, "Handbook of Organic Structural Analysis," W. A. Benjamin, Inc., New York, N. Y., 1965, p 44. (b) G. Schröder [*Chem. Ber.*, **97**, 3131 (1964)] reports that homotropilidenes with a similar arrangement of parallel double bonds absorb at *ca.* 232 mμ (ε 3000–6000).

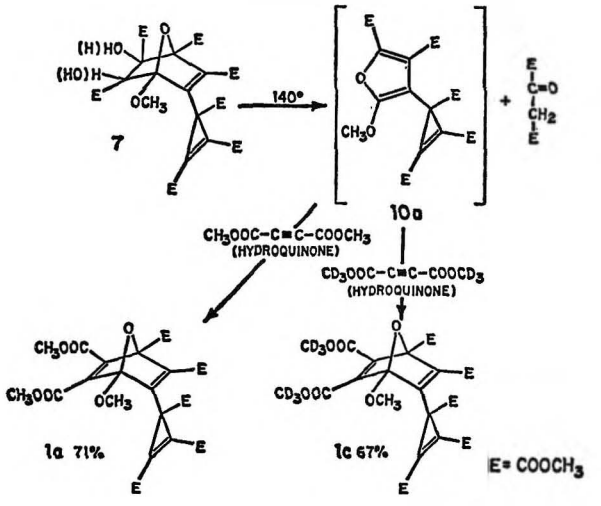
(15) (a) H. E. Zimmerman and G. L. Grunewald, *J. Amer. Chem. Soc.*, **88**, 183 (1966); (b) H. E. Zimmerman, R. W. Binkley, R. S. Givens, and M. A. Sherwin, *ibid.*, **89**, 3932 (1967); (c) R. S. H. Liu, *ibid.*, **90**, 215 (1968).

(16) (a) H. Prinzbach, M. Arguelles, and E. Druckrey, *Angew. Chem.*, **78**, 1057 (1966); (b) E. Payo, L. Cortes, J. Montacon, C. Rivas, and G. de Pinto, *Tetrahedron Lett.*, 2415 (1967).

We did not find any catalysts which would significantly increase the rate of formation of **1**, although several typical free-radical inhibitors (*e.g.*, hydroquinone, phenothiazine) in trace quantities markedly slowed the reaction. When the tetramerization is attempted in the presence of 0.15 mol of hydroquinone (100° for 3 days), little or no tetramer is formed and a 1:1 adduct with hydroquinone (**17**) is isolated. A radical-chain mechanism might explain these results.

The mechanism proposed by Le Goff and LaCount[3] involves initial 1,3-dipolar addition of dimethyl acetylenedicarboxylate with itself to produce a carbenoid intermediate which in turn reacts with a third mole of acetylenedicarboxylic ester to give the cyclopropenylfuran **10a**. The latter undergoes a conventional Diels–Alder reaction to form **1a**. That the cyclopropenylfuran **10a** is unusually reactive was suggested by studies of the pyrolysis of **7** at 140°. Under these conditions, the presumed intermediate furan **10a** was converted completely into the dimer **10b**. Therefore, two experiments to trap the furan **10a** were carried out. (1) A mixture of **7** with excess dimethyl acetylenedicarboxylate and hydroquinone was heated to 140° for 1 hr. The tetramer **1a** was formed, presumably from the reaction of **10a** with the acetylene, and no **10b** was isolated. In a control experiment, dimethyl acetylenedicarboxylate and hydroquinone gave little or no **1a** under similar conditions. (2) The pyrolysis of **7** was carried out in the presence of excess hexadeuteriodimethyl acetylenedicarboxylate, and the hexadeuterated tetramer analog **1c** was isolated in 67% yield. These experiments verify that the very reactive furan **10a** is formed from **7** at 140° and that it reacts readily with dimethyl acetylenedicarboxylate under these conditions to form the tetramer **1a** (Scheme III). The feasibility of the last step of the Le Goff–LaCount mechanism is thus established.

SCHEME III



Experimental Section[17]

All melting points are corrected. Nmr spectra were obtained with a Varian A-60 spectrometer. Saturated chloroform-*d* or acetone-d_6 solutions with tetramethylsilane as an internal standard were used as noted. Peak center positions are reported as δ_H (parts per million) downfield from tetramethylsilane; number of protons (by integration) is given in brackets. Infrared spectra were determined in potassium bromide wafers with a Perkin-Elmer 21 spectrophotometer unless otherwise noted. Prominent peaks are noted: s = strong, m = medium, w = weak, b = broad, v = very.

Tetramer of Dimethyl Acetylenedicarboxylate. Tetramethyl 4-Methoxy-5[1,2,3-tris(methoxycarbonyl)-2-cyclopropen-1-yl]-7-oxabicyclo[2.2.1]hepta-2,5-diene-1,2,3,6-tetracarboxylate (1a).—Freshly distilled dimethyl acetylenedicarboxylate (209 g) was heated for 10 days in an oil bath maintained at 85°. The viscous, amber, oily product was poured into a covered crystallizing dish, seeded, and allowed to crystallize for 4 days. It was suction filtered in a sintered-glass funnel. The crystals (36 g) were twice triturated with *ca.* 100 ml of ether and then with a small smount of methanol and were sucked dry. The filtrate and the ether washes were combined and seeded with **1a**. Hexane (*ca.* 60 ml) was added dropwise over a period of several hours to obtain a second crop of 12.5 g. The white, crystalline product was essentially pure **1a**. The filtrate was vacuum distilled, and 111 g of dimethyl acetylenedicarboxylate was recovered. The yield of tetramer **1a** was 49%.

A portion of the product was recrystallized from methanol to give fine white needles: mp 103.5–105°; λ^{CH_3CN} (no maximum >200 mμ) 205 mμ (ε 18,000), 225 shoulder (15,800), 235 (11,400), 250 (5660); ν_{max}^{KBr} 3030 (w), 2980 (m), 2860 (w), 1880 (m), 1740–1720 (s), 1630 (m), 1440 (s), 1320 (s), 1260 (b,s), 1213 (s), 1140 (s), 1062 (s), 1014–1008 (m), 983 (w), 966 (w), 945 (w), 920 (w), 904 (m), 855 (w), 824 (w), 826 (m), 813 (w), 784 (m), 758 (m), 734 (w), 723 cm^{-1} (m); the Raman spectrum in chloroform (4558 Å excitation) exhibited strong peaks at 2955, 1890, 1730, 1650, and 1450 cm^{-1}; nmr (acetone-d_6) δ 3.590 [3], 3.647 [3], 3.715 [3], 3.763 [3], 3.827 [3], 3.853 [3], 3.862 [3], 3.935 [3]. The solubility of this product in the following solvents was measured at 28° (solvent, solubility in grams of solute per 100 ml of solvent): dichloromethane, 133; acetonitrile, 125; chloroform, 91; dioxane, 56; benzene, 22; tetrahydrofuran, 20; methanol, 2.1; diethyl ether, 0.2.

A second crystalline modification, mp 113–115°, was obtained by evaporation of a chloroform solution of **1a**. This modification could be obtained as large, well-formed prisms from 1:1 acetonitrile–xylene. The infrared spectra of both crystalline modifications were identical in solution.

Tetramer of Diethyl Acetylenedicarboxylate. Tetraethyl 4-Ethoxy-5-[1,2,3-tris(ethoxycarbonyl)-2-cyclopropen-1-yl]-7-oxabicyclo[2.2.1]hepta-2,5-diene-1,2,3,6-tetracarboxylate (1b).—A 30-g sample of freshly distilled diethyl acetylenedicarboxylate was heated in an oil bath to 85° for 11 days, The unreacted ester was carefully distilled under reduced pressure, bp 46° (0.18 mm), using a bath temperature of 80°. The viscous, amber, oily residue weighed 9.50 g. (A 48-g sample of diethyl acetylenedicarboxylate was allowed to stand at 25° for 3.5 years. When similarly distilled, it yielded 8.8 g of oily residue of somewhat better purity than that obtained by the thermal process.)

The above oil (1 g) was chromatographed on a silicic acid column using methylene chloride as eluent. The center fractions exhibited uniform infrared spectra. The viscous, oily product was vacuum dried for 7 days: λ^{CH_3CN} 220 mμ shoulder (ε 17,000) (no maximum >200 mμ); ν_{max} (oil) 2980 (s), 1875 (m), 1730 (vs), 1655 (w), 1630 (m), 1470 (m), 1448 (m), 1395 (m), 1372 (s), 1312 (b,s), 1258 (b, vs), 1175 (m), 1140 (b,s), 1095 (mw), 1060 (m), 1025 (b,s), 917 (b,w), 853 (b, m), 842 cm^{-1} (b,w).

Anal. Calcd for $C_{32}H_{40}O_{16}$: C, 56.46; H, 5.92. Found: C, 56.19; H, 5.98.

Pyrolysis of Tetramer 1a. 2-Methoxy-3,4,5-tris(methoxycarbonyl)furan (2).—**1a** (30 g) was heated to 100° (0.1 mm) in a sublimation apparatus connected to a vacuum pump through a liquid nitrogen-cooled trap. After 5 hr, 1.75 g of dimethyl acetylenedicarboxylate was obtained from the trap, and 2.04 g of crude, white, crystalline sublimate **2** was isolated. The pot residue weighed 25.0 g.

The crude **2** was sublimed at 105° (0.03 mm) and the sublimate was recrystallized from benzene–hexane to yield colorless crystals: mp 118.0–119.2° (lit. mp 117–118,[10a] 121°[10c]); λ_{max}^{EtOH} 275 mμ (ε 14,500), 245 shoulder (8910) [lit.[10c] 273 (15,400), 248 sh (10,900)]; nmr (chloroform-*d*) δ 3.82 [3], 3.92 [3], 3.97 [3], 4.26 [3] (lit.[10c] δ 3.83 [3], 3.88 [3], 3.98 [3], 4.28 [3], calculated from reported τ values); ν_{max} 3010 (w), 2950 (m), 1760–1717 (s), 1606 (s), 1584 (s), 1490 (ms), 1464 (m), 1432 (ms), 1412 (ms), 1360 (m), 1327 (s), 1253–1243 (s), 1187 (ms), 1147 (s), 1105

(17) We wish to thank Miss E. Wallace for determining the Raman and ultraviolet spectra of the compounds reported and Miss N. Schlichter for the infrared spectra. We wish to thank Dr. G. S. Reddy for the 100-Mc nmr studies of the photolysis product **13**. Deuterium analyses were done by J. Nemeth, Urbana, Ill.

(s), 1061 (s), 997 (m), 950 (m), 815 (s), 786 (s), 768 (w), 727 (m), 666 (w) (lit.[10c] 1750, 1620, 1590, 1160, 1110, 1070 cm^{-1}). Compound **2** was also obtained by the pyrolysis of compounds **8** and **11** at 180°.

Reaction of 1a with Hydrogen Bromide. Trimethyl 3-Hydroxy-6-methoxy-5[2-bromo-1,2,3-tris(methoxycarbonyl)cyclopropyl]trimellitate (3a).—A solution of 30 g of **1a** in 300 ml of benzene was cooled to 10°, and dry hydrogen bromide was bubbled through for 10 min. The solution was allowed to stand for 30 min at room temperature, and dry nitrogen was then bubbled through the solution for 30 min to remove excess hydrogen bromide. (Methyl bromide was identified in the volatile fraction by mass spectrometry.) Solvent was removed under reduced pressure and 30 ml of methanol was added to the residual oil. After 3 days, the yellow crystalline precipitate (9.9 g) was filtered off and washed with methanol. An additional 5.5 g was obtained from the filtrates; the total yield of **3a** was 49%. A portion of the product was twice recrystallized from methanol[18] to give very light yellow crystals: mp 147–148.4°; λ_{max}^{EtOH} 336 mμ (ε 7330) 255 sh (6100); $\lambda_{max}^{CH_3CN}$ 330 mμ (ε 7560) 252 sh (6550), 209 (28,900); ν_{max} 3500 (vw), 3000 (w), 2950 (m), 2840 (w), 1745 (vs), 1680 (m), 1605 cm^{-1} (m); nmr (benzene), δ 3.39 [3], 3.49 [3], 3.52 [3], 3.55 [4], 3.62 [3], 3.77 [3], 3.99 [3], 11.47 [1].

Anal. Calcd for $C_{22}H_{23}O_{14}Br$: C, 44.68; H, 3.89; Br, 13.52. Found: C, 44.73; H, 3.85; H, 13.44.

This analysis was checked by high-resolution mass spectroscopy using an Associated Electronic Industries MS-9 spectrometer (for peak at 590 mass units, 590.0279[19] (calcd 590.0272).

Reaction of 1a with Hydrogen Chloride. Trimethyl 3-Hydroxy-6-methoxy-5[2-chloro-1,2,3-tris(methoxycarbonyl)cyclopropyl]trimellitate (3b).—A solution of 20 g of **1a** in 150 ml of benzene was saturated with hydrogen chloride and held at room temperature for 5 days. Solvent and excess hydrogen chloride were removed under reduced pressure. The residue in methylene chloride was washed with water and dried ($MgSO_4$). Solvent was removed under reduced pressure and the residue was crystallized from methanol.[18] The crude, white, crystalline product (6.55 g) was recrystallized from methanol to yield colorless crystals: mp 172.6–173.4°; λ_{max}^{EtOH} 335 (ε 6890), 255 sh (5960); nmr (acetone-d_6) 3.22 [1], 3.73 [3], 3.83 [3], 3.85 [6], 3.91 [6], 3.97 [6].

Anal. Calcd for $C_{22}H_{23}O_{14}Cl$: C, 48.31; H, 4.24; Cl, 6.84. Found: C, 48.57; H, 4.20; Cl, 6.90.

Reaction of 1 with Methanol. Tetramethyl 3-Hydroxy-6,6-dimethoxy-5-[1,2,3-tris(methoxycarbonyl)-2-cyclopropen-1-yl]-cyclohexa-1,4-diene-1,2,3,4-tetracarboxylate (5).—A solution of 50 g of **1a** in 100 ml of dichloromethane was diluted with 1100 ml of methanol. A small amount (*ca.* 200 ml) of hydrogen chloride gas was bubbled through the solution. The solution was allowed to stand at room temperature for 5 days. Solvent was removed on a rotary evaporator using a water pump vacuum. The residue in dichloromethane was washed twice with water, dried ($MgSO_4$), concentrated, and crystallized from methanol[18] to yield 22.0 g (42%) of colorless crystals in four crops. A portion was recrystallized from methanol for analysis: mp 165.2–167.4°; λ_{max}^{EtOH} 203 mμ (ε 20,700); ν_{max} 3450 (m), 3030 (w), 2970 (m), 2860 (w), 1885, (m), 1755 (vs), 1685 (w), 1645 cm^{-1} (w); nmr (acetone-d_6) 3.10 [3], 3.18 [3], 3.65 [3], 3.67 [3], 3.71 [3], 3.73 [3], 3.79 [3], 3.82 [3], 3.86 [3], 5.13 [1] (exchanges with CF_3COOH).

Anal. Calcd for $C_{25}H_{28}O_{17}$: C, 50.00; H, 4.70. Found: C, 49.92; H, 4.98.

Hydrolysis of 1a. Separation of 7 and 8a.—A stirred solution of 106 g of **1a** in 2.5 l. of dioxane was slowly diluted with 2.5 l. of water. The course of the hydrolysis was followed by thin layer chromatography on silica gel "G" plates (E. Merck A.G., Darmstadt, Germany; plates made by Analtech, Inc., Wilmington, Del.). Using 1:1 acetone–hexane, R_f values of **1a**, **7**, and **8a** were *ca.* 0.6, 0.5, and 0.1, respectively. After 10 days, little or no **1a** could be detected. The solvent was evaporated at room temperature. The residue was dissolved in dichloromethane, dried ($MgSO_4$), and concentrated to obtain a viscous, yellow oil weighing 103.5 g.

A solution of 15.2 g of this oil in 25 ml of chloroform was chromatographed on a silica gel H column (E. Merck, Darmstadt, Germany, distributed by Brinkman Instruments Co., Westbury, N. Y.) with 40% acetone in hexane solvent to yield in the first fractions 6.0 g of crude **7**. This material was dissolved in 15 ml of acetone, and hexane was added to the cloud point. Colorless crystalline **7** (3.75 g, 25%) slowly deposited (see next section for properties).

The remaining 88.3 g of yellow oil was dissolved in 110 ml of methanol. The solution gradually deposited 26.6 g (26%) of **8a** (see below for properties).

Tetramethyl 2(3)-Hydroxy-1-methoxy-6-[1,2,3-tris(methoxycarbonyl)-2-cyclopropen-1-yl]-7-oxabicyclo[2.2.1]-hept-5-ene-2,3,4,5-tetracarboxylate (7).—The crude crystalline **7** described in the preceding section was twice recrystallized from acetone–hexane to yield short prisms: mp 126–126.6°; no ultraviolet peak above 195 mμ was detected; λ^{CH_3ON} 200 mμ (ε 10,900), 230 (9860), 250 (7040); a shoulder appeared at 235 mμ (ε 9660) in ethanol solution; ν_{max} 3470 (m), 3030 (w), 2950 (m), 2850 (w), 1882 (m), 1735 (vs), 1642 cm^{-1}; nmr (acetone-d_6) δ 3.56 [3], 3.62 [1], 3.64 [3], 3.67 [3], 3.71 [3], 3.75 [3], 3.79 [3], 3.94 [3], 3.98 [3], 5.07 [1] (exchanges with D_2O). The tertiary hydrogen resonance at δ 3.62 is shifted downfield of all the methoxyl peaks in benzene solvent.

Anal. Calcd for $C_{24}H_{28}O_{17}$: C, 49.15; H, 4.47. Found: C, 49.19; H, 4.46.

Tetramethyl 2-[3-Oxo-1,2,3-tris(methoxycarbonyl)propyl]-1-methoxy-7-oxabicyclo[2.2.1]hepta-2,5-diene-3,4,5,6-tetracarboxylate (8a).—The crude crystalline **8a** obtained from the hydrolysis of **1a** (see above) was twice recrystallized from methanol[18] to yield short, triangular prisms: mp 146.5–147.7°; $\lambda_{max}^{CH_3CN}$ 258 mμ (ε 12,000), 215 shoulder (13,880); λ_{max}^{EtOH} 260 (ε 12,080); λ_{max}^{EtOH} (0.1 *N* NaOH) 270 (14,000); ν_{max} (Nujol) 3530 (w), 1755–1730 (vs), 1685 (s), 1620 cm^{-1} (m); nmr (acetone-d_6 at 25°), partially resolved methoxyl peaks at δ 3.47, 3.50, 3.65, 3.69, 3.71, 3.75, 3.77, 3.88, *t*-H_α 2.67 (keto), *t*-H_β 4.59 (enol) and 4.70 (keto), enolic hydroxyl 12.52. The relative peak intensities and positions varied considerably with solvent, temperature, and concentration.

Anal. Calcd for $C_{24}H_{28}O_{17}$: C, 49.15; H, 4.47. Found: C, 49.15; H, 4.69.

Tetramethyl 2-[1-Deuterio-3-oxo-1,2,3-tris(methoxycarbonyl)-propyl]-1-methoxy-7-oxabicyclo[2.2.1]hepta-2,5-diene-3,4,5,6-tetracarboxylate (8b).—A solution of 5 g of **1a** in 100 ml of dioxane was treated with 100 ml of deuterium oxide. The reaction was considerably slower than with water. After 30 days, little or no **1a** could be detected by thin layer chromatography (see above). Solvent was removed under reduced pressure, and the oily residue was twice crystallized from acetone–hexane and once from methanol, giving white crystalline **8b**, mp 143–144.4°. The nmr spectrum was the same as that of **8a** except that the two peaks assigned to the *t*-β-hydrogens at δ 4.59 and 4.70 ppm were absent.

Anal. Calcd for $C_{24}H_{26}DO_{17}$: C, 49.07, H + D = 4.63; excess atom % D, 3.85. Found: C, 49.27; H + D = 4.63; excess atom % D, 3.82.

Reaction of 5 with Hydrogen Bromide. Trimethyl 5-[2-Bromo-1,2,3-tris(methoxycarbonyl)cyclopropyl]-3,6-dihydroxytrimellitate (6).—A solution of 24.1 g of **5** in 500 ml of benzene was treated with excess hydrogen bromide at room temperature. The solution was allowed to stand overnight at room temperature, and part of the solvent and excess hydrogen bromide were removed on a rotary evaporator under reduced pressure. The resulting solution was diluted with dichloromethane, dried ($MgSO_4$), and concentrated. The residual viscous, yellow oil was crystallized from *ca.* 75 ml of methanol giving light yellow **6** (10.7 g 46%): mp 196.2–197.5 (from the filtrate, 4.0 g of **3a** was isolated); λ_{max} 375 mμ (ε 6520), 266 (6640), 225 sh (15,100); nmr (acetone-d_6) δ 3.00 [1], 3.67 [3], 3.80 [3], 3.85 [3], 3.90 [3], 3.95 [3], 4.01 [3]; ν_{max} 3420 (m), 3020 (w), 2920 (m), 1750 (vs), 1685 (s), 1575 (w), 1500 cm^{-1} (w).

Anal. Calcd for $C_{21}H_{21}O_{14}Br$: C, 43.69; H, 3.67; Br, 13.84. Found: C, 43.83; H, 3.71; Br, 13.94.

This compound was also obtained in nearly quantitative yield by treatment of **7** in benzene with hydrogen bromide.

Dimethyl Ether of 6. Methyl Ether of 3a. Trimethyl 5-[2-Bromo-1,2,3-tris(methoxycarbonyl)cyclopropyl]-3,6-dimethoxytrimellitate (4).—A solution of 15 g (0.025 mol) of **3a** in 30 ml

(18) The following method of recrystallization from methanol was found to be superior to the conventional one. No heating is required. The compound to be recrystallized was dissolved in chloroform or dichloromethane. Solvent was then removed under reduced pressure on a rotary evaporator, avoiding the introduction of seed crystals. The resulting oily residue was dissolved in a small amount of warm methanol, decolorizing charcoal was added, and the solution was filtered rapidly through a pressure funnel into a clean flask. The filtrate was seeded if necessary to induce crystallization.

(19) We wish to thank Professor R. J. Crawford at the University of Alberta for this spectral measurement.

of dichloromethane was treated with 0.028 mol of diazomethane in ethanol–ether at 0°. Excess diazomethane was destroyed with acetic acid, and the solution was concentrated and crystallized from 50 ml of methanol to give 12.7 g (two crops) of 4, mp 127–128.4°,[18] λ_{max}^{EtOH} 302 mμ (ε 4510).

Anal. Calcd for $C_{22}H_{25}O_{14}Br$: C, 45.63; H, 4.16. Found: C, 45.93; H, 4.12.

This compound was also obtained in high yield by treatment of 6 with 2 equiv of diazomethane.

Adduct of 1a with Triphenylphosphine (11).—A solution of 1.14 g of **1a** in 300 ml of ether was treated with a solution of 0.53 g of triphenylphosphine in 20 ml of ether. The deep red solution was filtered. It slowly deposited 1.62 g (97%) of **11**. Larger quantities of **11** were prepared by mixing a solution of 20 g of **1a** in 100 ml of benzene with 18 g (excess) of triphenylphosphine in 50 ml of benzene. The red solution was added dropwise while stirring to 1.6 l. of pentane. The bright orange-red crystals (29 g, 99%) were washed with pentane.

A portion recrystallized from dichloromethane–carbon tetrachloride formed deep-red crystals: mp 213–214°; λ_{max}^{EtOH} 468 mμ (ε 10,300); ν_{max} 3080 (w), 3020 (w), 2970 (m), 2960 (w), 1730 (vs), 1635 (ms), 1490 (m), 1440 (vs), 1320 (b,s), 1260 (b, vs), 1200 (s), 1140 (s), 1107 (s), 1075 (m), 1035 (b, m), 975 (w), 915 (w), 860 (w), 815 (w), 780 (b,m), 760 (m), 715 (m), 693 cm^{-1} (m).

Anal. Calcd for $C_{42}H_{39}O_{16}P$: C, 60.72; H, 4.74; P, 3.73. Found: C, 60.35; H, 5.02; P, 3.67.

Photoisomer of 1a. Octamethyl Semibullvalenoctacarboxylate (13).—A solution of 2.5 g of **1a** in 700 ml of ether was photolyzed for 8 hr in a water-cooled, quartz flask using a Rayonet photochemical reactor with 16 G-8-T5 germicidal lamps.

Solvent was removed under reduced pressure, and the residue was crystallized from methanol to give **13** (white crystals): mp 162–163.2°; λ_{max} 225 mμ (ε 12,400); λ_{min} 205 mμ (ε 11,000) (lit.[3] λ_{max} 222 mμ, ε 12,300); ν_{max} 3020 (w), 2960 (mw), 2860 (w), 1755–1742 (vs), 1626 (m), 1460 (s), 1335 (s), 1280 (b, vs), 1210 (s), 1175 (s), 1093 (m), 1058 (m), 1025 (m), 990 (b,m), 918 (w), 890 (w), 853 (mw), 846 (m), 813 (m), 774 (w), 744 (m), 667 cm^{-1} (w); nmr (acetone-d_6) δ 3.78 [6], 3.76 [12], 3.72 [6] (integration checked at 100 Mc; no change in the spectrum occurred on cooling to −90°); nmr (chloroform-*d*) τ 6.21 [18], 6.26 [6] (a shoulder appears on the low-field side of the τ 6.21 peak) (lit.[3] τ 6.21 [18], 6.26 [6]).

Anal. Calcd for $C_{24}H_{24}O_{16}$: C, 50.71; H, 4.26. Found: C, 50.91; H, 4.33.

Reaction of Dimethyl Acetylenedicarboxylate with Hydroquinone. Dimethyl 2-(4-Hydroxyphenyloxy)but-2-ene-1,4-dioate (17).—A mixture of 100 g of dimethyl acetylenedicarboxylate and 100 g of hydroquinone was stirred in an oil bath at 100° under nitrogen for 3 days. The product was dissolved in ether and extracted with excess 10% aqueous sodium carbonate solution. The ether layer was washed with citric acid solution and dried ($MgSO_4$). On distillation under reduced pressure (oil-bath temperature = 100°) 67 g of dimethyl acetylenedicarboxylate was recovered. The residue crystallized slowly giving 5.0 g of crude **17**. Recrystallization from benzene gave 4.25 g of yellow crystals: mp 105–106.2°; λ_{max} 226 mμ (ε 16,900), 284 (3100), 320 sh (ε 1690); nmr (chloroform-*d*) δ 8.08 [1], 6.81 [4], 6.43 [1], 3.71 [3], 3.68 ppm [3].

Anal. Calcd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.29; H, 4.85.

Pyrolysis of 7. Isolation of Dimethyl Oxalacetate and the Dimer of Dimethyl 3-[1,2,3-Tris(methoxycarbonyl)-2-cyclopropen-1-yl]-2-methoxyfuran-4,5-dicarboxylate (10b).—A 15 mm × 200 mm tube jacketed at its upper end with a watercooled condenser was charged with 2.00 g of **7** and about ten 6-mm glass beads. It was evacuated to 0.3-μ pressure and heated at its lower end to 140°. The solid white **7** melted and vigorously evolved a vapor which condensed as large colorless crystals in the cooled portion of the tube. Heating was continued for 5 hr. The tube was cooled and inverted, and the crystalline sublimate was washed out with acetone. Solvent was removed under reduced pressure, and the white solid residue was recrystallized from hexane to obtain 0.34 g (62%) of dimethyl oxalacetate, mp 72–74°, whose infrared spectrum was identical with that of a sample of the authentic material, mp 71.5–73°, prepared by the method of Fenton and Jones.[20]

(20) H. J. H. Fenton and H. O. Jones, *J. Chem. Soc.*, **77**, 77 (1900).

The nonvolatile residue in the tube (1.64 g) was crystallized from methanol to yield 0.83 g (57%) of light-yellow crystals of **10b**: mp *ca.* 190° dec; λ_{max} 300 mμ (ε 10,400); nmr (chloroform-*d*) 3.29 [3], 3.59 [3], 3.60 [3], 3.67 [3], 3.71 [3], 3.75 [6], 3.78 [3], 3.87 [3], 3.90 [3], 3.96 [3], 3.99 [3]; ν_{max} 3660 (w), 3430 (w), 3030 (m), 2960 (m), 1883 (m), 1745 (vs), 1635 (m), 1580 cm^{-1} (ms).

Anal. Calcd for $C_{36}H_{36}O_{24}$: C, 50.71; H, 4.26; mol wt, 853. Found: C, 50.31; H, 4.44; mol wt, 829 (vapor pressure osmometry, 37% in CH_2Cl_2).

Trapping of 10a by Pyrolysis of 7 in the Presence of Dimethyl Acetylenedicarboxylate. Synthesis of 1a.—A mixture of 0.20 g of **7**, 0.5 g of dimethyl acetylenedicarboxylate, and 6.7 mg of hydroquinone in a sealed tube was heated to 140° for 1 hr. The oily product was cooled and seeded with **1a**. After 3 days, the crystalline mass was slurried with 3 ml of ether, cooled to 5°, allowed to stand overnight, and filtered. The crystals after washing with ether weighed 0.138 g (71%). The infrared spectrum was identical with that of **1a** as described above. After recrystallization from ether–pentane, the white crystals melted at 103.6–104.7°.

In the control experiment, 0.7 g of dimethyl acetylenedicarboxylate and 8.1 mg of hydroquinone were heated to 140° for 1 hr. On seeding with **1a**, no crystals deposited. The infrared spectrum of the oily product (1880 cm^{-1}) indicated that little or no **1a** was present.

Trapping of 10a by Pyrolysis of 7 in the Presence of Dimethyl Acetylenedicarboxylate-d_6. Synthesis of 1c.—A mixture of 0.30 g of **7**, 0.47 g of dimethyl acetylenedicarboxylate-d_6, and 10 mg of hydroquinone was sealed in a glass tube under nitrogen, heated to 140° for 1 hr, cooled, and seeded with a small crystal of **1a**. Work-up as in the preceding section gave 0.196 g of **1c** in two crops and 0.25 g of unreacted dimethyl acetylenedicarboxylate-d_6. After recrystallization from ether–pentane the white needles of **1c** melted at 106.5–107.2°: ν_{max} 2960 (w), 2255 (w), 2180 (mw), 2120 (w), 2080 (mw), 1880 (m), 1725 (vs), 1625 cm^{-1} (m); nmr (acetone-d_6) δ 3.584 [3], 3.642 [3], 3.707 [3], 3.839 [3], 3.848 [3], 3.920 [3].

Anal. Calcd for $C_{24}H_{18}D_6O_{16}$: C, 50.18; H + D, 5.26; excess atom % D, 25.0. Found: C, 50.44; H + D, 5.44; excess atom % D, 24.95.

Dimethyl Acetylenedicarboxylate-d_6.—Methanol-d_4 (5 g) (Merck Sharp and Dohme of Canada, Ltd.) was placed in an ice-cooled 50-ml flask, and 2.2 ml of sulfuric acid was added cautiously. To the cold solution, 2.0 g of the potassium acid salt of acetylenedicarboxylic acid was added. The flask was stoppered, and the mixture was stirred for 12 days at room temperature. The mixture was filtered, and the more volatile portion of the filtrate was distilled in a vacuum line at room temperature in order to recover unreacted deuteriomethanol (1.9 g). The residue was stirred with ice and dichloromethane. The solid material from the filtration was stirred with ice water and dichloromethane. The dichloromethane extracts were combined and washed with water, dilute aqueous potassium bicarbonate, and water, then dried ($CaCl_2$), concentrated, and distilled to yield 1.1 g of dimethyl acetylenedicarboxylate-d_6: bp 51–52° (3.2 mm); $n^{26}D$ 1.4427; mp 0.0–0.3°; ν_{max} 3440 (w), 2270 (m), 2200 (m), 2130 (w), 2080 (m), 1730 (vs), 1490 (w), 1290 (b, vs), 1088 (s), 970 (ms), 934 (w), 901 (m), 883 (m), cm^{-1} (ms).

Anal. Calcd for $C_6D_6O_4$: C, 48.64; D, 8.16. Found: C, 48.60; D, 7.99.

Registry No.—**1a**, 16199-47-6; **1b**, 16214-86-1; **1c**, 16291-02-4; **2**, 5202-32-4; **3a**, 16199-08-9; **3b**, 16199-21-6; **4**, 16199-09-0; **5**, 16199-10-3; **6**, 16199-11-4; **8a**, 16199-12-5; **8b**, 16199-13-6; **10b**, 16199-22-7; **11**, 16240-69-0; **13**, 16286-16-1; **17**, 16199-23-8; dimethyl acetylenedicarboxylate-d_6, 16199-24-9.

Acknowledgments.—We wish to acknowledge with thanks the many helpful comments of our colleagues. In addition, we wish to thank Professor J. D. Roberts who initially suggested to the authors structure **1** for the tetramer and Dr. T. Fukunaga, Dr. R. S. H. Liu, and Professor D. Applequist, Professor S. J. Cristol, and Professor D. Cram for valuable discussions.

Reduction of Alkyl- and Arylacetylenes by an Electrochemical Method[1]

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Received February 12, 1968

It was established that dialkylacetylenes were reduced to *trans* olefins when an electric current was passed through a methylamine solution of lithium chloride and the acetylene. These *trans* olefins were arising directly from the reduction, since the corresponding *cis* olefins were not isomerized under the reaction conditions. Conjugated aromatic acetylenes could not be reduced selectively to aromatic olefins. Alkylbenzenes were the major product in such cases. A nonconjugated, terminal, aromatic acetylene was reduced principally to the aromatic olefin. Nonconjugated, internal aromatic acetylenes were reduced quite cleanly to the *trans* aromatic olefin. When 3-octyne was reduced in a divided electrochemical cell, extensive isomerization occurred, with the isomeric *trans* olefins predominating in the product. Potential pathways for the formation of these olefins were investigated.

The blue solution formed by dissolving sodium[2,3] in liquid ammonia or lithium[4] in certain low-molecular-weight amines has proved to be an excellent reagent for reducing dialkylacetylenes to *trans* olefins.

Dialkylacetylenes can also be reduced electrochemically to *cis* olefins[5] at a spongy nickel cathode in an ethanol solution of sulfuric acid or potassium hydroxide.

Previously,[1] it was shown that aromatic compounds could be reduced electrochemically in either a divided or an undivided electrolytic cell in a solution of lithium chloride dissolved in methylamine. Alkylbenzenes in the undivided cell (anode and cathode compartments not separated) were reduced to dihydro products in excellent yield. In the divided cell (anode and cathode separated by asbestos) the same alkylbenzenes were reduced equally well to tetrahydro products.

In similar systems[6a] polarographic studies[6b] indicated that the aromatic compounds are being reduced by lithium metal formed *in situ* by the passage of the electric current.

The foregoing observations suggested that selective electrochemical reductions of alkyl- and arylacetylenes should be feasible in a methylamine solution of lithium chloride. A series of alkyl- and arylacetylenes was reduced in the undivided cell[1] to determine the nature and stereochemistry of the product. A representative dialkylacetylene was also reduced in the divided cell to test whether the nature of the reduction product is influenced by a change in cell design.

Dialkylacetylenes.—When samples of 2- and 3-octyne and 5-decyne were reduced in an undivided cell, by passage of the theoretical current to reduce one double bond, good yields of the *trans* olefins were obtained (see Table I). The stereochemistry of the products was established by comparing their physical properties (*e.g.*, infrared and nmr spectra and retention times on the gas chromatograph) with authentic samples.[2]

The observation that *cis* olefins are not isomerized under the conditions of the electrochemical reduction indicated that the *trans* olefins were formed directly and were not the result of an isomerization.

TABLE I

ELECTROCHEMICAL REDUCTIONS OF DIALKYLACETYLENES

Compound	Yield, %	Olefin, %	Acetylene, %	Olefin composition, % *trans*	% *cis*
2-Octyne[a]	75	69	31	92	8
3-Octyne[b]	50	96	4	98	2
5-Decyne[c]	80	82	18	97	3
3-Octyne[d,e]	58	100	0	98	2

[a] The product was analyzed on a Perkin-Elmer 226 capillary gas chromatograph using a 150-ft, 0.01-in.-diameter, UCON Polar column at 45°. [b] The product was analyzed on an Aerograph gas chromatograph using a 20-ft, 30% dibutyl tetrachlorophthalate column at 45°. [c] The product was analyzed on a F & M Model 500 gas chromatograph using a 14-ft, 25% β,β'-oxydipropionitrile column at 75°. [d] In this reduction the theoretical current to reduce two double bonds (38,600 C) was passed through the electrochemical cell. [e] The product was analyzed on an Aerograph gas chromatograph using a 25-ft, 25% β,β'-oxydipropionitrile column at 25°.

These results are in sharp contrast to those of Campbell and Young[5] in that *trans* olefins are formed in our case instead of *cis*. It seems likely that the *cis* products observed[5] were arising from a reduction on the surface of the spongy nickel cathode.[7] Our stereochemical results would indicate that our reductions are *not* occurring on the cathode surface, but rather in solution. This supports the proposal[6b] that the active reducing agent is lithium formed *in situ* and dissolved in the amine solvent. Reductions of acetylenes in the latter system have been shown[4] to form *trans* olefins.

It was also established that internal olefins are relatively resistant to reduction in the undivided cell. Thus, 3-octyne was *not* reduced to *n*-octane by the passage of sufficient current to reduce two double bonds.

The electrochemical reduction of dialkylacetylenes to *trans* olefins has an advantage over the sodium–ammonia and lithium–ethylamine reductions in that direct handling of the alkali metals can be avoided. Also, the low cost of lithium chloride relative to lithium and the fact that it can be reused[8] since it is in essence a current carrier make the electrochemical method rather attractive.

Arylacetylenes.—The electrochemical reduction of dialkylacetylenes to *trans* olefins and the electroreductions of aromatic compounds to dihydro aromatics[1] suggested that selective reductions of triple bonds in the presence of aromatic rings might be achieved electrochemically.

(1) This is paper X in a series entitled "Reduction of Organic Compounds by Lithium in Low Molecular Weight Amines." See *J. Amer. Chem. Soc.*, **86**, 5272 (1964), for the previous paper.

(2) K. N. Campbell and L. T. Eby, *ibid.*, **63**, 216, 2683 (1941).

(3) B. B. Elsner and P. F. M. Paul, *J. Chem. Soc.*, 3156 (1953).

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(5) K. N. Campbell and E. E. Young, *ibid.*, **65**, 965 (1943).

(6) (a) I. Wender, H. W. Sternberg, and R. E. Markby, *J. Electrochem. Soc.*, **110**, 425 (1963); (b) *ibid.*, **113**, 1060 (1966).

(7) C. L. Wilson, *Trans. Electrochem. Soc.*, **76**, 353 (1939).

(8) Unpublished studies by Dr. E. M. Kaiser of these laboratories.

TABLE II

ELECTROCHEMICAL REDUCTIONS OF AROMATIC ACETYLENES

Compound	Yield, %	Alkylbenzene, %	2,5-Dihydro-alkylbenzene, %	Aromatic olefin, %	2,5-Dihydro aromatic olefin, %	Recovered acetylene, %
$C_6H_5C{\equiv}CH$[a]	80	45	1	4	0	50
$C_6H_5C{\equiv}C{-}C_2H_5$[b]	80	43	2	11	0	44
$C_6H_5(CH_2)_2C{\equiv}CH$[c]	80	8	0	64[d]	13	15
$C_6H_5(CH_2)_2C{\equiv}C{-}CH_3$[e]	62	0	0	65[e]	10[f]	25

[a] The product was analyzed on an Aerograph gas chromatograph on a 20-ft, 25% Carbowax 1540 column at 135°. [b] The product was analyzed on a F & M Model 720 gas chromatograph using a 12-ft, 20% silicone oil 710 column at 180°. [c] The product was analyzed on Aerograph gas chromatograph using a 20-ft, 20% Zonyl E-7 column at 120°. [d] The nmr spectrum of 4-phenyl-1-butene (CCl_4) showed a five-proton singlet at τ 2.98, a one-proton multiplet at 4.40, a two-proton multiplet at 5.05, and a four-proton multiplet at 7.51. [e] The nmr spectrum of *trans*-5-phenyl-2-pentene (CCl_4) showed a five-proton singlet at τ 3.0, a two-proton multiplet at 4.70, a four-proton multiplet at 7.7, and a three-proton doublet at 8.4. The *cis* isomer (CCl_4) had a five-proton singlet at τ 2.96, a two-proton multiplet at 4.65, a four-proton multiplet at 7.55, and a three-proton doublet at 8.5. [f] The nmr spectrum of *trans*-5-(2,5-dihydrophenyl)-2-pentene (CCl_4) showed a two-proton multiplet at τ 4.32, a three-proton multiplet at 4.60, four-proton multiplets at 7.40 and 7.97, and a three-proton multiplet at 8.35.

When phenylacetylene and 1-phenyl-1-butyne were reduced in the undivided cell,[1] the major products were ethylbenzene and *n*-butylbenzene, respectively (see Table II), despite the passage of sufficient current to reduce only one double bond.[9] These results parallel previous work[4] wherein phenylacetylene was reduced to a mixture of ethylbenzene and styrene at a spongy nickel cathode.

Considerably greater selectivity was noted in the reduction of 4-phenyl-1-butyne. When the theoretical current to reduce one double bond was passed through an undivided cell containing this compound, the major product was 4-phenyl-1-butene. Only small amounts of *n*-butylbenzene and 4-(2,5-dihydro-phenyl)1-butene formed as shown in Table II.

The ultimate in selectivity was achieved in the reduction of 5-phenyl-2-pentyne in the undivided cell, wherein the major product was *trans*-5-phenyl-2-pentene. Small amounts of 5-(2,5-dihydrophenyl)-2-pentene (see Table II) were also formed. It would seem that the electrochemical method holds promise for the selective reduction of nonconjugated, internal aromatic acetylenes. It is also evident that an aromatic ring is more readily reduced in such systems than an internal double bond as evidenced by formation of the *trans*-5-(2,5-dihydrophenyl)-2-pentene rather than *n*-amyl benzene.

Divided Cell Reduction of 3-Octyne.—To investigate the divided cell reduction of dialkylacetylenes, 3-octyne was reduced in an electrolytic cell where the anode and cathode compartments were separated by an asbestos divider.[1] Considerable isomerization occurred in this case, but, again, *trans* products predominated as shown in Table III.

TABLE III

DIVIDED CELL REDUCTION OF 3-OCTYNE

Products	Retention time (vpc), min
trans-2-Octene (33%)	173
cis-2-Octene (4%)	255
trans-3-Octene (37%)	154
cis-3-Octene + 1-octene (0.4%)	230
trans-4-Octene (24%)	140
cis-4-Octene (0.4%)	208
n-Octane (0.5%)	73

(9) It has been shown (unpublished work from this laboratory by S. Mels) that styrene is reduced to ethylbenzene under the reaction conditions.

The most likely agent causing the isomerization was deemed to be lithium methylamide. Since methylamine is the only source of protons during the electrochemical reduction, the formation of one molecule of olefin requires the formation of two molecules of lithium methylamide. It has been shown[1] that the function of the cell divider is to prevent the immediate destruction of lithium methylamide by the methylamine hydrochloride which forms at the anode. Thus, the lithium methylamide tarries in solution to catalyze the isomerization of the organic compounds.

A possible explanation for the isomerization products observed, is that the acetylene is reduced to the *trans*-olefin first, which is then isomerized to the observed products. This possibility has not been entirely excluded, but investigations by Whiting and coworkers[10] on the isomerization of *cis*- and *trans*-octenes by lithium alkylamide–ethylenediamine solutions suggest that the isomerization of *trans*-3-octene is not the major source of the reaction products observed.

The predominance of the *trans* olefins in the divided cell product suggested that 3-octyne itself was being isomerized, *followed* by a reduction of the isomeric acetylenes to the observed products. When 3-octyne was stirred in a lithium methylamide–methylamine solution to test this possibility, all the possible isomeric octynes were produced. Such base-catalyzed isomerizations of acetylenes are well documented[11] and are thought to proceed through allene intermediates. There remained the possibility that our divided cell products (Table III) were arising from a reduction of these allene intermediates rather than from the isomeric acetylenes. To check this point 1,2- and 2,3-octadiene were reduced in the undivided cell (to minimize their isomerization). The major product from the reduction of 1,2-octadiene was *trans*-2-octene (77%), while 2,3-octadiene yielded principally *trans*-2- and *trans*-3-octene in almost equal amounts.[12]

(10) M. D. Carr, J. R. P. Clarke, and M. C. Whiting, *Proc. Chem. Soc.*, 333 (1963).

(11) T. L. Jacobs, R. Akawie, and R. G. Cooper, *J. Amer. Chem. Soc.*, **73**, 1273 (1951); J. Bainvel, B. Wojtkowiak, and R. Romanet, *Bull. Soc. Chim. Fr.*, 978 (1963); J. H. Wotiz, W. E. Billups, and D. T. Christian, *J. Org. Chem.*, **31**, 2069 (1966).

(12) These results are rather different from the preliminary report [D. Devaprabhakara and P. D. Gardner, *J. Amer. Chem. Soc.*, **86**, 648 (1963)] of the reduction of 1,2- and 2,3-nonadiene by sodium in liquid ammonia. The former compound was reported to reduce principally to *cis*-2-nonene and the latter to a 50:50 mixture of *cis*- and *trans*-2-nonene. Since the reduction method employed was quite different from ours, further work will be needed to determine whether any real discrepancies exist.

The possibility existed that the intermediate allenes could be reducing at a much faster rate than the acetylenes, and, as a consequence, the products formed in the divided cell were arising predominantly from reduction of the allenes. In an attempt to shed light upon this point, a 50:50 mixture of 2-octyne and 1,2-octadiene was reduced only partially in the undivided cell. Analysis of the recovered starting material showed it to contain 37% 1,2-octadiene and 63% 2-octyne.

At first sight, this result would seem to indicate that 1,2-octadiene is reducing somewhat faster than 2-octyne. Such a conclusion is not necessarily valid, however, since it was found that the 1,2-octadiene is partially isomerized to 2-octyne during the electrochemical reduction. When pure 1,2-octadiene was reduced for half the theoretical time to reduce only one double bond, the recovered starting material contained 20% 2-octyne. The latter is definitely formed during the reduction, as 1,2-octadiene was not isomerized merely by lithium chloride in methylamine.

The above results suggest that, in the divided cell, 3-octyne is reduced to *trans*-3-octene and, as the lithium methylamide concentration gradually increases, the 3-octyne begins to isomerize to allenes and the isomeric octynes. *Both* the allenes and octynes are then reduced to the observed products.

Experimental Section

General Procedure for the Reduction of Dialkyl- and Aromatic Acetylenes in an Undivided Electrolytic Cell.—Dialkyl- and aromatic acetylenes were reduced in the undivided electrolytic cell previously described.[1] The cell was charged with 34 g (0.8 mol) of lithium chloride, 900 ml of anhydrous methylamine, and 0.1 mol of the acetylene to be reduced. A current of 2 A was passed through the cell for 2 hr and 40 min (19,300 C). At the end of this time the solvent was allowed to evaporate through a water condenser. The residue was hydrolyzed with 300 ml of water, and the aqueous solution was extracted with ether. The ether extracts were dried ($CaSO_4$); the solvent was ether. The ether extracts were dried ($CaSO_4$) and the solvent then removed. Distillation of the residue yielded the product, which was analyzed by vapor phase chromatography. The results for the reduction of 2-octyne,[2] 3-octyne,[2] and 5-decyne[2] are summarized in Table I. The results obtained for phenylacetylene, 1-phenyl-1-butyne,[13] 4-phenyl-1-butyne,[14] and 5-phenyl-2-pentyne are shown in Table II.

Attempted Reduction of 3-Octyne (Undivided Cell, Excess Current).—Eleven grams (0.1 mol) of 3-octyne was reduced in the undivided electrolytic cell[1] by passing a current of 2 A. through the system for 5 hr and 20 min (38,600 C). Distillation, following the usual work-up, afforded 6.0 g (58%) of product (bp 120°). The product composition is shown in Table I (entry 4).

5-Phenyl-2-pentyne.—4-Phenyl-1-butyne (116 g, 0.9 mol) was treated with 40 g (1.0 mol) of sodium amide dissolved in 800 ml of liquid ammonia followed by the addition of methyl iodide (200 g, 1.5 mol). The mixture was hydrolyzed with 6 *N* ammonium hydroxide, and the solvent was allowed to evaporate. Extraction with pentane was followed by the usual work-up. Distillation yielded 75 g (52%) of product, bp 101° (13 mm).

Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.63; H, 8.60.

***cis*- and *trans*-5-Phenyl-2-pentene.**—The *cis* isomer (5.2 g, 70%; bp 200°) was obtained by catalytic hydrogenation (60 psi; Raney nickel) of a solution of 5-phenyl-2-pentyne (7.5 g, 0.05 mol) in 60 ml of pentane. Analysis by vpc (Table II, footnote *a*) showed the product was 48% *cis*-5-phenyl-2-pentene, 17% *trans*-5-phenyl-2-pentene, and 35% *n*-amylbenzene. Each of these components was isolated by vpc and identified by its nmr spectrum. The retention times of the *trans* isomer and *n*-amylbenzene also matched those of authentic samples.

Anal. Calcd for $C_{11}H_{14}$ (*cis*): C, 90.35; H, 9.65. Found: C, 90.42; H, 9.80.

The *trans* isomer (20 g, 55%; bp 200°) was prepared by coupling benzylmagnesium chloride [from 25 g (1 g-atom) of magnesium and 31.7 g (0.25 mol) of benzyl chloride in 700 ml of dry ether] with *trans*-crotyl chloride (23 g, 0.25 mol). Analysis by vpc (Table II, footnote *a*) showed the product was 71% *trans*-5-phenyl-2-pentene, 11% *cis*-5-phenyl-2-pentene, and 18% 4-phenyl-3-methyl-1-butene. Each of these components was isolated by vpc and its identity established by nmr spectra.

Anal. Calcd for $C_{11}H_{14}$ (*trans*): C, 90.35; H, 9.65. Found: C, 90.55; H, 9.75.

Electrochemical Reduction of 3-Octyne (Divided Cell).—3-Octyne (11 g, 0.1 mol) was placed in the cathode compartment of a divided electrolytic cell.[1] Current was passed through the cell for 2 hr and 40 min (19,300 C, 2 A). The solvent was evaporated through water condensers, and the residue in each half cell was hydrolyzed by the slow addition of water. The aqueous solutions were combined and the organic material isolated in the usual manner. Distillation yielded 5.2 g (47%) of product boiling at 121°. Analysis by vpc at 25° using three columns connected in series (β,β'-oxydipropionitrile–$AgNO_3$, 40%, 8 m; diethylene glycol–$AgNO_3$, 40%, 2 m; diethylene glycol–$AgBO_3$, 40%, 8 m) showed that the product consisted of the compounds listed in Table III. Identification was made by comparing retention times of each of the compounds with those of authentic samples. The latter were either commercially available (*n*-octane, 1-octene, *trans*-2-octene) or were synthesized by the method described in ref 2.

Isomerization of 3-Octyne.—Lithium methylamide (0.15 mol) was prepared by adding 1 g of lithium wire to a solution of methylamine containing a catalytic amount of ferric chloride. Then 3-octyne (10.0 g, 0.09 mol) was added, and the mixture was stirred for 2 hr and 40 min. The solvent was allowed to evaporate, and the residue was hydrolyzed (water). The organic material was worked up in the usual manner. Distillation afforded 3.5 g (35%) of product boiling at 132°. Analysis by vpc (17-ft, 20% dibutyl tetrachlorophthalate column at 72°) showed that the product contained all four isomeric octynes as adjudged by a comparison of retention times with authentic samples. The approximate product composition was 4-octyne (36%), 3-octyne (25%), 2-octyne (32%), and 1-octyne (12%).

Electrochemical Reduction of 1,2-Octadiene (Undivided Cell).—In a 200-ml three-neck flask fitted with a Dry Ice condenser and two (1.5 by 1.5 cm) platinum electrodes were placed in lithium chloride (8.5 g, 0.2 mol), 200 ml of methylamine, and 1,2-octadiene[15] (3.0 g, 0.027 mol). A current of 1 A was passed through the cell for 1 hr and 27 min (5220 C). After the addition of 50 ml of diethyl ether, the solvent was allowed to evaporate through a water condenser. The residue was hydrolyzed, and the organic material was worked up in the usual manner. Distillation yielded 2.0 g (66%) of product boiling at 122°. Analysis by vpc (Perkin-Elmer 226 capillary gas chromatograph; 150-ft, 0.01-in.-diameter UCON Polar column at 55°) showed (comparison of retention times) that the product consisted of 1-octene (6%), *trans*-2-octene (63%), *cis*-2-octene (12%), and 1,2-octadiene and 2-octyne (6%). The retention time (minutes) of each product was 4.8, 5.3, 5.5, and 12.3, respectively.

Competitive Reduction of 1,2-Octadiene and 2-Octyne (Undivided Cell).—In the electrolytic cell described above, a mixture of 1,2-octadiene[15] (3.0 g, 0.027 mol) and 2-octyne (3.0 g, 0.027 mol) was partially reduced by passing a current of 1 A through the system for 1 hr and 20 min (5220 C). Ether (75 ml) was added, and the solvent was evaporated. The usual work-up, followed by distillation, yielded 4.6 g (76%) of product boiling at 124–130°. Analysis by vpc (see previous conditions) showed that the product consisted of 1-octene (3%), *trans*-2-octene (43%), *cis*-2-octene (5%), 2-octyne (32%), and 1,2-octadiene (19%).

Partial Reduction of 1,2-Octadiene (Undivided Cell).—A 3-g (0.027 mol) sample of 1,2-octadiene[15] was reduced in the undivided cell by passing a current of 1 A through the system for 40 min (2610 C). The usual work-up and distillation yielded 2.0 g (66%) of product boiling at 122–128°. Analysis by vpc (Perkin-Elmer 226 capillary gas chromatograph) using the conditions previously described, showed that the product consisted

(13) T. M. Morgan, *J. Chem. Soc.*, **29**, 162 (1876).

(14) J. R. Johnson and W. L. Mc Ewen, *J. Amer. Chem. Soc.*, **48**, 475 (1926).

(15) B. Wojtkowiak and R. Romanet, *Bull. Soc. Chim. Fr.*, 805 (1962).

of 1-octene (5%) *trans*-2-octene (39%), *cis*-2-octene (6%), 1,2-octadiene (40%), and 2-octyne (11%).

Attempted Isomerization of 1,2-Octadiene with Lithium Chloride.—A 3-g (0.027 mol) sample of 1,2-octadiene was stirred for 1 hr and 27 min in a solution of lithium chloride dissolved in methylamine. The usual work-up and distillation yielded 2.2 g (74%) of a product boiling at 130°. Analysis by vpc (capillary gas chromatograph described above) showed that the product contained only 1,2-octadiene.

Electrochemical Reduction of 2,3-Octadiene (Undivided Cell).—A 3-g (0.027 mol) sample of 2,3-octadiene[15] was reduced in the undivided cell using the procedure described above for 1,2-octadiene. The organic material was worked up in the usual manner and distillation yielded 2 g (66%) of product boiling at 122°. Analysis on a Perkin-Elmer 226 gas chromatograph, using the conditions previously described, showed that the product consisted of *cis*- plus *trans*-3-octene (47%), *trans*-2-octene (48%), and *cis*-2-octene (5%). Analysis on an Aerograph gas chromatograph using a 25-ft, β,β′-oxydipropionitrile column at 30° showed the product composition to be *trans*-3-octene (45%), *cis*-3- plus *trans*-2-octene (50%), and *cis*-2-octene (5%). The amount of *cis*-3-octene by difference is approximately 2 ± 5%.

Registry No.—2-Octyne, 2809-67-8; 3-octyne, 15232-76-5; 5-decyne, 1942-46-7; phenylacetylene, 536-74-3; 1-phenyl-1-butyne, 622-76-4; 4-phenyl-1-butyne, 16520-62-0; 5-phenyl-2-pentyne, 16487-62-0; 4-phenyl-1-butene, 768-56-9; *trans*-5-phenyl-2-pentene, 16091-23-9; *cis*-5-phenyl-2-pentene, 16487-65-3; *trans*-5-(2,5-dihydrophenyl)-2-pentene, 16487-66-4; 1,2-octadiene, 1072-19-1; 2,3-octadiene, 16487-68-6.

Acknowledgment.—This research was sponsored by the Petroleum Research Fund of the American Chemical Society and by the Air Force Office of Scientific Research, Office of Aerospace Research, U. S. Air Force under AFOSR Grant 822-67.

Photochemical Reduction of β- and γ-Keto Sulfones

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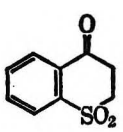
Received March 6, 1968

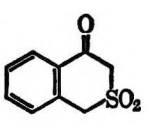
The preparation of several new γ-keto sulfones related to thiochroman-4-one 1,1-dioxide has been carried out by hydrogen peroxide oxidation of the corresponding cyclic sulfides. The preparation of the β-keto sulfone, isothiochroman-4-one 2,2-dioxide, is also described. Ultraviolet irradiation of these keto sulfones in methanol has been found to lead in most cases to the corresponding pinacols, by bimolecular reduction of the carbonyl group. The photochemical reduction seems to be relatively insensitive to the substitution pattern, although the lack of reaction in two cases is attributed to steric effects of neighboring groups.

The photochemical reactions of the carbonyl group in sulfur-containing heterocyclic systems have not so far been investigated extensively. Berchtold and Johnson[1] recently reported the photochemical conversion of two cyclic γ-keto sulfides to ring-contracted β-thiolactones and speculated on the possibility of a charge–transfer mechanism being responsible. Ultraviolet irradiation of isothiochroman-4-ones has been shown[2] to give the corresponding thiochroman-3-ones as the major nonpolymeric products. Additional evidence for the possibility of charge–transfer interactions in cyclic γ-keto sulfides has also been obtained as a result of studies of the ultraviolet spectra of some cage compounds.[3]

In the present investigation we report the effect of ultraviolet irradiation on thiochroman-4-one 1,1-dioxide[4] **1** and several monosubstituted thiochromanone



1



10

sulfones of the same series, most of which have not been previously reported. The sulfones were chosen to include examples of both electron-releasing (alkyl) and electron-withdrawing (carboalkoxyl) substituents at various sites in the thiochromanone system. These γ-keto sulfones and the β-keto sulfone **10** derived from isothiochroman-4-one[2] were the subject of our investigation into the effect of the $-SO_2-$ group on the photochemical properties of the carbonyl function in such compounds. Ultraviolet data for the keto sulfones studied appear in the Experimental Section (Table IV).

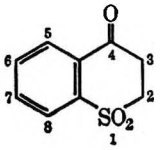
Results and Discussion

The sulfones used in this investigation (Table I) were obtained from the corresponding sulfides by oxidation with hydrogen peroxide in hot acetic acid, except in the case of isothiochroman-4-one 2,2-dioxide **10** (see Experimental Section) where the use of a 5:2 mixture of acetic acid–acetic anhydride and lower temperatures gave much better yields.

Cyclization of the appropriate carboxylic acids to produce the required keto sulfides may be accomplished in several ways, but in general we have found concentrated sulfuric acid to be a satisfactory reagent for this purpose, with the exception of isothiochroman-4-one, which was best obtained using phosphorus pentoxide in benzene, and of 8-carbomethoxythiochroman-4-one, obtained using polyphosphoric acid. The 5- and 7-methylthiochroman-4-ones were obtained in yields of 35 and 20%, respectively, by the cyclization of β-(3′-methylthiophenoxy)propionic acid, and the isomers were separated by chromatography on alumina. When attempts were made to oxidize thiochroman-4-one-2-carboxylic acid to the corresponding sulfone without prior esterification, it was found that hydrogen peroxide in acetone at 25° produced the known 4-thiochromone-2-carboxylic acid in 15% yield. Such a dehydrogenation was rather unexpected, and indicates that internal hydrogen bonding may prevent the

(1) P. Y. Johnson and G. A. Berchtold, *J. Amer. Chem. Soc.*, **89**, 2761 (1967).
(2) W. C. Lumma, Jr., and G. A. Berchtold, *ibid.*, **89**, 2761 (1967).
(3) L. A. Paquette and L. D. Wise, *ibid.*, **89**, 6659 (1967).
(4) F. Arndt, *Chem. Ber.*, **58**, 1612 (1925).

TABLE I
MONOSUBSTITUTED THIOCHROMAN-4-ONE 1,1-DIOXIDES



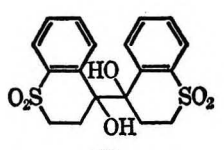
Substituent	Compd no.	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
None	1	130–131[a]	80	$C_9H_8O_3S$	...	...	...	...	...	...
2-Methyl	2	127–128[b]	83	$C_{10}H_{10}O_3S$	57.1	4.8	15.2	57.25	4.9	15.2
3-Methyl	3	146–147[b]	42	$C_{10}H_{10}O_3S$	57.1	4.8	15.2	57.2	4.8	15.25
5-Methyl	4	130–132[c]	85	$C_{10}H_{10}O_3S$	57.1	4.8	15.2	57.1	4.8	15.2
7-Methyl	5	159–160[b]	50	$C_{10}H_{10}O_3S$	57.1	4.8	15.2	57.1	4.85	15.1
8-Methyl	6	124–125[b]	50	$C_{10}H_{10}O_3S$	57.1	4.8	15.2	57.1	4.8	15.25
2-Carbomethoxy	7	111–112[c]	60	$C_{11}H_{10}O_5S$	52.0	3.9	12.6	51.9	3.8	12.6
3-Carbomethoxy	8	152–153[c]	70	$C_{11}H_{10}O_5S$	52.0	3.9	12.6	51.8	4.0	12.6
8-Carbomethoxy	9	133–134[c]	91	$C_{11}H_{10}O_5S$	52.0	3.9	12.6	51.8	4.1	12.5

[a] Lit.[4] mp 130–132°. [b] Recrystallized from ethanol. [c] Recrystallized from methanol.

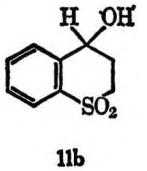
desired oxidation at the sulfur atom. When the carboxylic acid was first esterified, however, oxidation with excess hydrogen peroxide in acetic acid proceeded normally to produce the sulfone.

Ultraviolet irradiation of thiochroman-4-one 1,1-dioxide **1** in acetonitrile or benzene in a quartz vessel produced no change in the starting material after several hours. However, when the irradiation was conducted in a solvent like methanol which is much more likely to act as a hydrogen donor to the excited C=O group, photochemical reduction of the γ-keto sulfone took place, with the formation of the corresponding pinacol **11a** in 31% yield after 18 hr. No starting ketone was recovered, nor any other identifiable product, the remaining material being viscous and polymeric in nature.

The pinacol **11a** was characterized by a very high melting point (275°) and extremely low solubility in all the usual organic solvents. The infrared spectrum (Nujol) revealed bands at 3420 (OH), 1280 (asymmetric SO_2), and 1165 cm^{-1} (symmetric SO_2), but nmr data were not obtained because of solubility difficulties. The mass spectra of this pinacol and of the other pinacols listed in Table II appeared to be somewhat unusual and we plan to make this the subject of a separate publication. The analytical data (Table II) were in accord with both the reduction product **11a** and the thiochromanol **11b** arising from simple reduction of the ketone. Authentic thiochroman-4-ol 1,1-dioxide **11b** was prepared by sodium borohydride reduction[5] of the corresponding ketone, and was clearly not identical (Table III) with our photoreduction product.



11a



11b

Additional evidence for the pinacol structure **11a** was obtained by oxidation with sodium dichromate in sulfuric acid which afforded the starting ketone **1** in 60% yield, thus ruling out the possibility that any skeletal rearrangement had occurred during the photoreduction. Finally, thiochroman-4-one 1,1-dioxide could be reduced with activated zinc dust in acetic acid to a product which was identical in melting point, mixture melting point, and infrared spectrum with our photochemical reduction product.

The other sulfones listed in Table I and isothiochroman-4-one 2,2-dioxide **10** were then subjected to irradiation under essentially similar conditions in dilute (<1%) methanolic solution and the results are summarized in Table II.

It was not felt necessary to synthesize all the corresponding simple reduction products **11b–20b**, so that in Table III are listed only some examples of secondary alcohols obtained by sodium borohydride reduction which serve to emphasize the obvious distinction from the pinacols listed in Table II.

No products other than the pinacols have been detected in any of the above irradiations. Little starting material could be recovered and the residues obtained on removal of the insoluble pinacol were almost entirely polymeric in nature. In a comparative study it was found that isothiochroman-4-one 2,2-dioxide **10** when irradiated in quartz gave comparable amounts of pinacol about five times faster than the same solution irradiated in Pyrex. In the only case (compound **1**) where isopropyl alcohol was used as solvent, it was found to produce no easily observable enhancement in the rate of pinacol formation, while it suffered from the disadvantage of being a much poorer solvent for the sulfone than methanol. Although no serious attempts to optimize the conditions of pinacol formation have been made, our most recent experiments with the use of alternative solvents such as chloroform or 2-butylamine show that the reaction times may be substantially reduced (to as little as 1 hr). The isolated yields of pinacols, however, remained almost the same.

The photochemical reduction of aromatic ketones to produce pinacols is a familiar reaction.[6,7] The reaction seems to be relatively insensitive in the present series to the electronic effects of substituents, although the absence of pinacol formation where there is a carbomethoxy group located at the 8 position (**9**), *meta* oriented to the carbonyl function, may be significant.

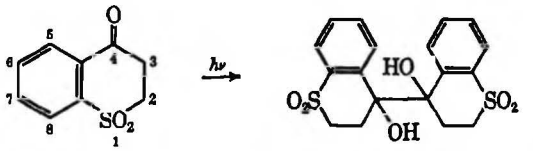
(5) F. J. Lotspeich, *J. Org. Chem.*, **30**, 2068 (1965).

(6) See, for example, S. G. Cohen and R. J. Baumgarten, *J. Amer. Chem. Soc.*, **89**, 3471 (1967), and references contained therein.

(7) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p 139 ff.

TABLE II

PINACOLS OBTAINED BY PHOTOCHEMICAL REDUCTION OF THIOCHROMANONE SULFONES[a]

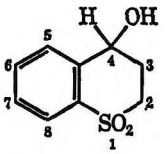


Starting ketone	Irradiation time, hr	Pinacol compd no.	Yield,[b] %	Mp,[c] °C	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
1	18	11a	31	275	54.8	4.6	16.25	54.5	5.0	16.2
2-CH_3, 2	5	12a	23	295	55.7[d]	5.3[d]	14.85[d]	56.1	5.5	14.7
3-CH_3, 3	7	13a	15	235	55.7[d]	5.3[d]	14.85[d]	55.7	5.4	14.9
5-CH_3, 4	24	14a	[e]	...	...	...	...	...	...	...
7-CH_3, 5	12	15a	17	273	56.9	5.2	15.2	57.1	5.2	15.2
8-CH_3, 6	20	16a	17	265	56.9	5.2	15.2	56.75	5.2	15.3
2-$COOCH_3$, 7	8	17a	13	290	51.8	4.3	12.55	51.6	4.2	12.5
3-$COOCH_3$, 8	60	18a	5[f]	223	51.8	4.3	12.55	51.9	4.35	12.5
8-$COOCH_3$, 9	6	19a	[g]	...	...	...	...	...	...	...
10	0.7	20a	30	305	54.8	4.6	16.25	54.6	4.5	16.3

[a] All irradiations were conducted in methanol. [b] Actual isolated yield. [c] All recrystallized from dimethyl sulfoxide. [d] Crystallized as a hemihydrate. [e] Unchanged starting material recovered. [f] 50% starting material recovered. [g] Only polymeric material obtained.

TABLE III

THIOCHROMANOLS BY SODIUM BOROHYDRIDE REDUCTION



Substituent	Compd no.	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
None	11b	95–96[a,b]	40[c]	$C_9H_{10}O_3S$	...	...	...	...	...	...
3-Methyl	13b	117–118[a]	55	$C_{10}H_{12}O_3S$	56.6	5.7	15.1	56.4	5.7	15.2
8-Carbomethoxy	19b	114–115[c]	44	$C_{11}H_{12}O_5S$	51.6	4.7	12.5	51.6	4.55	12.4
Isothiochroman-4-ol 2,2-dioxide	20b	*d*	55	$C_9H_{10}O_3S$	...	...	...	*e*	*e*	*e*

[a] Recrystallized from benzene. [b] Lit.[5] mp 95–97°. [c] Reaction carried out in methanol–dioxane reportedly gives better yields. [d] Boiling point *ca.* 145° (0.1 mm). [e] Because of the high boiling point and consequent slight decomposition a satisfactory analysis could not be obtained. The infrared spectrum ($CHCl_3$) showed bands at 3580 (OH), 1350 (asymmetric SO_2), and 1135 (symmetric SO_2), and no carbonyl band; nmr ($CDCl_3$), τ 6.65 d (2 H, J = 5.2 cps), 6.17 s (OH, disappears upon shaking with D_2O), 5.78 d (2 H, J = 6.5 cps), 4.85 t (1 H, J = 5.2 cps), 2.43–3.01 m (4 H aromatic)—all in accord with the expected structure.

It was, however, noted that the ketone was completely destroyed in this instance, being converted quantitatively into polymeric material in 6 hr, so that, until we possess information on the nature of the competing polymerization mechanism, any definite conclusions would be unwarranted.

Further reference to Table II reveals that large amounts of starting material were recovered in the case of the 5-methyl and 3-carbomethoxy substituents, and this fact, together with the failure to form pinacols to any extent in these cases, suggests that steric inhibition is at its maximum in these two cases, as one would expect. The steric crowding of the adjacent carbonyl due to the planar 5-methyl substituent is obviously greater than that due to the 3-methyl substituent, which can adopt the pseudo-axial orientation. There is at present no evidence to distinguish between steric hindrance to the formation of a ketyl radical by hydrogen abstraction and steric hindrance to the coupling of the ketyl radicals so formed.

Further work is planned to extend this investigation to more elaborate keto sulfones derived from the isothiochroman-4-one series, and an investigation of the irradiation of keto sulfoxides related to the keto sulfones studied in the present account is already under way.

Experimental Section

The infrared spectra were recorded on a Perkin-Elmer Model 237B grating spectrometer and the nmr spectra on a Varian A-60 instrument, with tetramethylsilane as internal standard. Microanalyses were carried out in the laboratory of A. B. Gygli, Toronto. All melting points and boiling points are uncorrected.

Preparation of Monosubstituted Derivatives of Thiochroman-4-one.[8]—2-Methylthiochroman-4-one and 3-methylthiochroman 4-one[4] were prepared by the base-catalyzed addition of thiophenol to crotonic acid and methyl α-methacrylate, respectively, followed by ring closure with concentrated sulfuric acid. 5- and 7-methylthiochroman-4-one[9] were both obtained by the sulfuric acid cyclization of the reaction product of *m*-thiocresol and β-propiolactone. Chromatography of the mixture on grade I alumina and elution with *n*-hexane–benzene (60:40) gave first the liquid 5-methyl isomer, followed by the solid 7-methyl isomer, in the ratio of 5:3.

8-Methylthiochroman-4-one[10] was prepared by the method of Hurd and Hayao, starting from *o*-thiocresol and β-propiolactone.

(8) J. C. Petropoulos, M. A. McCall, and D. S. Tarbell, *J. Amer. Chem. Soc.*, **75**, 1130 (1953).

(9) I. Degani, R. Fochi, and G. Spunta, *Boll. Sci. Fac. Chim. Ind. Bologna*, **24** [2–3], 75 (1966); *Chem. Abstr.*, **66**, 46292*n* (1967).

(10) C. D. Hurd and S. Hayao, *J. Amer. Chem. Soc.*, **76**, 5065 (1954).

2-Carbomethoxythiochroman-4-one[11] was prepared by the addition of thiophenol to diethyl maleate, followed by hydrolysis. Cyclization of the resulting succinic acid, followed by reesterification, gave the desired product.

3-Carbomethoxythiochroman-4-one[12] was prepared from thiochroman-4-one by methoxalylation and decarbonylation of the resulting α-keto ester. All the above thiochromanones agreed closely in melting point (or boiling point) with the reported values.

8-Carbomethoxythiochroman-4-one.—Methyl *o*-mercaptobenzoate[13] (5.7 g, 0.034 mol) was mixed with β-propiolactone (3.0 g, 0.04 mol) and heated at 100–110° for 8 hr. After cooling, extraction with hot petroleum ether (bp 60–70°)–benzene mixture gave needle-shaped crystals of β-(2-carbomethoxythiophenoxy)propionic acid (5.0 g, 61%), mp 99–100°.

Anal. Calcd for $C_{11}H_{12}O_5S$: C, 55.00; H, 5.00; S, 13.33. Found: C, 55.17; H, 5.28; S, 13.28.

The acid (2.0 g, 0.008 mol) was cyclized to the corresponding thiochromanone by addition to polyphosphoric acid, prepared from phosphorus pentoxide (10.0 g, 0.07 mol) and phosphoric acid (12 ml), at 100°. After heating for 2 hr, the mixture was allowed to stand at room temperature for 6 hr, poured into ice–water, and extracted with ether. The combined extracts were washed ($NaHCO_3$, H_2O), dried, and evaporated. The oil originally obtained soon solidified and on recrystallization from benzene gave white crystals (0.36 g, 20%), mp 66–67°, used without further purification for conversion into the sulfone.

Preparation of the Thiochromanone Sulfones (1–9).—These were all prepared by oxidation of the appropriate thiochromanone with hydrogen peroxide. The analytical data, melting points, and yields for these compounds are collected in Table I. Infrared and nmr spectra were in accord with expectation. To illustrate the general method and the relevant spectral data, we describe the preparation of 8-methylthiochroman-4-one 1,1-dioxide 6.

8-Methylthiochroman-4-one (2.0 g, 0.011 mol) was dissolved in acetic acid (8 ml) and 30% hydrogen peroxide (8 ml, 0.1 mol) was added. After heating at 100° for 45 min, the product 6 (50%), mp 124–125°, was collected by cooling and diluting with water (an essentially similar result was obtained without heating, if the reactants were allowed to stand overnight): infrared ($CHCl_3$) 1705 (CO), 1325 (asymmetric SO_2), and 1155 cm^{-1} (symmetric SO_2); nmr ($CDCl_3$), τ 7.27 s (CH_3); symmetric multiplet centered at 6.48 ($2CH_2$), 1.95–2.50 m (3 H aromatic.)

Isothiochroman-4-one 2,2-Dioxide 10.—Isothiochroman-4-one[2] (5.0 g, 0.03 mol), prepared by the P_2O_5 cyclization of S-benzylthioglycolic acid, was dissolved in a mixture of acetic acid (50 ml) and acetic anhydride (20 ml). The solution was cooled to 0° and 30% hydrogen peroxide (35 ml, 0.44 mol) was added slowly with stirring. The mixture was stirred for a further 4 hr at 25°, cooling in ice from time to time when the temperature showed signs of rising. Dilution with water and extraction with methylene chloride led on evaporation to a solid product, recrystallized from acetone (2.5 g, 42%), as white crystals: mp 163–164°; infrared ($CHCl_3$) 1695 (CO), 1335 (asymmetric SO_2), and 1125 cm^{-1} (symmetric SO_2); nmr (acetone-d_6), τ 6.25 (slight splitting, $J < 2$ cps, CH_2), 5.90 (CH_2), 2.90–3.33 m (3 H), 2.47–2.68 m (1 H).

Anal. Calcd for $C_9H_8O_3S$: C, 55.10; H, 4.08; S, 16.33. Found: C, 54.98; H, 3.94; S, 16.36.

Irradiation of the Keto Sulfones.—Ultraviolet irradiations were normally carried out in quartz vessels, using a 125-W medium-pressure Hanovia mercury lamp, in an atmosphere of nitrogen. The results of these experiments and data on the pinacols obtained are recorded in Table II. The following example will serve to illustrate the general method.

2-Carbomethoxythiochroman-4-one 1,1-dioxide (0.9 g) was irradiated in degassed methanol (150 ml). After 8 hr, the ketonic carbonyl band at about 1700 cm^{-1} in the infrared spectrum had completely disappeared. Evaporation of the solvent, followed by the addition of acetone, led to the formation of a white solid (pinacol), mp 289–290°, in 13% yield. Chromatography of the residual gummy material on silica gel led only to traces of unreacted starting material and to intractable gums.

(11) F. Bossert, *Ann. Chem.*, **680**, 40 (1964).
(12) T. Moriwake, *J. Med. Chem.*, **9**, 163 (1966).
(13) British Patent 767,027 (1957) (Schenley Industries, Inc.); *Chem. Abstr.*, **51**, 17998e (1957).

TABLE IV

ULTRAVIOLET SPECTRAL DATA[a] ON KETO SULFONES 1–10

Compound	λ_{max}, mμ (ε)		
Thiochroman-4-one 1,1-dioxide (1)	246 (9,500)	286 (1,600)	294 (1,400)
Isothiochroman-4-one 2,2-dioxide (10)	251 (11,000)	291 (1,700)	300 (1,500)
2-Methylthiochroman-4-one 1,1-dioxide (2)	246 (13,100)	286 (2,300)	294 (2,100)
3-Methylthiochroman-4-one 1,1-dioxide (3)	245 (8,600)	285 (1,400)	293 (1,300)
5-Methylthiochroman-4-one 1,1-dioxide (4)	247 (7,800)	294 (2,600)	303 (2,300)
7-Methylthiochroman-4-one 1,1-dioxide (5)	258 (11,800)	283 (2,100)	294 (1,700)
8-Methylthiochroman-4-one 1,1-dioxide (6)	250 (9,000)	294 (2,500)	302 (2,300)
2-Carbomethoxythiochroman-4-one 1,1-dioxide (7)	246 (9,200)	285 (1,800)	293 (1,700)
3-Carbomethoxythiochroman-4-one 1,1-dioxide (8)	235 (12,000)	...	309 (10,000)
8-Carbomethoxythiochroman-4-one 1,1-dioxide (9)	240 (8,100)	287 (1,000)	295 (900)

[a] All spectra were recorded in methanolic solution on a Unicam SP-800 spectrophotometer.

Ultraviolet spectral data on keto sulfones 1–10 is given in Table IV above.

Reduction of Thiochroman-4-one 1,1-Dioxide with Zinc in Acetic Acid.—The zinc dust (0.2 g, 0.003 g-atom) used in this reaction was first moistened with copper sulfate solution. Thiochroman-4-one 1,1-dioxide (0.2 g, 0.001 mol) was then heated with the zinc at 100° in 75% aqueous acetic acid (10 ml) for 15 min. The white insoluble solid so obtained was washed with concentrated hydrochloric acid to remove any unreacted zinc. This solid (0.11 g, 55%) had mp 273–274° on recrystallization from dimethyl sulfoxide, undepressed on admixture with the pinacol obtained by irradiation, and the infrared spectra of the two samples were superimposable.

Oxidation of Pinacol 11a with $Na_2Cr_2O_7$–H_2SO_4.—The pinacol (130 mg) obtained from thiochroman-4-one 1,1-dioxide by irradiation was mixed with water (0.2 ml) and treated with a solution of sodium dichromate (0.12 g) and sulfuric acid (0.13 g) in water (0.5 ml) at 55° for 2 hr. At this point, acetic acid (2 ml) was added, and after continued stirring for 1 hr, the white insoluble pinacol had completely disappeared. The mixture was diluted with water, and the product extracted with methylene chloride. Washing of the extracts ($NaHCO_3$, H_2O), drying, and evaporation gave a white solid (78 mg, 60%), mp 128–129°, undepressed on admixture with a genuine sample of thiochroman-4-one 1,1-dioxide.[4] The infrared spectra of the two samples were identical.

$NaBH_4$ Reduction of the Keto Sulfones.—The thiochromanols prepared by this procedure are listed in Table III. Compounds **11b**, **13b**, and **20b** were prepared using Lotspeich's procedure.[6] This was felt to be unsuitable for the reduction of keto esters and the following method was used in the case of 8-carbomethoxythiochroman-4-one 1,1-dioxide **9**.

Compound **9** (230 mg, 0.9 mmol) was dissolved in 95% ethyl alcohol (25 ml) to which had been added boric acid (0.1 g). Sodium borohydride (120 mg, 3.1 mmol) was then added in small amounts with stirring, and the mixture allowed to stand for 3 hr. Removal of the ethanol under vacuum and dilution with water was followed by acidification with dilute HCl. Extraction with ether led to the isolation of 8-carbomethoxythiochroman-4-ol 1,1-dioxide **19b** (100 mg, 44%), described further in Table III.

Oxidation of Thiochroman-4-one-2-carboxylic Acid with H_2O_2.—This compound (100 mg) was treated with acetone (5 ml) and 30% hydrogen peroxide (1 ml) and allowed to remain at 25° for 2 days. The yellow crystals (15 mg, 15%) which had appeared near the end of this time were collected by filtration, washed with benzene, and recrystallized from acetic acid, mp 233–234°.

Anal. Calcd for $C_{10}H_8O_3S$: C, 58.25; H, 2.91; S, 15.53. Found: C, 58.33; H, 2.84; S, 15.43.

The infrared spectrum of this compound showed bands (KBr) at 3450 (free OH), 3000–2400 (bonded OH), 1750 and 1715 cm^{-1} (monomeric and dimeric COOH and 1600 cm^{-1} (CO) but no bands characteristic of SO or SO_2. From this information and the

analytical data it was considered to be 4-thiochrom-one-2-carboxylic acid, lit.[14] mp 234–235°.

Registry No.—2, 16808-50-7; 3, 16723-50-5; 4, 16723-52-7; 5, 16723-53-8; 6, 16723-54-9; 7, 16723-55-0; 8, 16723-56-1; 9, 16723-57-2; 10, 16723-58-3; 11a, 16723-59-4; 11b, 2765-44-8; 12a, 16723-60-7; 13a, 16723-61-8; 13b, 16723-68-5; 15a, 16723-62-9; 16a, 16723-63-0; 17a, 16723-64-1; 18a, 16723-65-2; 19b, 16723-69-6; 20a, 16723-66-3; 8-carbomethoxythiochroman-4-one, 16723-70-9; β-(2-carbomethoxythiophenoxy)propionic acid, 16723-72-1; 4-thiochromone-2-carboxylic acid, 16723-71-0.

Acknowledgment.—The authors gratefully acknowledge financial support of this work by the National Research Council of Canada and the Department of University Affairs for the Province of Ontario.

(14) J. Schmutz, M. Lausner, R Hirt, and M. Sanz, *Helv. Chim. Acta*, **34**, 767 (1951).

Chemistry of Aliphatic Disulfides. XVII. Studies on the Alkoxide Cleavage of 3,6-Dibenzoyl-1,8-diphenyl-4,5-dithia-1,8-octanedione[1,2]

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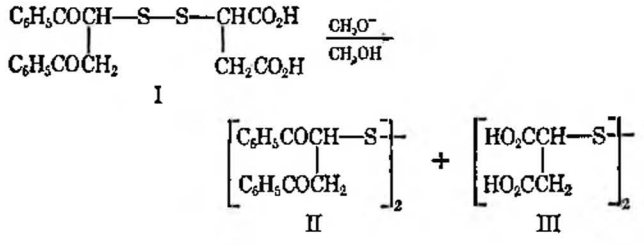
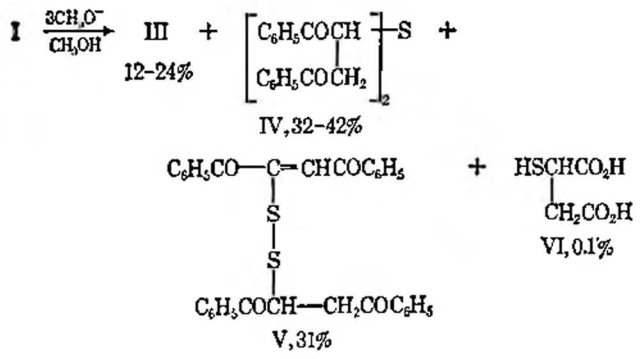
Received February 15, 1968

Treatment of 3,6-dibenzoyl-1,8-diphenyl-4,5-dithia-1,8-octanedione (II) with potassium ethoxide in ethanol provides 3,5-dibenzoyl-1,7-diphenyl-4-thia-1,7-heptanedione (IV) and potassium 1,4-diphenyl-2-butene-1,4-dione-2-mercaptide (VII) as the major products. A mechanism for cleavage of II involving α elimination of a mercaptide is proposed. Compound II is shown to be formed by disulfide interchange during the alkoxide cleavage of 6,7-dibenzoyl-3-carboxyl-4,5-dithiaheptanoic acid (I).

In a previous study,[4] the alkoxide cleavage of 6,7-dibenzoyl-3-carboxy-4,5-dithiaheptanoic acid (I) was examined. The products (III–V) formed by the action of 3 equiv of methoxide ion on I suggested that I was initially converted into 3,6-dibenzoyl-1,8-diphenyl-4,5-dithia-1,8-octanedione (II) and 2,2′-dithiosuccinic acid (III). Although II could not be

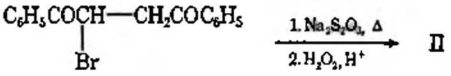


isolated, its presence was implied by the formation of IV and V, which were presumably produced by the action of methoxide ion on II. Since III was present as the tetrasodium salt, further cleavage of the negatively charged disulfide by methoxide should be minimal and indeed III was isolated in reasonable yield.



Although the mechanism for base-catalyzed disulfide interchange (I → II + III) has not been rigorously established, the process probably involves the direct attack of base on the sulfur–sulfur bond rather than initial abstraction of hydrogen atoms α or β to the disulfide bond. The further decomposition of II, however, seemed likely to involve α and/or β elimination of mercaptide.[5,6] Thus a study of the action of alkoxide on II might be expected to provide data on the relative importance of these two pathways and give some indication of the favored route for base-catalyzed decomposition of symmetrical and unsymmetrical disulfides.

Ethoxide Cleavage of II.—The desired substrate, II, was prepared by oxidation of the corresponding Bunte salt. The oxidation provided a mixture of diastereo-



isomers which were readily separated by fractional recrystallization to give a 49% yield of an isomer, mp 115–116°, and a 14% yield of an isomer, mp 137°. Both isomers were cleaved by the action of alkoxide under similar conditions and no significant differences in product analysis were observed.

Treatment of II with 1 equiv of potassium ethoxide in ethanol provided 3,5-dibenzoyl-1,7-diphenyl-4-thia-1,7-heptanedione (IV) in 71.6% yield and potassium 1,4-diphenyl-2-butene-1,4-dione-2-mercaptide (VII) in

(1) This investigation was supported by Public Health Service Fellowship 5-F3-GM-31, 871-02, and by Research Grant RG-7966 from the National Institute of General Medical Sciences, U. S. Public Health Service.

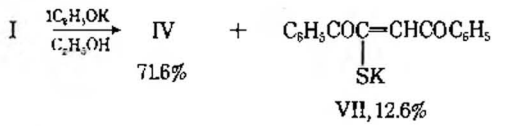
(2) For part XVI of the series, see R. G. Hiskey and A. J. Dennis, *J. Org. Chem.*, **33**, 563 (1968).

(3) Special Fellow, National Institute of General Medical Sciences, 1967–1968.

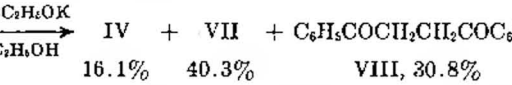
(4) R. G. Hiskey and J. A. Kepler, *ibid.*, **29**, 3678 (1964).

(5) N. A. Rosenthal and G. Oster, *J. Soc. Cosmet. Chem.*, **5**, 286 (1954); *J. Amer. Chem. Soc.*, **83**, 445 (1961); J. P. Danehy and J. A. Kreuz, *ibid.*, **83**, 1109 (1961); D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 1 (1951); J. M. Swan, *Nature*, **179**, 965 (1957).

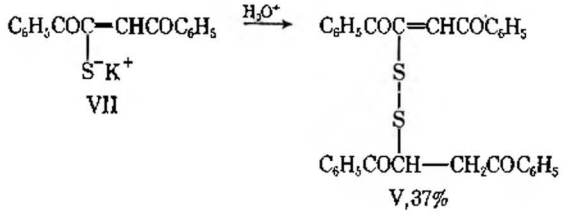
(6) The reaction of water-soluble disulfides with aqueous alkali has recently been studied by J. P. Danehy and W. E. Hunter, *J. Org. Chem.*, **32**, 2047 (1967).



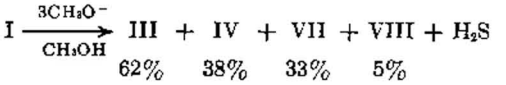
12.6% yield. When the added base concentration was increased to 2 equiv of ethoxide per equivalent of disulfide, 1,4-diphenyl-1,4-butanedione (VIII) was isolated in 30.8% yield. Under these conditions the yield of IV was reduced to 16.1% and the yield of VII increased to 40.3%.



Comparison of the cleavage of II, using 1 equiv of ethoxide, with the previous data obtained by cleavage of I[4] indicated that substantial amounts of the sulfide, IV, were produced in each case. However, cleavage of I provided significant amounts of the unsymmetrical disulfide, V, whereas the enethiolate, VII, was obtained in the present investigation. This apparent discrepancy was resolved by examination of the work-up procedures used in the two reactions. In the present investigation VII was obtained after the aqueous extract of the reaction mixture was adjusted to pH 9 using carbon dioxide; in our earlier studies V resulted by neutralization of the aqueous extract with hydrochloric acid. Thus VII is a likely precursor of V. Evidence for this relationship was obtained by neutralization of VII with dilute hydrochloric acid; under these conditions V was produced in 37% yield. Dimerizations of this type involving the enol and keto forms of thioketones have been previously reported for thioketones containing electron-withdrawing groups.[7]



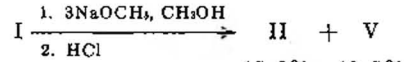
Methoxide Cleavage of I.—When I was treated with 3 equiv of potassium methoxide in methanol and the aqueous extract of the cleavage mixture adjusted to pH 9 with carbon dioxide, the enethiolate VII was obtained in 33% yield. In addition, VIII, which was



not reported in the previous studies, was isolated in 5% yield.

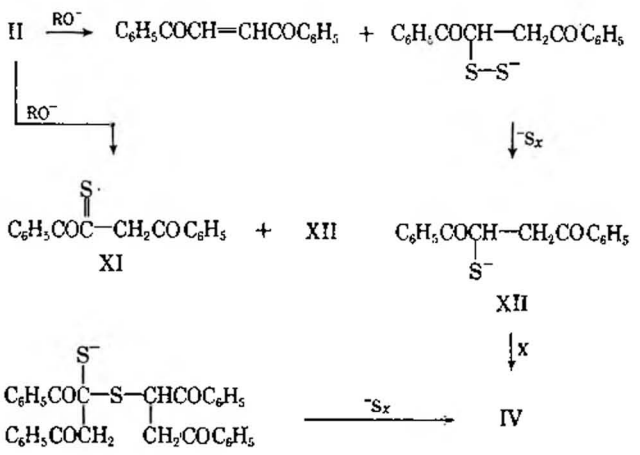
In order to obtain additional evidence on the possible formation of II, during the first stage of the alkoxide decompostion of I, cleavages of I using varying amounts of methoxide were followed by thin layer chromatography. The following information was obtained from the chromatograms: (1) I did not undergo either disulfide interchange or cleavage with 2 or less equiv of methoxide; (2) disulfide interchange of I to provide the symmetrical disulfide II occurred rapidly at methoxide levels greater than 2 equiv and the subsequent cleavage of II occurred at a slightly slower rate; and (3) disulfide interchange could be initiated by treatment of I with 2 equiv of methoxide and catalytic amounts of either the sodium salt of VI or 2-mercapto-1,4-diphenyl-1,4-butanedione (IX).

Additional evidence for disulfide interchange occurring during the alkoxide treatment of I was obtained by quenching the reaction with dilute hydrochloric acid after 5 min; II was isolated in 15.6% yield along with a 12.5% yield of the sulfide IV and 30.7% recovery of starting disulfide I.



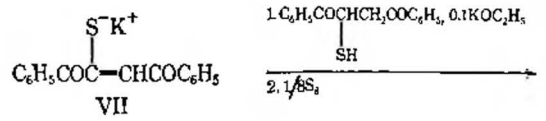
Alkoxide Cleavage of II.—Although the sulfide IV would be the expected product by either α or β elimination of a mercaptide from II, the intermediates in the two pathways could be distinguished (Scheme I). β elimination would proceed *via* 1,4-diphenyl-2-butene-1,4-dione (X), whereas α elimination would generate the thio ketone XI and the mercaptide XII.

SCHEME I



Attempts to isolate X or to detect the substance by thin layer chromatograms of the reaction mixture failed. Attempts to detect 1,4-dibenzoyl-2,6-diphenyl-6-hydroxyfulvene, which is usually a product when *trans*-1,4-diphenyl-2-butene-1,4-dione is treated with potassium ethoxide,[8] were also unsuccessful. In contrast, the enolate form (VII) of the thio ketone XI which would be one of the intermediates by α elimination was obtained in significant yields in cleavages of II.

Additional evidence favoring a mechanistic pathway involving α elimination was obtained by a study of the reaction of 2-mercapto-1,4-diphenyl-1,4-butanedione (IX) with VII. In the presence of catalytic amounts of potassium ethoxide and sulfur the sulfide IV was obtained in 67.4% yield. The formation of IV

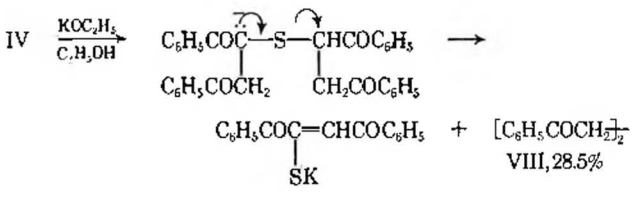


from VII and IX is consistant with the proposed formation of a hemidithioacetal intermediate in the conversion of II → IV.

(7) W. J. Middleton, E. G. Howard, and W. H. Sharkey, *J. Amer. Chem. Soc.*, **83**, 2589 (1961).

(8) R. C. Fuson, C. L. Fleming, and P. F. Warfield, *J. Org. Chem.*, **10**, 121 (1945).

The data obtained from the cleavage of II with 2 equiv of ethoxide can also be rationalized by an α elimination mechanism. When an appreciable base concentration is maintained, the sulfide IV also undergoes cleavage. For example, when IV was treated with 1 equiv of potassium ethoxide in ethanol, VII and VIII are obtained in yields of 25.7 and 28.5% along with a 20.9% recovery of IV.



VII, 25.7%

The fact that I undergoes initial disulfide interchange to produce II which then yields the thio ketone XI and mercaptide XII suggests that in this system the direct attack of alkoxide on the sulfur–sulfur bond is the favored process. Decomposition of the symmetrical disulfide II then occurs by α rather than β elimination.

Experimental Section[9]

Preparation of 3,4-Dibenzoyl-1,1,1-triphenyl-2-thiabutane.—To a solution of 21.4 g (0.09 mol) of *trans*-1,4-diphenyl-2-butene-1,4-dione in 400 ml of hot 2-propanol was added a solution of 25.0 g (0.09 mol) of triphenylmethylmercaptan in 250 ml of hot 2-propanol. Piperidine (1 ml) was added and the mixture stirred at 60° for 1 hr. After stirring an additional 12 hr at room temperature the colorless solid was removed by filtration and washed with 100 ml of 2-propanol to give 42.7 g (91.5%) of 3,4-dibenzoyl-1,1,1-triphenyl-2-thiabutane, mp 142–144°. Recrystallization from benzene–hexane raised the melting point to 145–146° (lit.[4] mp 146–147°).

Preparation of 6,7-Dibenzoyl-3-carboxy-4,5-dithiaheptanoic Acid (I).—A solution containing 2.12 g (0.0132 mol) of bromine in 60 ml of dry ethyl acetate was added to a stirred suspension of 6.0 g (0.0186 mol) of lead thiocyanate in 60 ml of dry ethyl acetate at ice bath temperature. After discharge of the bromine color 5.44 g (0.0594 mol) of anhydrous zinc chloride was added followed by dropwise addition over a 2-hr period of a solution containing 6.16 g (0.0012 mol) of 3,4-dibenzoyl-1,1,1-triphenyl-2-thiabutane in 200 ml of dry ethyl acetate. The mixture was stirred for an additional 0.5 hr at ice-bath temperature followed by addition of a solution containing 1.80 g (0.012 mol) of mercaptosuccinic acid in 80 ml of dry acetic acid. After 2 hr the ice bath was removed; the mixture was stirred at 24° for 5 hr; and then it was filtered giving a colorless filtrate. The ethyl acetate was removed *in vacuo* and the resulting acetic acid solution poured into 800 ml of cold water precipitating a colorless solid which was collected by filtration, washed with water, and dried *in vacuo* for 12 hr. After washing with 300 ml of warm *n*-hexane, the solid was dissolved in the minimum amount of acetone and applied to a 4.5 × 15 cm column of silica gel (100 g, 0.05–0.20 mm). The effluent was monitored by thin layer chromatograms [solvent system, chloroform (90)–methanol (5)–acetic acid (5)]. The unreacted S-trityl compound was eluted with chloroform followed by elution of the desired compound with ethyl acetate. Recrystallization from ethyl acetate–hexane gave 2.87 g (57%) of 6,7-dibenzoyl-3-carboxy-4,5-dithiaheptanoic acid (I), mp 185–188° (lit.[4] mp 187–188°).

Bromo-1,4-diphenyl-1,4-butanedione was prepared according to the procedure of Schultz,[10] mp 132–133° (lit.[11] mp 139°).

Preparation of 3,6-Dibenzoyl-1,8-diphenyl-4,5-dithia-1,8-octanedione (II).—To a solution of 12.7 g (0.04 mol) of 2-bromo-1,4-diphenyl-1,4-butanedione in 120 ml of hot absolute ethanol was added a solution of 9.9 g (0.04 mol) of sodium thiosulfate pentahydrate in 120 ml of water. The mixture was heated at reflux temperature for 1.5 hr. The solvent was removed *in vacuo* and the solid residue treated with 150 ml of water. The mixture was filtered leaving a small amount of solid. A solution of 7.2 ml of 30% hydrogen peroxide in 8 ml of 6 *N* sulfuric acid was added to the filtrate and the solution sitrred at 27° for 24 hr to give 9.0 g of crude product, mp 95–104°. The sample was recrystallized from 850 ml of methanol with the colorless solid forming at room temperature collected by filtration to give 1.54 g (14.3%) of II, mp 135–137°. Recrystallization from methanol raised the melting point to 137°.

Anal. Calcd for $C_{32}H_{26}O_4S_2$: C, 71.35; H, 4.87; S, 11.90; mol wt, 538. Found: C, 71.61; H, 4.98; S, 11.69; mol wt, 536, 538 (osmometry, benzene).

The infrared spectrum (KBr) showed a doublet at 1675 cm^{-1}. The nmr spectrum ($DCCl_3$) showed three multiplets centered at τ 2.5 (10.3 H), 5.2 (1.0 H), and 6.3 (1.8 H). The ultraviolet spectrum showed λ_{max}^{EtOH} 248 mμ (ϵ 50,000).

The filtrate from the separation of the higher melting isomer was reduced to a volume of 600 ml and cooled to give 5.26 g (49%) of II, mp 114–118°. Recrystallization from methanol changed the melting point to 115–116°.

Anal. Calcd for $C_{32}H_{26}O_4S_2$: C, 71.35; H, 4.87; S, 11.90; mol wt, 538. Found: C, 71.09; H, 4.80; S, 12.06; mol wt, 538 (mass spectrometry).

The infrared spectrum (KBr) showed a doublet at 1670 cm^{-1} and was quite similar but not identical with the spectrum of the higher melting isomer. The nmr spectrum ($DCCl_3$) showed three multiplets centered at τ 2.3 (10.5 H), 5.0 (1.0 H), and 6.3 (2.0 H). The ultraviolet spectrum showed λ_{max}^{EtOH} 246 mμ (ϵ 48,600).

3,5-Dibenzoyl-1,7-diphenyl-4-thia-1,7-heptanedione (IV) was prepared according to the procedure of Hiskey and Kepler,[4] mp 196–197° (lit.[4] mp 194–196°).

1,4-Diphenyl-1,4-butanedione (VIII) was prepared according to the procedure of Conant and Lutz,[11] mp 144–145° (lit.[12] mp 144–145°).

Preparation of 2-Mercapto-1,4-diphenyl-1,4-butanedione (IX).—To a solution containing 16.4 g (0.032 mol) of 3,4-dibenzoyl-1,1,1-triphenyl-2-thiabutane in 250 ml of chloroform and 500 ml of methanol was added a solution containing 0.544 g (0.032 mol) of silver nitrate and 2.53 g (0.032 mol) of pyridine in 15 ml of methanol. The solution was stirred at 27° in the dark for 4.5 hr. The reaction mixture was poured into 1.5 l. of methanol precipitating a solid which was washed with 100 ml of methanol and 500 ml of hexane to give 11.2 g of pale yellow solid, mp 107–109°.

A stirred suspension of 11.2 g of the silver mercaptide in 400 ml of methanol was treated with hydrogen sulfide for 15 min. Chloroform (400 ml) was added and the mixture warmed to 40°. Silver sulfide was removed by filtration and the filtrate evaporated *in vacuo* to give 7.3 g (85%) of colorless solid, mp 122–124°. Recrystallization from methanol raised the melting point to 124–125°.

Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22; S, 11.86; mol wt, 270. Found: C, 70.90; H, 5.27; S, 11.65; mol wt, 270 (mass spectrometry).

The solid gave a positive mercaptan test with sodium nitroprusside. The infrared spectrum (KBr) showed a weak peak at 2560 cm^{-1} and a strong doublet at 1675 cm^{-1}. The nmr spectrum ($DCCl_3$) showed a multiplet centered at τ 2.30 (9.8 H), an octet centered at 5.15 (1.0 H), an octet centered at 6.23 (1.9 H), and a doublet centered at 8.02 (1.0 H). The ultraviolet spectrum showed λ_{max}^{EtOH} 246 mμ (ϵ 43,600).

Preparation of 3-Benzoyl-1,6-diphenyl-4-thia-1,6-hexanedione.—To a solution of 270 mg (1 mmol) of 2-mercapto-1,4-diphenyl-1,4-butanedione and 84 mg (1 mmol) of potassium ethoxide in 15 ml of absolute ethanol was added a solution containing 199 mg (1 mmol) of 2-bromoacetophenone in 10 ml of absolute ethanol. The reaction mixture was stirred at 70° for 1 hr. The mixture was cooled, the resulting white solid was removed by filtration and washed with water to give 337 mg (87%) of 3-benzoyl-1,7-diphenyl-4-thia-1,6-hexanedione, mp 128–133°. Recrystallization from ethanol raised the melting point to 140°.

(9) Melting points were taken on a Fisher-Johns block and are uncorrected. Spectra were determined on Perkin-Elmer Models 237B and 257 (infrared), Perkin-Elmer Model 202 (ultraviolet), Varian Associates A-60 (nmr), and Hitachi Perkin-Elmer RMU-6E (mass spectrometry). Osmometric molecular weights were determined using a Mechrolab Model 301A vapor pressure osmometer. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(10) P. C. Schultz, *Ber.*, **35**, 168 (1902).

(11) J. B Conant and R. E. Lutz, *J. Amer. Chem. Soc.*, **45**, 1303 (1923).

(12) B. Holmberg, *Ark. Kemi Mineral. Geol.*, **6**, 1 (1916).

Anal. Calcd for $C_{24}H_{20}O_3S$: C, 74.20; H, 5.19; S, 8.26; mol wt, 388. Found: C, 74.23, 74.49; H, 5.23, 5.18; S, 8.36, 8.45; mol wt, 388 (mass spectrometry).

The infrared spectrum (KBr) showed strong peaks at 1665 and 1680 cm^{-1}. The nmr spectrum ($DCCl_3$) showed a multiplet centered at τ 6.05 (2.0 H) along with an ABX system which consisted of two doublets centered at τ 5.00 (1.0 H, J_{AX} = 4 cps, J_{BX} = 9 cps) and an apparent octet centered at τ 6.29 (1.7 H, J_{AB} = 19 cps, J_{AX} = 4 cps, J_{BX} = 9 cps).

Cleavage of 6,7-Dibenzoyl-3-carboxy-4,5-dithiaheptanoic Acid (I) with 3 Equiv of Potassium Methoxide.—To a solution of 836 mg (2 mmol) of 6,7-dibenzoyl-3-carboxy-4,5-dithiaheptanoic acid (I) in 65 ml of dry methanol was added with stirring a solution containing 0.42 g (6 mmol) of potassium methoxide in 10 ml of methanol. The solution took on a yellow color which changed to red within 30 min. The solution was stirred at 27° for 20 hr. The solid was removed by filtration and washed with methanol to give a colorless solid and red filtrate.

The solid was washed with 25 ml of water to give 89 mg (17.6%) of 3,5-dibenzoyl-1,7-diphenyl-4-thia-1,7-heptanedione (IV), mp 181–185°. Recrystallization from ethanol–chloroform raised the melting point to 193–195° (lit.[4] mp 194–196°). The sample was found to be identical with authentic IV by mixture melting point determination and infrared spectra comparison.

The filtrate from separation of IV was evaporated *in vacuo* leaving a red solid which was treated with 50 ml of water. Filtration left 133 mg of a mixture of IV and 1,4-diphenyl-1,4-butanedione (VIII). The mixtue was triturated in 10 ml of hot ethanol. Filtration gave an additional 101 mg (20%) of IV (total yield of IV, 190 mg 37.6%). The filtrate was cooled to give 22 mg (4.6%) of VIII, mp 140–143°. Recrystallization from ethanol raised the melting point to 144–145° (lit.[11] mp 144–145°). The sample was found to be identical with authentic VIII by mixture melting point determination and infrared spectra comparison.

The aqueous filtrates were combined and treated with carbon dioxide until pH 9 was reached. The solution was evaporated *in vacuo* leaving a red solid which was treated with a solution containing 2 ml of absolute ethanol in 50 ml of ether. The mixture was filtered to give a yellow solid and red filtrate.

The solid was dissolved in 10 ml of water and acidified with 6 *N* hydrochloric acid. The solution was evaporated *in vacuo* leaving a white solid which was extracted with 300 ml of ether. The ether was removed *in vacuo* to give 188 mg (62%) of 2,2′-dithiodisuccinic acid (III), mp 160–165°. Recrystallization from ethyl acetate–hexane raised the melting point to 164–166° (lit.[12] mp 167–168°). The sample was found to be identical with authentic III by infrared spectra comparison.

The filtrate from the separation of the salt of III was evaporated *in vacuo* to give 202 mg (33%) of potassium 1,4-diphenyl-2-butene-1,4-dione-2-mercaptide (VII), mp 116–121° (lit.[2] mp 118–121°). The sample was found to be identical with authentic sample by infrared spectra comparison.

Thin Layer Chromatographic Studies of Disulfide Interchange of 6,7-Dibenzoyl-3-carboxy-4,5-dithiaheptanoic Acid (I).—The methanolic sodium methoxide solution used in the disulfide interchange studies was standardized by titration with standard 0.100 *M* hydrochloric acid and found to be 0.046 *M*. Thin layer chromatography was conducted on 3 × 7 cm Eastman K301R2 silica gel sheets. The solvent system was benzene–hexane (7:3) with iodine vapor used for development.

A. Treatment of I with Sodium Methoxide.—I (9.6 mg, 0.023 mmol) was treated with 1 ml (0.046 mmol) of 0.046 *M* sodium methoxide solution. Periodic checks by thin layer chromatography during a 1.5-hr period gave no indication of disulfide interchange or cleavage. Increments (0.1 ml, 0.0046 mmole) of 0.046 *M* sodium methoxide were added with thin layer chromatography checks made after 2, 10, and 15 min. The addition of the first increment giving a ratio of I:$NaOCH_3$ 1:2.2 brought about no observable change. The addition of a second increment of 0.1 ml of sodium methoxide giving I:$NaOCH_3$ 1:2.4 showed after 10 min a spot of same R_f value as 3,6-dibenzoyl-1,8-diphenyl-4,5-dithia-1,8-octanedione (II). The addition of a third increment of 0.1 ml of sodium ethoxide giving I:$NaOCH_3$ 1:2.6 showed after 2 min a weak spot of same R_f value as II along with a strong spot of same R_f value as 3,5-dibenzoyl-1,7-diphenyl-4-thia-1,7-hexanedione (IV).

B. Treatment of I with 2 Equiv of Sodium Methoxide and the Sodium Salt of 2-Mercapto-1,4-diphenyl-1,4-butanedione.—I (19.2 mg 0.046 mmol) was treated with 2 ml of (0.092 mmol) of 0.046 *M* sodium methoxide. A solution of 1.32 mg (0.0046 mmol) of 2-mercapto-1,4-diphenyl-1,4-butanedione (IX) and 0.1 ml (0.0046 mmol) of 0.046 *M* sodium methoxide solution was added giving a ratio of I:$NaOCH_3$:mercaptide 1:2:0.1. After 2 min the thin layer chromatogram showed a spot of the same R_f value as II. Periodic checks gave no trace of cleavage products.

C. Treatment of I with 2 Equiv of Sodium Methoxide and the Sodium Salt of Mercaptosuccinic acid.—I (19.2 mg, 0.046 mmol) was treated with 2 ml (0.092 mmol) of 0.046 *M* sodium methoxide solution. A solution of 0.73 mg (0.0046 mmol) of mercaptosuccinic acid and 0.3 ml (0.0138 mmol) of 0.046 *M* sodium methoxide solution was added. Thin layer chromatograms revealed no changes within 15 min. A second increment of 0.73 mg (0.0046 mmol) of mercaptosuccinic acid and 0.3 ml (0.0138 mmol) of sodium methoxide was added giving a ratio of I:$NaOCH_3$:mercaptide 1:2:0.2. After 10 min a spot having the same R_f value as II was observed on the thin layer chromatogram. Periodic checks gave no trace of cleavage products.

Cleavage of 6,7-Dibenzoyl-3-carboxy-4,5-dithiaheptanoic Acid (I) with Sodium Methoxide in Methanol. Isolation of 3,6-Dibenzoyl-1,8-diphenyl-4,5-dithia-1,8-octanedione (II).—A solution of 836 mg (2 mmol) of 6,7-dibenzoyl-3-carboxy-4,5-dithiaheptanoic acid (I) in 65 ml of dry methanol was treated with a solution containing 32.4 mg (6 mmol) of sodium methoxide in 10 ml of methanol. The reaction mixture was stirred at 27° for 5 min and acidified with 6 *N* hydrochloric acid. The solvent was removed *in vacuo* and the resulting solid dried *in vacuo* for 24 hr. The solid was dissolved in a minimum amount of chloroform and applied to a 1 × 36 cm column of silica gel (15 g, 0.05–0.20 mm). The effluent was monitored by thin layer chromatography [solvent system, chloroform (90)–methanol (5)–acetic acid (5)]. Using chloroform as the eluent, the first fraction gave 64 mg (12.5%) of 3,5-dibenzoyl-1,7-diphenyl-4-thia-1,7-heptanedione (IV), mp 188–190° (lit.[4] mp 194–196°).

The second fraction provided 83 mg (15.6%) of 3,6-dibenzoyl-1,8-diphenyl-4,5-dithia-1,8-octanedione (II), mp 111–114°. Recrystallization from methanol raised this to 114–116°. The sample was found to be identical with the lower melting isomer, mp 115–116°, of an authentic sample by mixture melting point determination and infrared spectra comparison.

Elution with ethyl acetate provided 359 mg (30.7%) of starting disulfide I, mp 182–186°. No attempt was made to isolate other cleavage products.

Cleavage of 3,6-Dibenzoyl-1,8-diphenyl-4,5-dithia-1,8-octanedione (II) with 1 Equiv of Potassium Ethoxide.—To a solution of 0.168 g (0.002 mol) of potassium ethoxide in 45 ml of absolute ethanol was added 1.08 g (0.002 mol) of 3,6-dibenzoyl-1,8-diphenyl-4,5-dithia-1,8-octanedione (II, mp 115–116°). The disulfide reacted immediately giving a clear red solution. After 10 min solid formation was observed. The mixture was stirred at 27° for 24 hr. The solid was filtered and washed with water to give 0.53 g (52%) of 3,5-dibenzoyl-1,7-diphenyl-4-thia-1,7-heptanedione (IV), mp 183–186°. Recrystallization from ethanol–chloroform raised the melting point to 195–197° (lit.[4] mp 194–196°). The sample was found to be identical with authentic sample by mixture melting point determination and infrared spectra comparison.

The filtrate from separation of IV was evaporated *in vacuo* leaving a red residue which was triturated in 50 ml of water. Filtration gave an additional 0.20 g (19.6%) of IV, mp 178–184°. The total yield of IV was 0.73 g (71.6%). The aqueous filtrate was treated with carbon dioxide until pH 9 was reached. The solution was evaporated *in vacuo* leaving red solid which was treated with 10 ml of ethanol. The mixture was filtered removing potassium carbonate and the filtrate evaporated *in vacuo* to give 0.18 g (12.6%) of potassium 1,4-diphenyl-2-butene-1,4-dione-2-mercaptide (VIII), mp 119–122° (lit.[13] mp 118–121°). The sample was found to be identical with an authentic sample by infrared spectra comparison.

Acidification of Potassium 1,4-Diphenyl-2-butene-1,4-dione-2-mercaptide (VIII).—To a solution of 1.90 g (0.0062 mol) of potassium 1,4-diphenyl-2-butene-1,4-dione-2-mercaptide (VII) in 50 ml of water was added 6 *N* hydrochloric acid until pH 1 was reached. The resulting turbid mixture was extracted with two 50-ml portions of ethyl ether. The ether extracts were dried and evaporated *in vacuo* leaving a yellow solid which was recrystallized from ethanol–chloroform to give 0.60 g (36.8%) of 3,6-dibenzoyl-1,8-diphenyl-4,5-dithia-2-octene-1,8-dione (V), mp 162–167° (lit.[4] mp 174–180°). The sample was found to be identical with authentic V by infrared spectra comparison.

Cleavage of 3,6-Dibenzoyl-1,8-diphenyl-4,5-dithia-1,8-octanedione (II) with 2 Equiv of Potassium Ethoxide.—To a solution of 0.168 g (0.002 mol) of potassium ethoxide in 20 ml of absolute ethanol was added 0.538 g (0.002 mol) of 3,6-dibenzoyl-1,8-diphenyl-4,5-dithia-1,8-octanedione (II, mp 137°). The disulfide reacted immediately giving a clear red solution. The mixture was stirred at 27° for 24 hr. The solid was filtered and washed with water to give 0.082 g (16.1%) of 3,5-dibenzoyl-1,7-diphenyl-4-thia-1,7-heptanedione (IV), mp 182–185°. Recrystallization from ethanol–chloroform raised the melting point to 193–195° (lit.[4] mp 194–196°).

The filtrate from separation of IV was evaporated *in vacuo* leaving a red residue which was triturated in 50 ml of water. Filtration gave 0.153 g (30.8%) of 1,4-diphenyl-1,4-butanedione (VIII), mp 137–141°. Recrystallization from ethanol raised this to 143–145° (lit.[11] mp 144–145°). The sample was found to be identical with an authentic sample by mixture melting point determination and infrared spectra comparison.

The aqueous filtrate from separation of VIII was treated with carbon dioxide until pH 9 was reached. The solution was evaporated *in vacuo* leaving a red solid which was treated with 20 ml of absolute ethanol. The mixture was filtered removing potassium carbonate and the filtrate evaporated *in vacuo* to give 0.247 g (40.3%) of potassium 1,4-diphenyl-2-butene-1,4-dione-2-mercaptide (VII), mp 117–120° (lit.[13] mp 118–121°).

Treatment of 3,5-Dibenzoyl-1,7-diphenyl-3-thia-1,7-heptanedione (IV) with 1 Equiv of Potassium Ethoxide.—To a solution of 0.168 g (0.002 mol) of potassium ethoxide in 20 ml of absolute ethanol was added 1.04 g (0.002 mol) of 3,5-dibenzoyl-1,7-diphenyl-3-thia-1,7-heptanedione (IV). The sulfide reacted immediately giving a red solution containing a small amount of solid. The mixture was stirred at 26° for 24 hr. The solid was filtered and washed with water to give 0.37 g of a mixture of IV and 1,4-diphenyl-1,4-butanedione (VIII). The mixture was triturated in 20 ml of warm ethanol. Filtration gave 0.22 g (20.9%) of recovery IV, mp 186–190° (lit.[4] mp 194–196°). The filtrate was cooled to give 0.11 g (11.5%) of VIII, mp 142–144° (lit.[11] mp 144–145°).

The original filtrate was evaporated *in vacuo* leaving a red gum which was partitioned between 60 ml of water and 60 ml of ether. The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give an additional 0.16 g (17%) of VIII, mp 138–143°. Total yield of VIII was 0.27 g (28.5%). Recrystallization from ethanol raised the melting point to 143–145° (lit.[11] mp 144–145°).

The aqueous layer was treated with carbon dioxide until pH 9 was reached. The solution was evaporated *in vacuo* to give 0.32 g (25.7%) of potassium 1,4-diphenyl-2-butene-1,4-dione-2-mercaptide (VII), mp 116–119° (lit.[2] mp 118–121°).

Addition of 2-Mercapto-1,4-diphenyl-1,4-butanedione (IX) to Potassium 1,4-Diphenyl-2-butene-1,4-dione-2-mercaptide (VII).—Potassium ethoxide (8.4 mg 0.1 mol) in 0.1 ml of ethanol was added to 270 mg (1 mmol) of IX in 5 ml of ethanol. The mixture was cooled and filtered to give 346 mg of a mixture of 3,5- was added to a solution of 306 mg (1 mmol) of VII in 5 ml of ethanol. After 30 min 32.1 mg (0.125 mmol) of sulfur was added and the mixture stirred at 28°. After 24 hr the mixture dibenzoyl-1,7-diphenyl-4-thia-1,7-heptanedione (IV) and sulfur. The mixture was triturated in 20 ml of acetone. Filtration gave 18 mg of sulfur, mp 115–117°. The filtrate was evaporated *in vacuo* to give 341 mg (67.4%) of IV, mp 176–179°. Recrystallization from ethanol–chloroform raised the melting point to 193–195° (lit.[4] mp 194–196°).

Registry No.—II, 4006-76-2; IX, 16704-51-1; 3-benzoyl-1,6-diphenyl-4-thia-1,6-hexanedione, 16704-52-2.

Di-*t*-Butylthioketene

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Received March 21, 1968

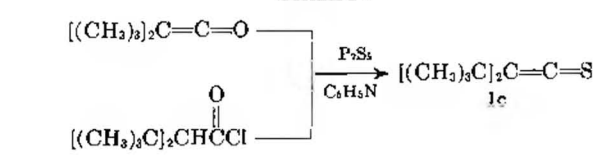
Di-*t*-butylthioketene (1c) may be prepared by heating either di-*t*-butylacetyl chloride or di-*t*-butylketene with phosphorus pentasulfide in pyridine. Thioketene 1c, in contrast to other nonhalogenated thioketenes reported previously, shows no tendency to dimerize or polymerize on storage at room temperature. It may be converted into O esters (3) of di-*t*-butylthioacetic acid by reaction with methyl or ethyl alcohol, into di-*t*-butylthioacetanilide (4) by reaction with aniline, and into the S-oxide by oxidation with hydrogen peroxide or monoperphthalic acid. Spectral evidence indicates that there is a substantial barrier to rotation about the C_1–C_2 bond axis of the esters (3) and the anilide (4).

Although there have been several attempts to prepare thioketenes since the discovery of ketene and its homologs, these have usually given only polymers or dimers.[1–4] Apparently, only two attempts to prepare the monomers have been successful. Howard prepared thioketene (1a) by pyrolysis of *t*-butyl ethynyl sulfide and found it to be unstable at temperatures above −80°.[5] More recently, Raasch prepared bis(trifluoromethyl)thioketene (1b) by pyrolysis of its dimer, 2,4-bis[2,2,2-trifluoro-1-(trifluoromethyl)-ethylidene]-1,3-dithietan, and found that the monomer is stable for many months when kept in glass bottles at room temperature.[6] Raasch attributed the stability of this thioketene to the strongly electron-withdrawing trifluoromethyl groups.

Newman, *et al.*, described the preparation of di-*t*-butylketene and commented upon its extreme unreactivity, which is apparently due to steric hindrance.[7]

In the hope that a similarly substituted thioketene would also be more stable than its less sterically hindered homologs, we undertook the preparation of di-*t*-butylthioketene (1c). We prepared the compound successfully by the reactions summarized in Scheme I.

SCHEME I



When a solution of di-*t*-butylketene in pyridine was refluxed with phosphorus pentasulfide for 15 hr, it was

(1) H. Staudinger, G. Rathsam, and F. Kjelsberg, *Helv. Chim. Acta*, **3**, 853 (1920).

(2) A. Schönberg, E. Frese, and K.-H. Brosowski, *Chem. Ber.*, **95**, 3077 (1962).

(3) A. Schönberg, L. V. Vargha, and H. Kaltschmidt, *Ber.*, **64**, 2582 (1931).

(4) E. U. Elam and H. E. Davis, *J. Org. Chem.*, **32**, 1562 (1967).

(5) F. G. Howard, Jr. (to E. I. du Pont de Nemours and Co.), U. S. Patent 3,035,030 (1962).

(6) M. S. Raasch, *Chem. Commun.*, 577 (1966); M. S. Raasch (to E. I. du Pont de Nemours and Co.), U. S. Patent 3,275,609 (1963).

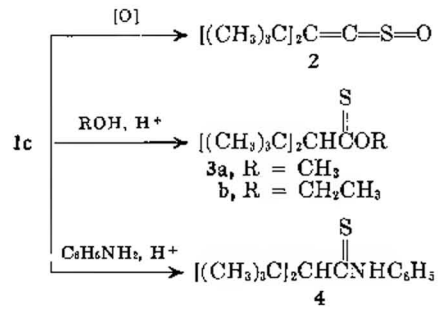
(7) M. S. Newman, A. Arkell, and T. Fununaga, *J. Amer. Chem. Soc.*, **82**, 2498 (1960).

converted smoothly into **1c**, which was isolated in 41% yield by distillation of the reaction mixture.[8] Thioketene **1c** is a deep purple oil, bp 59–60° (6 mm), which showed no tendency to dimerize or polymerize after standing at room temperature for many months, after exposure (in a cyclohexene solution) to sunlight for 20 days, or after irradiation by a medium-pressure mercury lamp for 24 hr. The identity of the compound was established by elemental analysis and by the presence of a strong peak in the mass spectrum at *m/e* 170.1119, corresponding to the molecular ion. The infrared spectrum contained a band at 1745 cm^{-1}, in good agreement with the position previously reported for the thioketene band in **1a** (1750 cm^{-1})[5] and **1b** (1783 cm^{-1}).[6] The nmr spectrum ($CDCl_3$) consisted of a singlet at 1.27 ppm.

A more convenient synthesis of the thioketene, which avoids isolation of di-*t*-butylketene, consists of refluxing the ketene precursor, di-*t*-butylacetyl chloride, with phosphorus pentasulfide in pyridine solution. Under these conditions, **1c** was obtained in 64% yield from the acid chloride.

Although, as already noted, **1c** is a relatively unreactive compound, a number of reactions were carried out successfully (Scheme II). Oxidation with monoperphthalic acid in ether or with hydrogen peroxide in methanol afforded di-*t*-butylthioketene S-oxide (2) in good yield. The structure **2** for this compound was supported by the usual elemental analysis and spectral data. The infrared spectrum contained absorptions at 1074 and 1036 cm^{-1}, which are consistent with the absorptions previously reported for sulfines (S-oxides of thioaldehydes or thio ketones);[9–11] the nmr spectrum ($CDCl_3$) consisted of a singlet at 1.35 ppm.

SCHEME II



Compound **2**, the first reported thioketene S-oxide, or allenic sulfine is also comparatively stable. As far as we are aware, the only sulfine that has been reported which contained only alkyl substituents is thioacetone S-oxide; this oxide was too unstable for isolation.[9] The stability of **2** is comparable with that of aromatic thio ketone S-oxides.[10] Compound **2** was apparently unaffected by methanol or by aqueous sodium bicarbonate solution used to extract by-product phthalic acid. Exactly 1 equiv of per acid was required to oxidize **1c** to **2**, and excess oxidizing agent (perphthalic acid or hydrogen peroxide) did not appear to oxidize or degrade **2**. Attempts to purify **2** by distillation on a Nester–Faust spinning-band column at 0.8 mm led to decomposition, however, and a sample deteriorated after standing at room temperature for a few weeks. The decomposition products were not identified.

There was no evidence of reaction when methyl or ethyl alcohol solutions of **1c** were allowed to stand at room temperature in the absence of catalyst, but there was a slow reaction to give the corresponding O-alkyl thio esters when a trace of hydrochloric acid was added. The esters **3a** and **3b** were characterized by elemental analyses and by high-resolution mass spectra. The mass spectrum of each ester showed prominent peaks corresponding to the expected parent molecular ion. The infrared spectra showed no absorption in the 1675-cm^{-1} region, which would have been expected had any appreciable amount of the isomeric S-alkyl thio ester been present.

Although these esters gave only one peak on two glpc columns (Carbowax 20M and Silicone QF-1) and gave the correct elemental analyses, the resonance in the nmr spectra ($CDCl_3$) due to the methynyl hydrogen unexpectedly appeared as two peaks at δ 3.05 ppm (0.76 H, **3a**; 0.73 H, **3b**) and 2.59 ppm (0.23 H, **3a**) or 2.61 ppm (0.24 H, **3b**). In addition, the resonance due to the methoxyl protons of **3a** was split into two peaks at δ 3.99 ppm (2.37 H) and 3.85 ppm (0.73 H). The assignment of two peaks to the methynyl hydrogen of **3a** was confirmed by the greatly reduced intensity of the peaks at 3.05 and 2.59 ppm in the spectrum of the corresponding methanol-*d* adduct. When a tetrachloroethane solution of the ethanol adduct **3b** was heated to 100°, the peaks at 3.05 and 2.61 coalesced into a broad singlet at 2.98 ppm.

The evidence suggests that this splitting is due to the existence of a substantial barrier to rotation between carbon atoms 1 and 2. The possibility that this splitting is caused by the presence of the isomeric S-alkyl thio ester was rejected because there was no absorption in the carbonyl stretching region of the infrared spectrum, as noted previously. The possibility that the doublet is due to the presence in the sample of enethiol tautomer **5** was rejected because there was no exchange with D_2O and no observable reaction or exchange with trifluoroacetic acid-*d*. Saturation of the absorption at 3.05 ppm in **3b** with a strong radio-frequency field greatly decreased the intensity of the peak at 2.61 ppm, indicating a transfer of spin saturation from the irradiated peak to the peak at 2.61 and providing further evidence that the species are in rapid equilibrium and eliminating an impurity as the source of the additional peak.[12] Finally, the possibility that the splitting is caused by a rapid, reversible equilibrium between monomeric thio ester and a dimer or trimer was also considered and rejected because there was no change in the relative amounts of the components of the doublet with change in concentration.

In an appreciable barrier to rotation about the C_1–C_2 bond of the esters does exist, it is reasonable to expect that the band in the infrared spectrum due to the C–H stretching vibration of the tertiary hydrogen would

(8) An unsuccessful attempt to prepare diphenylthioketene by a similar method has been reported; *cf.* H. Staudinger, "Die Ketene," Ferdinand Enke, Stuttgart, 1912, p 128.

(9) W. A. Sheppard and J. Diekman, *J. Amer. Chem. Soc.*, **86**, 1891 (1964).

(10) J. Strating, L. Thijs, and B. Zwanenburg, *Rec. Trav. Chim.*, **83**, 631 (1964); *Tetrahedron Lett.*, 65 (1966); *Rec. Trav. Chim.*, **86**, 641 (1967); B. Swanenburg, L. Thijs, and J. Strating, *ibid.*, **86**, 577 (1967).

(11) See also a recent review on sulfines and sulfenes: G. Opitz, *Angew. Chem. Intern. Ed. Engl.*, **6**, 107 (1967).

(12) B. M. Fung, *J. Chem. Phys.*, **47**, 1409 (1967).

actually be a doublet. To observe this, the 2-deuterio ester was prepared by the reaction of **1c** with methanol-*d*. The C–D stretching frequency of the product appeared at 2160 cm^{-1}. A shoulder which appeared on this band at 2150 cm^{-1} was considered to be further indication of the presence of rotational isomers. The relative intensities of the main absorption band at 2160 cm^{-1} and the shoulder were of the same order as the intensities of the resonances due to the methynyl proton in the nmr spectrum.

When **1c** was refluxed with aniline in the presence of a trace of sulfuric acid, di-*t*-butylthioacetanilide (**4**) was obtained in 57% yield. This compound, which has not been reported previously, was characterized by elemental analysis and spectral data. Thioanilide **4** was obtained, after repeated recrystallization, as a pale yellow, crystalline solid, mp 130–131.5°. The nmr spectrum of a freshly prepared solution in *o*-dichlorobenzene showed sharp singlets at 1.22 and 2.25 ppm. After this solution had been allowed to stand overnight at room temperature, two resonances were observed in each of these regions, at 1.22, 1.13, and 2.25 and 3.11 ppm. When the freshly prepared solution was heated to 80°, the methyl and methynyl resonances were observed as doublets; at 160° the components of these doublets broadened but did not coalesce. When the solution which had been heated was allowed to cool to room temperature, the methyl and methynyl resonances remained as doublets. Saturation of the methynyl resonance at 3.11 ppm with a strong radiofrequency field at a temperature of 80° caused a large decrease in the intensity of the resonance at 2.25 ppm. As with the esters, this was interpreted as an indication that, at this temperature, the species responsible for the doublet are in rapid equilibrium. When this experiment was repeated after the solution had cooled to room temperature, the intensity of the peak at 2.05 ppm was not affected by saturation of the 3.11-ppm absorption.

Our interpretation of these observations is that the barrier to rotation about the C_1–C_2 bond in the thioanilide **4** is even higher than that in the esters **3a** and **3b**. Apparently, the single conformer obtained by recrystallization is stable for long periods (at least several weeks) in the crystalline state at room temperature, but it is able to isomerize slowly in solution at room temperature or rapidly at 80°.

$R_2C{=}C{=}S$

1a, R = H
b, R = CF_3
c, R = $C(CH_3)_2$

$[(CH_3)_3C]_2C{=}\overset{\overset{SH}{|}}{C}OR$

5

Experimental Section[13]

Preparation of Di-*t*-butylthioketene (1c) from Di-*t*-butylketene.—A mixture of 4.0 g (26 mmol) of di-*t*-butylketene[7] and 4.0 g (18 mmol) of phosphorus pentasulfide in 50 ml of pyridine was refluxed 15 hr. Glpc indicated almost complete conversion of ketene into product. The mixture was cooled and the liquid was decanted. The residue was extracted with two portions of warm pyridine. The combined pyridine solutions were distilled rapidly, without fractionation, at pressures between 60 and 35 mm to remove inorganic material. The purple distillate was concentrated at reduced pressure and distilled on a short Nester–Faust spinning-band column to afford 1.8 g (40.6%) of di-*t*-butylthioketene (**1c**), as a deep purple oil: bp 59–60° (6.0 mm); nmr spectrum ($CDCl_3$), singlet at 1.27 ppm; uv max (cyclohexane) 239 mμ (log ε 3.62), 211 (4.51). There was also a weak visible absorption (cyclohexane) at 570 mμ (ε 7.8). The infrared absorption at 1745 cm^{-1} is consistent with the absorptions attributed to the thioketene group of bis(trifluoromethyl)thioketene (1783 cm^{-1})[8] and thioketene (1750 cm^{-1}).[6] Major peaks in the mass spectrum (70 eV) were at *m/e* (relative intensity) 57 (100), 99 (31), 41 (18), 170.1119 (18, calcd for parent 170.1129), 29 (9).

Anal. Calcd for $C_{10}H_{18}S$: C, 70.52; H, 10.65; S, 18.83. Found: C, 70.53; H, 10.50; S, 19.00.

Preparation of Di-*t*-butylthioketene (1c) from Di-*t*-butylacetyl Chloride.—A mixture of 14.6 g (77 mmol) of di-*t*-butylacetyl chloride,[7] 14.6 g (66 mmol) of phosphorus pentasulfide, and 200 ml of pyridine was stirred at reflux under nitrogen for 21.5 hr. At the end of this period, glpc indicated that the only volatile materials present were pyridine and thioketene **1c**. The pyridine solution was decanted and distilled without fractionation initially at 42 mm; in the latter stages of the distillation, the pressure was reduced to 5 mm. Pyridine was removed by redistillation at 30 mm through a 2 × 25 cm column packed with Penn State metal packing. The purple residue was distilled through a small Vigreux column to afford 8.3 g (63.6%) of thioketene **1c**, bp 60–63° (6 mm). The product was pure, according to glpc, and the glpc retention time and infrared spectrum were identical with those of the product obtained from di-*t*-butylketene.

Oxidation of 1c to Di-*t*-butylthioketene S-Oxide (2). A. With Monoperphthalic Acid.—A 1.0-g (±2%) sample of thioketene **1c** was diluted with 10 ml of anhydrous ether and an 11.2% solution of monoperphthalic acid in ether[14] was added dropwise until the purple color disappeared. This oxidation required 9.47 ml of solution (0.99 equiv of monoperphthalic acid). A duplicate run required 1.06 equiv. Glpc indicated only one significant product and no starting material. The ethereal solution was filtered and then washed with sodium bicarbonate solution to remove by-product phthalic acid. The solution was dried over $MgSO_4$, and the solvent was removed. Analysis of the residue by glpc indicated that the product was approximately 98% one component. Pure **2**, mp 34–35°, was obtained by low-temperature recrystallization from pentane or by preparative glpc: uv max (cyclohexane) 330 mμ (log ε 2.80), 315 (2.88), 251 (4.13), 210 (4.72); mass spectrum (70 eV) *m/e* (rel intensity) 57 (100), 130 (27), 41 (24), 115 (15), 29 (14), 113 (12), 186 (1, parent).

Anal. Calcd for $C_{10}H_{18}OS$: C, 64.46; H, 9.74; S, 17.21. Found: C, 64.62; H, 9.59; S, 17.37.

B. With Hydrogen Peroxide.—A mixture of about 0.1 ml of di-*t*-butylthioketene (**1c**), 0.1 ml of 30% hydrogen peroxide, and 0.6 ml of methanol was allowed to stand at room temperature with occasional shaking. The purple color disappeared after 6 days. Glpc indicated substantially complete conversion into one product having the same retention time as **2**. The compound was isolated by glpc, and its identity was confirmed by comparison of the infrared and mass spectra with those of the product obtained by oxidation of **1c** with monoperphthalic acid. Analysis of the reaction mixture by glpc indicated that it had not changed after standing 1 month.

Addition of Methanol to Thioketene (1c).—Di-*t*-butylthioketene (**1c**) (about 0.3 g or 1.7 mmol) was mixed with two volumes of methanol and allowed to stand 1 day at room temperature. Glpc indicated that no reaction had occurred. A trace of 12 *M* hydrochloric acid was added. After 1 week, the purple color had disappeared and glpc indicated substantially complete conversion to one product. The mixture was diluted with ether and dried over $MgSO_4$, and the solvent was removed under reduced pressure without heating. Th product, O-methyl di-*t*-butylthioacetate (**3a**), was purified by preparative glpc. The proposed structure was supported by infrared absorptions at 2950, 1395, 1366, 1242, 1185, and 1121 cm^{-1} and mass spectrum (70 eV) *m/e* (rel intensity) 131 (100), 57 (75), 146 (42), 41 (19), 202.1401

(13) Melting points were taken on a Thomas–Hoover melting point apparatus in open capillary tubes and are corrected. Ultraviolet spectra were recorded on a Bausch and Lomb Spectronic 505 instrument. Infrared spectra were determined with Perkin-Elmer 421 and 137 spectrophotometers with potassium bromide pellets of solids and with neat samples of liquids on sodium chloride plates. Mass spectra were recorded on a Consolidated Engineering Type 21-620 instrument. Nmr spectra were obtained using a Varian A-60 spectrometer, except for the spectra of **3a–b** and **4**, for which a Varian HA-100 instrument was used.

(14) G. B. Payne, *Org. Syn.*, **42**, 77 (1962).

(16, calcd for parent 202.1391), 99 (13). The nmr spectrum is described in the discussion section.

When the experiment was repeated with methanol-*d*, the infrared spectrum of the product contained a closely spaced doublet at 2160 cm^{-1} which was attributed to the C–D stretching vibration of deuterium attached to carbon atom 2 of the ester.

Anal. Calcd for $C_{11}H_{22}OS$: C, 65.29; H, 10.96; S, 15.85. Found: C, 65.33; H, 10.72; S, 15.63.

Addition of Ethyl Alcohol to Thioketene 1c.—A mixture of 1 g (5.9 mmol) of di-*t*-butylthioketene (1c), 5 ml of absolute ethyl alcohol, and 1 drop of 12 *M* hydrochloric acid was refluxed under nitrogen for 1.5 hr. The reaction mixture was cooled and the solvent was removed under vacuum (0.5 mm) without heating. Glpc on two columns indicated that the resulting pale orange-pink oil was at least 95% pure. This product, O-ethyl di-*t*-butylthioacetate (**3b**), was purified by preparative glpc. The structure assignment was supported by infrared absorptions at 2953, 1391, 1357, 1237, 1172, and 1144 cm^{-1} and by mass spectrum (70 eV) *m/e* (relative intensity) 145 (100), 57 (43), 160 (34), 216.1555 (18, calcd for parent 216.1548), 117 (14), 41 (8). The nmr spectrum is described in the discussion section.

Anal. Calcd for $C_{12}H_{24}OS$: C, 66.61; H, 11.18; S, 14.82. Found: C, 66.74; H, 11.19; S, 15.10.

Addition of Aniline to Thioketene 1c.—There was no evidence of reaction after a mixture of 1 g (5.9 mmol) of di-*t*-butylthioketene (1c) and 10 g (108 mmol) of aniline had been refluxed for 1 hr under nitrogen. One drop of concentrated sulfuric acid was added and reflux was continued for 3 hr. At the end of this time, glpc indicated that all but traces of 1c had reacted, giving mainly one product. The mixture was cooled, diluted with ether, and washed thoroughly with dilute hydrochloric acid and finally with water. The ethereal solution was dried over $MgSO_4$ and concentrated. The residue was recrystallized from cyclohexane to afford 0.79 g of pale yellow needles, mp 130–131.5°. A second crop was obtained, giving total yield of 0.88 g (57%) of di-*t*-butylthioacetanilide (**4**), mp 130–131° after further recrystallization from cyclohexane and hexane. The nmr spectrum ($CDCl_3$) consisted of a methyl singlet at 1.26 ppm (18 H), a methynyl singlet at 2.29 ppm (1 H), and an aromatic multiplet at 7.07–7.55 ppm (5 H). The broad N–H peak at ~8.2–8.8 ppm was not integrated. Results of a more detailed study of the nmr spectrum of an *o*-dichlorobenzene solution of this compound are given in the discussion section. The structural assignment was also supported by infrared absorptions at 3165, 1524, 1295, 1135, 755, and 697 cm^{-1} [15] and by mass spectrum (70 eV) *m/e* (relative intensity) 214 (100), 77 (18), 229 (17), 158 (16), 57 (14), 41 (14), 191 (10), 263 (0.4, parent).

Anal. Calcd for $C_{16}H_{25}NS$: C, 72.95; H, 9.57; N, 5.31; S, 12.17. Found: C, 72.91; H, 9.72; N, 5.44; S, 12.17.

Registry No.—**1c**, 16797-75-4; **2**, 16797-76-5; **3a**, 16797-77-6; **3b**, 16797-70-9; **4**, 16797-78-7.

Acknowledgment.—We thank Dr. E. Bright Wilson, Jr., for a helpful discussion of the nmr spectra of **3a**, **3b**, and **4**, and for suggestions that evidence for the existence of rotamers in **3a** might be observed in the infrared spectrum of the reaction product of **1c** with methanol-*d*.

(15) These are consistent with the thioamide absorptions reported by K. A. Jensen and P. H. Nielsen, *Acta Chem. Scand.*, **20**, 597 (1966).

Synthesis and Photoisomerization of the Stereoisomeric 1,4-Dichlorospiropentanes[1]

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Reduction of 1,1,4,4-tetrachlorospiropentane has afforded *syn*- and *anti*-1,1,4-trichlorospiropentanes, which have been distinguished by their dipole moments. Further reduction of the trichlorospiropentanes has yielded the *syn,syn*-, *syn,anti*-, and *anti,anti*-1,4-dichlorospiropentanes, whose configurations have been assigned from the configurations of the trichlorides which yield them. Photolysis in the gas phase of individual dichlorides has produced interconversion of *syn,syn* with *syn,anti* and *anti,anti* with *syn,anti* presumably by a bond-breaking and reformation process. The direct interconversion of *syn,syn* with *anti,anti*, expected if the excited states have planar carbon skeletons, has not been observed, but a competing polymerization process has made it impossible to determine whether any electronically excited states return to ground state prior to chemical reactions.

Spiropentane (1) has long been known to have a structure with a perpendicular arrangement of the two

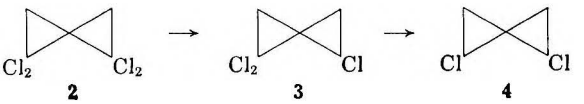


1

rings,[2] but a recent extended Hückel molecular orbital calculation by Hoffmann[3] has ledt o the prediction that the lowest electronically excited states of spiropentane prefer a geometry with all carbons coplanar. Excitation should thus lead to relative rotation of the two rings, and such rotation might be demonstrable in appropriately substituted spiropentanes because of the stereoisomerization that would result if the excited states return to spiropentanes. We report here one such test.

1,1,4,4-Tetrachlorospiropentane (2) was prepared from allene, ethyl trichloroacetate, and sodium methoxide (method of Parham and Bhausar[4]). The infrared and nmr spectra agreed with those reported by Seyferth[5] for 2.

Compound 2 was reduced with tri-*n*-butyltin hydride to a mixture of *syn*- and *anti*-1,1,4-trichlorospiropentanes (**3a** and **3b**, respectively) and *syn,syn*-, *syn,anti*-, and *anti,anti*-1,4-dichlorospiropentanes (**4a**, **4b**, and **4c**, respectively). A very small amount of chlorospiro-



2 3 4

pentane[6] was also formed. Compounds **3a** and **3b** were formed in a ratio of 1:2.9; **4a**, **4b**, and **4c** were formed in a ratio of 0.3:1.6:1. The ratio of trichlorides to dichlorides depended upon the ratio of reagents used, but, within each group, the ratio of isomers was nearly constant over a 100-fold variation of the ratio of tri-*n*-butyltin hydride to 2. The trichlorides and dichlo-

(1) Abstracted from the Ph.D. Thesis of E. G. Alley, University of Illinois, 1968.

(2) J. Donohue, G. L. Humphrey, and V. J. Schomaker, *J. Amer. Chem. Soc.*, **67**, 332 (1945).

(3) R. Hoffmann, *Tetrahedron Lett.*, 3819 (1965).

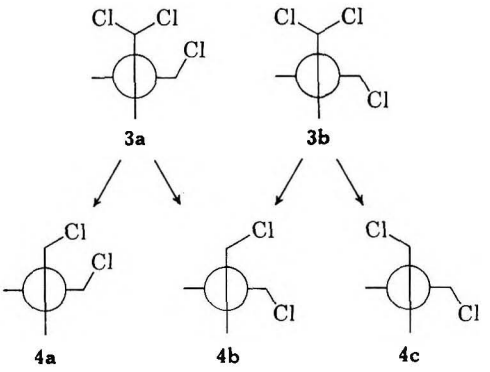
(4) W. E. Parham and M. D. Bhavsar, *J. Org. Chem.*, **29**, 1575 (1964).

(5) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y. Mui, H. D. Simmons, Jr., A. J. H. Treiber, and S. R. Dowd, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).

(6) D. E. Applequist, G. F. Fanta, and B. W. Henrikson, *ibid.*, **82**, 2368 (1960).

rides were analyzed and separated preparatively by glpc.

The dipole moments of the two trichlorides were found to be 1.27 and 3.04 D. The calculated moment for the *anti* isomer is 1.04 D, and that for the *syn* isomer is 3.38 D. The isomer with the moment 1.27 D was therefore assigned the *anti* geometry (**3b**). The configurations of the dichlorides were assigned from the facts that one (**4a**) was formed from reduction of **3a** only, one (**4b**) from both **3a** and **3b**, and one (**4c**) from **3b**



only. The nmr spectra of the dichlorides all showed multiplets for –CHCl– and $-CH_2-$ at δ 3.4–3.6 and 1.1–1.8, respectively, in the expected 1:2 ratios.

An alternative method of reduction of 2 was treatment with *t*-butyllithium in pentane at −110°, followed by addition of isobutyl alcohol. The same products were obtained, but the **3b**/**3a** ratio was just 1.3, and the dichlorides **4a**, **4b**, and **4c** were in the ratio 1.5:2.2:1. This method was therefore the more favorable one for the preparation of the *syn,syn* isomer (**4a**).

If the lowest lying excited electronic states of the dichlorospiropentanes have a geometry with all carbons coplanar, and if the excited states return to ground states of 1,4-dichlorospiropentanes, then isomers **4a** and **4c** should interconvert upon irradiation while isomer **4b** should show no reaction.[7] An important concern, of course, is that the chlorine substituents may have perturbed the spiropentane system in such a way as to change the lowest excited-state geometry, and another possible difficulty is photochemistry involving C–Cl bond breaking. Hope that the experiments would not be rendered invalid for either of these reasons was found in the fact that chlorine substitution does not significantly affect the ultraviolet spectrum of spiropentane, which consists of end absorption only. At 254 mμ, the liquid phase extinction coefficients of spiropentane, 1,4-dichlorospiropentane (mixed **4b** and **4c**), and tetrachlorospiropentane (2) are 0.4, 0.5, and 0.4, respectively.

Photochemical studies of the 1,4-dichlorospiropentanes were made by both sensitized and direct methods. Sensitization was attempted by irradiation of benzene solutions of **4a** and **4c** with 2537-Å light. Benzene has been used to sensitize the isomerization of 1,2-dimethylcyclopropanes.[8] No evidence was found for any isomerization, nor did the amounts of dichlorides present diminish by other reactions. No conclusion can be drawn regarding the geometry of the spiropentane triplet, since it was not possible to show that any energy transfer had occurred.

(7) A single enantiomer of **4b** would show racemization.

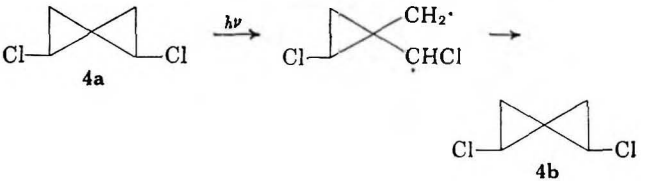
(8) J. A. Bell, *J. Amer. Chem. Soc.*, **87**, 4966 (1965).

Direct photochemical studies of **4a**, **4b**, and **4c** were carried out in the gas phase, because of the low extinction coefficients and hence serious problems with solvent absorption. A zinc resonance lamp, which has 46% of its output at 2138 Å,[9] was used as the light source to take advantage of the improved extinction coefficients at lower wavelength (ϵ 8 at 2150 Å for a mixture of **4b** and **4c** in the liquid phase). Ammonia was used as a chemical actinometer to measure quantum yields.[10]

When **4c** was irradiated in the gas phase until 22% of it had disappeared, mainly by formation of a polymer, a 9% conversion into **4b** was observed. No **4a** could be detected. Likewise, **4a** irradiated until 36% had disappeared gave a 1% conversion into **4b**, but no **4c**. Finally, **4b** was photolyzed to give 3% **4c** and 0.2% **4a**. The pattern of isomers formed is thus exactly contrary to the predictions of extended Hückel theory.

The measurement of quantum yields was complicated greatly by the polymer, which in every case quickly coated the walls of the photolysis chamber, restricting the transmission of light. It was possible to show, nevertheless, that both **4a** and **4c** formed polymer with quantum yields considerably above one. The unfortunate consequence is that it cannot be concluded that any electronically excited dichlorospiropentane molecules returned to ground-state dichlorospiropentanes. Hence, the absence of interconversion of **4a** and **4c** does not rule out the planar excited state predicted by Hoffmann.

The isomerization observed could have involved a secondary chain process, such as chlorine atom transfers.[11] Another possible path, perhaps more likely in view of existing precedent,[12,13] is photochemical cleavage of the 1,2 bond, followed by reclosure of the ring.



Experimental Section[14]

1,1,4,4-Tetrachlorospiropentane.—To a stirred mixture of 10.8 g (0.2 mol) of sodium methoxide and 4.0 g (0.1 mol) of allene in 50 ml of dry olefin-free pentane at 0–15° was added 38.2 g (0.2 mol) of ethyl trichloroacetate in 50 ml of pentane over a period of 0.5 hr. The temperature was maintained at about 10° for 1 hr, and then the mixture was stirred at room temperature for 3 hr. After this time 16.4 g (0.3 mol) of sodium methoxide was added and the mixture cooled to 0°. Ethyl trichloroacetate (57.3 g, 0.3 mol) was added over a period of 0.5 hr, and the temperature maintained at 5–15°. The temper-

(9) T. A. Cutting, "Manual of Spectroscopy," Chemical Publishing Co., New York, N. Y., 1949, p 185.

(10) E. O. Wiig, *J. Amer. Chem. Soc.*, **57**, 1559 (1935).

(11) J. I. G. Cadogan, D. H. Hey, and P. G. Hibbert, *J. Chem. Soc.*, 3939 (1965).

(12) G. R. De Mare, L. G. Walker, O. P. Strausz, and H. E. Gunning, *Can. J. Chem.*, **44**, 457 (1966). These authors interpret the photosensitized rearrangement and decomposition of spiropentane in terms of initial cleavage of the 1,3 bond, but their results seem equally consistent with initial 1,2 cleavage.

(13) J. J. Gajewski, *Chem. Commun.*, 920 (1967).

(14) Microanalyses were done by Mr. Josef Nemeth and associates. Nmr spectra were recorded on a Varian Model A-60 instrument; infrared spectra on Perkin-Elmer Models 137, 237, and 521; and ultraviolet spectra on Bausch and Lomb Model 505 and Cary Model 15 spectrophotometers.

ature was then maintained at 10–15° for 1 hr and then the mixture stirred at room temperature for 3 hr. Water (100 ml) was added and this mixture stirred with 80 g (2.0 mol) of sodium hydroxide in 500 ml of water for 2 hr, at reflux temperature. The pentane layer was removed and dried. Distillation of the dried solution yielded 10.0 g (50%) of a colorless liquid, bp 43–44° (1.8 mm). This material was shown by glpc (10% Apiezon L on Anakrom ABS at 150°) to be 98% 1,1,4,4-tetrachlorospiropentane.

Runs up to twice the size of this one were successful. During the addition of the ethyl trichloroacetate, an exothermic reaction occurred and in the larger runs the temperature was more difficult to control. If the temperature exceeded 20°, the reaction was uncontrollable.

The product from these syntheses was further purified by preparative glpc (20% Apiezon L on Chromosorb P). The flow rate was 75–100 ml/min. The first 20 min of each peak, when 0.5-ml injections were made, was not collected. The refractive index of this purified material was n^{26}D 1.5014 (lit.[5] n^{24}D 1.5447).

Reduction of 1,1,4,4-Tetrachlorospiropentane.[15]—A solution of 8.24 g (0.04 mol) of 1,1,4,4-tetrachlorospiropentane and 14.00 g (0.048 mol) of tri-*n*-butyltin hydride was heated at 135–140° for 30 min. Distillation of the reaction mixture yielded 3.4 g, bp up to 45° (2 mm), and 2.3 g, bp 45–60° (2 mm). The two fractions were separated by glpc (20% tricresyl phosphate on Chromosorb P at 125°) into *anti,anti-* and *anti,syn*-1,4-dichlorospiropentanes (**4c** and **4b**), *anti*-1,1,4-trichlorospiropentane (**3b**), *syn,syn*-1,4-dichlorospiropentane (**4a**), and *syn*-1,1,4-trichlorospiropentane (**3a**), in that order of elution. The retention times at a flow rate of 60 ml/min were 19, 21, 26, 43, and 69 min, respectively.

Anal. Calcd for $C_5H_6Cl_2$: C, 43.79; H, 4.38. Found for a mixture of **4b** and **4c**: C, 43.86; H, 4.48. Found for **4a**: C, 44.01; H, 4.53. Calcd for $C_5H_5Cl_3$: C, 34.98; H, 2.92. Found for **3b**: C, 35.28; H, 2.92. Found for **3a**: C, 35.09; H, 2.99.

Infrared and nmr spectra are recorded elsewhere.[1] Infrared bands of particular value for identification (medium or strong bands below 1000 cm^{-1} in CCl_4) are as follows: **4a**, 645, 687, 835, 927, and 978 cm^{-1}; **4b**, 655, 681, 840, 888, 911, 937 and 963 cm^{-1}; **4c**, 654, 861, 882, and 929 cm^{-1}; **3a**, 659, 840, 891, 930, and 948 cm^{-1}; **3b**, 678, 870, and 916 cm^{-1}.

Dipole Moments of the Two 1,1,4-Trichlorospiropentanes.—The measurements were all made at 293°K. The solutions used to obtain the dielectric constant data were in benzene which had been purified by partially freezing it three times and then passing this benzene through a column of molecular sieves immediately before its use. The slope of the line obtained when a plot of mole fraction *vs.* dielectric constant was made for the *anti*-trichloride was 1.4 and for the *syn*-trichloride 12.4. The slope of the line obtained when the density of these solutions was plotted *vs.* mole fraction of trichloride was for the *anti*-trichloride 0.26 and for the *syn*-trichloride 0.25. The refractive index for the *anti*-trichloride was 1.4950 and for the *syn*-trichloride 1.5025. The density of the *anti*-trichloride was 1.333 g/cm^3, and for the *syn*-trichloride 1.366 g/cm^3. From these data and the known values for the dielectric constant,[16] molecular weight, and density of benzene the dipole moments were calculated. These calculated values were for the *anti*-trichloride μ = 1.270 and for the *syn*-trichloride μ = 3.040.

Reduction of *anti*-1,1,4-Trichlorospiropentane.—*anti*-1,1,4-Trichlorospiropentane (100 μl) and 220 μl of tri-*n*-butyltin hydride in a tube made by sealing both ends of a 6-in. piece of 5-mm Pyrex tubing were heated in an oil bath at 140° for 1 hr. The glpc retention times of the components of this mixture were compared with the retention times of the three 1,4-dichlorospiropentanes from reduction of **2**. The mixture contained only the first two dichlorides in order of elution, in the ratio 1:0.9. The second was collected and further identified by its infrared spectrum.

Reduction of *syn*-1,1,4-Trichlorospiropentane.—The reduction of the *syn*-trichloride was accomplished exactly as with the *anti* isomer. Glpc showed that only the second and third dichlorospiropentanes in order of elution were present, in the ratio 2.8:1. The first of these was collected and further identified by its infrared spectrum.

(15) D. Seyferth, H. Yamazaki, and D. L. Alleston, *J. Org. Chem.*, **28**, 703 (1963).

(16) R. Mecke and K. Rosswog, *Z. Electrochem.*, **60**, 47 (1956).

Reduction of 1,1,4,4-Tetrachlorospiropentane with *t*-Butyllithium.—To a stirred solution of 2.06 g (0.01 mol) of 1,1,4,4-tetrachlorospiropentane in 80 ml of tetrahydrofuran, 20 ml of ether and 20 ml of pentane at −110°, under an argon atmosphere, was added 20 ml (0.032 mol) of a 1.59 *M* solution of *t*-butyllithium in pentane at a rate such that the temperature did not exceed −100°. The solution was stirred 1 hr at −100 to −110° and then 20 ml of isobutyl alcohol was added at −110°. The solution was washed five times with water and the organic layer dried with sodium sulfate. The solution was analyzed by glpc. Retention times were used to identify the various components. The analysis showed that *anti,anti-*, *anti,syn-*, and *syn-syn*-1,4-dichlorospiropentanes and *anti-* and *syn*-1,1,4-trichlorospiropentanes were in the ratio 2.1:4.6:3.4:1.3:1.0 in this mixture.

After the solvents were removed, preparative glpc yielded 199 mg of a mixture of *anti,anti-* and *anti,syn*-1,4-dichlorospiropentanes, 77 mg of *syn,syn*-1,4-dichlorospiropentanes, and 48.5 mg of *anti*-1,1,4-trichlorospiropentane.

Photolysis of 4a and 4c in Benzene.—A solution of 23.3 mg of *syn,syn*-1,4-dichlorospiropentane, 6.6 mg of *n*-decane, and 0.5 ml of benzene was prepared. This mixture was irradiated at 2537 Å for 3 hr in a Srinivasan–Griffin reactor. Potassium ferrioxalate actinometry showed that an average of 2.6 × 10^{16} photons/sec passed through the reactor. The reaction mixture was analyzed by glpc initially and after 3 hr. No peaks were observed in the 3-hr sample that were not present in the 0-hr sample. The glpc analysis showed that 101% of the *syn,syn*-1,4-dichlorospiropentane was still present after 3 hr of irradiation.

In a similar experiment, the photolysis of *anti,anti*-1,4-dichlorospiropentane in benzene, for 8 hr, caused no change in the composition of the mixture as determined by glpc.

Gas Phase Photolysis of 4a, 4b, and 4c.—The photolysis chamber was a cylindrical quartz vessel with an axial hole for insertion of the zinc resonance lamp (Phillips 93196E, 25 W). Surrounding the chamber externally was a concentric cylindrical chamber for the ammonia actinometer.[10] Both chambers were connected to a high-vacuum system, which permitted efficient transfers of materials into and out of the chambers and accurate measurement of the nitrogen and hydrogen produced in the photolysis of ammonia. Details of the apparatus and its use are reported elsewhere.[1]

Each sample was purified before photolysis by treatment of a cyclohexane solution of the compound with 1% alkaline potassium permanganate solution for 15–20 min at 0°, followed by preparative glpc (20% Apiezon L on Chromosorb P at 150°). After introduction into the high-vacuum system, each sample was degassed by three freeze–thaw–pump cycles, with Dry Ice and isopropyl alcohol used as the freezing mixture.

In all cases, accurate measurements of light absorbed by the spiropentanes were made very difficult by the rapid formation of a polymer on the walls of the reaction chamber. As a result, it was necessary to measure the light passing through the empty (pumped down) chamber before, after, and even in the middle of a run to obtain an effective light intensity, from which the light absorbed could be estimated by comparison with actinometric measurements made during photolysis (*i.e.*, with spiropentane in the photolysis chamber).

The best datum obtained on **4c** was a quantum yield of at least 8 for disappearance of **4c** in a run in which 38 ± 7% of the **4c** had disappeared (glpc analysis) to form 7.5 ± 0.7% of **4b** and about 30% of polymer (measured by difference). The implied quantum yield of greater than 1 for formation of **4b** is not to be accepted without reservation, in view of the large errors introduced by the polymer formation. In photolysis of **4a**, a quantum yield of at least 4.1 was observed for disappearance of **4a** in a run in which 36 ± 4% of the **4a** was consumed and about 1% of **4b** was formed.

Registry No.—**3a**, 16717-31-0; **3b**, 16717-32-1; **4b**, 16717-34-3; 1,1,4,4-tetrachlorospiropentane, 3781-45-1.

Acknowledgment.—This work was supported in part by the National Science Foundation and in part by the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is made to the National Science Foundation and to the donors of the Petroleum Research Fund.

Tetrazolinyl Radicals[1]

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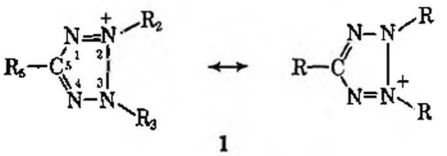
Received February 12, 1968

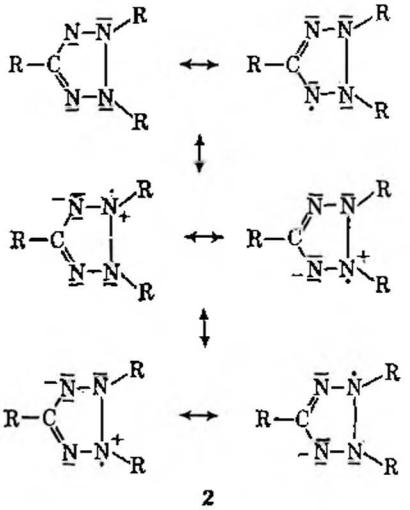
The electron spin resonance spectra of tetrazolinyl radicals are clarified and the structure is unequivocally assigned as cyclic.

We have previously reported the formation of a quite stable radical (not destroyed by oxygen) by the oxidation of formazans (RN=NCR=NNHR), by reduction of tetrazolium salts **1**, or by disproportionation



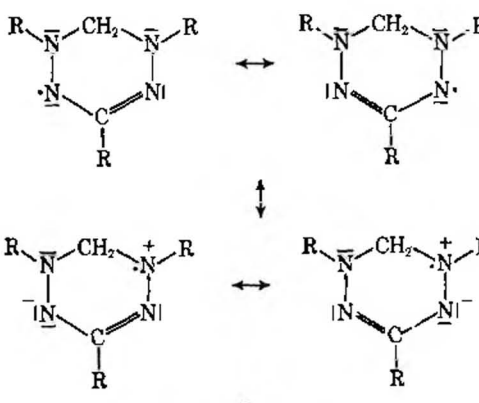
1

of a mixture of the two.[2] We now present further evidence in support of the cyclic tetrazolinyl structure **2** for this radical. In **2** one might expect to find that



2

all four nitrogen atoms have appreciable spin density since for the verdazyl radicals (**3**) the four nitrogen atoms are found to be nearly equivalent by esr spectroscopy.[3] Both **2** and **3** contain seven π electrons. On the other hand the open-chain structure isomeric with **2** contains only five π electrons. Moreover, it is obvious that for this structure (**4**) the spin should be concentrated on the terminal nitrogen atoms.



3

$$RN{=}NCR{=}N\dot{N}R \leftrightarrow RN{=}N\dot{C}RN{=}NR \leftrightarrow R\dot{N}N{=}CRN{=}NR$$

4

The previously reported spectra for the tetrazolinyl radicals in dimethyl sulfoxide solution were poorly resolved. The spectra showed nine broad lines separated by 6–7 G, a pattern consistent with four nearly equivalent nitrogen atoms. We have now obtained much better resolved spectra in benzene solution by abstraction of a hydrogen atom from the formazan by di(*p*-tolyl)nitrogen.[4,5] Figure 1 gives *ca.* one-half of the esr spectrum of 2,3-diphenyl-5-carbethoxytetrazolinyl radical thus formed. This spectrum demands a^N = 8.00, 8.00, 5.55, 5.55 G and a^H = 1.0 (six hydrogens) and 0.5 G (four hydrogens). Figure 2 gives the spectrum for 2,3-bis(3,5-dichlorophenyl)-5-carbethoxytetrazolinyl radical. This spectrum requires a^N = 7.5, 7.5, 5.7, 5.7 G and a^H = 0.86 (six hydrogens) G. See Figure 3 for the esr spectrum of 2,3-diphenyl-5-carbethoxytetrazolinyl radical substituted with ^{15}N at N-1 and N-4. The spectrum now requires a^{14N} = 8.0, 8.0; a^{15N} = 7.6, 7.6; a^H = 1.0 (six hydrogens) and 0.5 (four hydrogens) G. For 2,3-bis(3,5-dichlorophenyl)-5-carbethoxytetrazolinyl radical substituted with ^{15}N at N-1 and N-4, nitrogen splittings of 8.1 (^{15}N) and 7.5 (^{14}N) G were observed. The largest value of a^{14N} in both of the tetrazoylinyl radicals is found to be at N-2 and N-3. However, the value of a^N at N-1 and N-4 is appreciable. Substitution of ^{15}N (I = $^1/_2$) for ^{14}N (I = 1) causes an increase in a^N of 1.4 ± 0.03 fold (the gyromagnetic ratio of $^{15}N/^{14}N$ is 1.40).

Hyperfine splitting constants for these and other radicals are summarized in Table I.

McLachlan molecular orbital calculations have been performed for structures **5** and **6** as a final verification of our structural assignment. We have used the same parameters employed in calculations of the verdazyls.[6]

$$\beta_{N_bN_c} = \beta_{CC},\ \alpha_N = \alpha_C + 1.2\beta_{CC};\ \beta_{C_aN_b} = 1.2\,\beta_{CC};\ \beta_{N_cC_d} = \beta_{CC}$$

The results are summarized in Table II and compared with spin densities (ρ) calculated from the experimental hyperfine splitting constants by use of the McConnell equation $a^H = -23.7\rho^C$ and the Stone and Maki equation $a^N = 28.6\rho^N$.[7]

(1) This work was supported by a grant from the National Science Foundation (GP-6402X).

(2) O. W. Maender and G. A. Russell, *J. Org. Chem.*, **31**, 442 (1966).

(3) R. Kuhn and H. Trischmann, *Monatsh. Chem.*, **95**, 457 (1964); F. A. Neugebauer, *ibid.*, **98**, 231 (1967).

(4) F. D. Chataway and H. Ingle, *J. Chem. Soc.*, **67**, 1090 (1895); H. Wieland and S. Gambarjan, *Chem. Ber.*, **39**, 1499 (1906); H. Wieland and H. Lecher, *Ann. Chem.*, **392**, 156 (1912).

(5) F. A. Neugebauer, *Tetrahedron Lett.*, 2129 (1968).

(6) P. H. H. Fischer, *Tetrahedron*, **23**, 1939 (1967).

(7) E. W. Stone and A. H. Maki, *J. Chem. Phys.*, **39**, 1635 (1963).

TABLE I

HYPERFINE SPLITTING CONSTANTS OF TETRAZOLINYL RADICALS IN BENZENE SOLUTION

$R_2 = R_5$	R_5	$a_{1,4}^{14N}$	Registry No.	$a_{1,4}^{15N}$	Registry No.	$a_{2,3}^{N}$	a^{H}	g
C_6H_5	$C_2H_5O_2C$	5.55	16626-61-2	7.6	16626-68-9	8.00	1.0 (6), 0.5 (4)	2.0037
C_6H_5	$(CH_3)_3CO_2C$	5.50	16626-62-3	...		7.95	0.9 (6), 0.45 (4)	2.0037
3,5-$Cl_2C_6H_3$	$C_2H_5O_2C$	5.70	16626-63-4	8.1	16659-92-0	7.50	0.9 (6)	2.0038
4-$CH_3OC_6H_4$	$C_2H_5O_2C$	5.45	16626-64-5	...		8.65	1.0 (4), 0.5 (4)	
4-$C_2H_5O_2CC_6H_4$	$C_2H_5O_2C$	5.40	16626-65-6	...		7.25	0.95 (4), 0.5 (4)	2.0038
4-$NO_2C_6H_4$	$C_2H_5O_2C$	5.45	16626-66-7	...		6.65	Not assigned	
C_6H_5	C_6H_5	5.6	16626-67-8	8.0	16626-69-0	7.5	Not resolved	2.0037

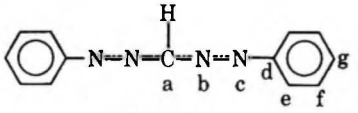
TABLE II

CALCULATED SPIN DENSITIES FOR 2,3-DIPHENYLTETRAZOLINYL RADICAL

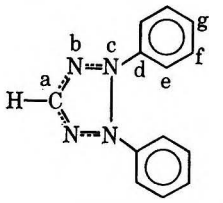
Position	Experimental[a] a, G	Experimental[a] $\lvert\rho_\pi\rvert$	Calcd ρ_π (for **5**)	Calcd ρ_π (for **6**)	Calcd ρ_π (for **6a**)	Calcd ρ_π (for **6b**)
a	...	...	0.1264	−0.0609	−0.0521	−0.0374
b	5.5	0.19	−0.0505	0.2275	0.1720	0.1016
c	8.0	0.28	0.2420	0.2271	0.2477	0.2464
d	...	...	0.0159	−0.0352	−0.0331	−0.0169
e	1.0	0.042	0.0905	0.0568	0.0660	0.0797
f	0.5	0.021	−0.0297	−0.0252	−0.0264	−0.0283
g	1.0	0.042	0.1080	0.0482	0.0693	0.0848

[a] For 2,3-diphenyl-5-carbethoxytetrazolinyl radical.

The data of Table II support the assignment of structure as **6** rather than **5**. This is also consistent



5, 17 π electrons



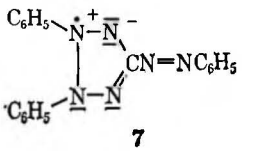
6, 19 π electrons, $\beta_{N_cN_c} = 0$

6a, 19 π electrons, $\beta_{N_cN_c} = 0.4\beta_{CC}$

6b, 19 π electrons, $\beta_{N_cN_c} = 1.0\beta_{CC}$

with the lack of an effect of the substituent R_5 upon $a_{1,4}^{N}$ (see Table I), since for **5** $\rho_{C\text{-}5}$ is large, but for **6** $\rho_{C\text{-}5}$ is small. On the other hand $a_{2,3}^{N}$ is affected by the substituent on N-2 and N-3. The value of $a_{2,3}^{N}$ varies from 8.65 G with R = *p*-anisyl to 8.0 with R = phenyl, 7.50 with R = 3,5-dichlorophenyl, 7.25 with R = *p*-carbethoxyphenyl, and 6.65 with R = *p*-nitrophenyl. Here again we encounter an example wherein spin density is correlated by the Hammett σ constant.[8]

In the calculations summarized in Table II all the heavy atoms in **5** and **6** were assumed to be sp^2 hybridized since these compounds are hydrazyl derivatives. In diphenylpicrylhydrazyl the nitrogen atoms have bond angles of ~120°, consistent with sp^2 hybridization.[9] It is possible to conceive of electronic configurations, or equilibria between electronic configurations, for an acyclic radical derived from the tetrazolium salt which would predict appreciable spin density at all four nitrogen atoms (for example, with 19 π electrons). However, these configurations do not appear to be ground-state configurations. Moreover, the observation that *only* four nitrogen atoms show appreciable hyperfine splittting in the esr spectrum of **7** derived from N,N′-diphenyl-C-phenylazoformazan[5] is completely inconsistent with this hypothesis and demands the cyclic structure for **6** and **7**.



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(8) H. LeMaire, Y. Marechal, R. Ramasséul, and A. Rassat, *Bull. Soc. Chim. Fr.*, 372 (1965).

(9) D. E. Williams, *J. Amer. Chem. Soc.*, **89**, 4280 (1967).

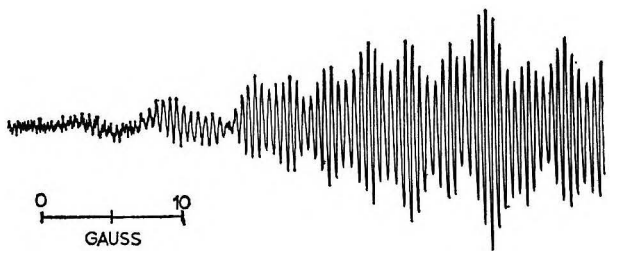

Figure 1.—Slightly more than one-half of the first derivative esr spectrum of 2,3-diphenyl-5-carbethoxytetrazolinyl radical in benzene solution.

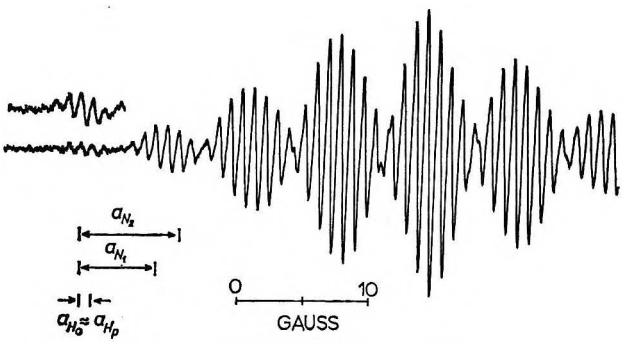

Figure 2.—Slightly more than one-half of the first derivative esr spectrum of 2,3-bis[3,5-dichlorophenyl]-5-carbethoxytetrazolinyl radical in benzene solution.

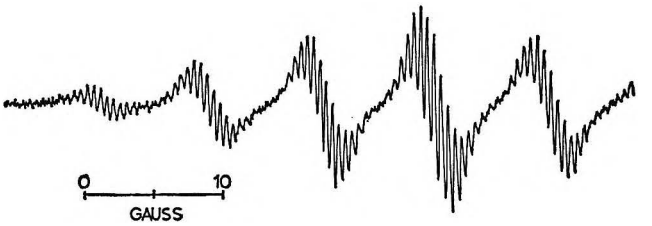

Figure 3.—Slightly more than one-half of the first derivative esr spectrum of 2,3-diphenyl-5-carbethoxytetrazolinyl radical substituted with ^{14}N at positions 1 and 4.

Experimental Section

The C-carbethoxyformazans were obtained by standard procedures.[10]

N,N′-Bis(4-methoxyphenyl)-C-carbethoxyformazan had mp 131–132°. *Anal.* Calcd for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.44; H, 5.59; N, 15.91.

N,N′-Bis(4-nitrophenyl)-C-carbethoxyformazan had mp 208–210°. *Anal.* Calcd for $C_{16}H_{20}N_6O_6$: C, 49.74; H, 3.65; N, 21.75. Found: C, 49.68; H, 3.53; N, 22.45.

The ^{15}N-labeled N,N′-diphenyl-C-carbethoxyformazan and N,N′-bis(3,5-dichlorophenyl)-C-carbethoxyformazan were prepared by the same procedure using $Na^{15}NO_2$ for the diazotization of aniline or 3,5-dichloroaniline.

The ^{15}N-labeled N,N′,C-triphenylformazan was prepared by the reaction of labeled benzene diazonium chloride (aniline and $Na^{15}NO_2$) with malonic acid.[11]

The tetrazolinyl radicals were generated by reaction of 0.2 ml of the formazan (0.001 *M*) in benzene with 0.2 ml of a 0.005 *M* solution of tetra-*p*-tolylhydrazine in benzene. The mixture was deoxygenated in a fused silica esr cell by a stream of prepurified nitrogen for 10 min. After closing the cell the mixture was heated to 60° for 10 sec (or the mixture was allowed to stand for 30 min at room temperature). The red-brown color of the solution changed into greenish brown after completion of the reaction.

Registry No.—N,N′-Bis(4-methoxyphenyl)-C-carbethoxyformazan, 16626-70-3; N,N′-bis(4-nitrophenyl)-C-carbethoxyformazan, 16626-71-4.

(10) H. von Pechmann, *Chem. Ber.*, **25**, 3175 (1892); F. A. Neugebauer, *Monatsh. Chem.*, **98**, 241 (1967).

(11) F. A. Neugebauer and B. Küchler, *Ann. Chem.*, **706**, 104 (1967).

Solvent Effects on the Oxidation of Alkyl Radicals by Lead(IV) and Copper(II) Complexes

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Received January 15, 1968

Oxidative decarboxylation of acids by lead(IV) acetate has been used to study solvent effects on the oxidation alkyl radicals by Pb^{IV} species. In the presence of copper catalyst, the rapid oxidation of alkyl radicals by Cu^{II} overwhelms the oxidation by Pb^{IV}. In both cases, alkenes (elimination) and alkyl esters (substitution) are products of electron-transfer oxidation of alkyl radicals by either Pb^{IV} or Cu^{II} oxidants. Homoallylic C_4H_7 radicals were chosen for study, since they represent optimum examples in which to observe these competing oxidative processes. Oxidative elimination of cyclobutyl radicals affords cyclobutene, whereas oxidative substitution produces a mixture of cyclobutyl, cyclopropylmethyl, and allylcarbinyl esters. Solvent effects on oxidative elimination and substitution of cyclobutyl radicals by Pb^{IV} as well as Cu^{II} have been scrutinized in order to differentiate these oxidants. Pb^{IV} is rather insensitive to solvent changes, and oxidative substitution is the preferred course of oxidation. The oxidation of cyclobutyl radicals by Cu^{II} species is highly dependent on solvent. In ethyl acetate or benzene, oxidative elimination to cyclobutene persists, whereas in acetonitrile oxidative substitution results. The dichotomy between oxidative elimination and substitution is resolved by a general mechanism which generally pertains to the oxidation of alkyl radicals by Pb^{IV} and Cu^{II}.

The decarboxylation of various acids by lead(IV) tetraacetate in benzene solutions has been induced thermally and photochemically.[1] A free-radical chain process prevails under these conditions, and the relevant propagation sequence has been postulated[1-3] as shown in eq 1 and 2. The kinetic chain length of the

$$R\cdot + Pb^{IV}O_2CR \longrightarrow R_{ox} + Pb^{III}O_2CR \quad (1)$$

$$Pb^{III}O_2CR \longrightarrow Pb^{II} + CO_2 + R\cdot, \text{ etc.} \quad (2)$$

R_{ox} = alkene, ester

decarboxylation is principally related to the facility of the oxidation step (eq 1). Decarboxylation of primary and secondary acids are relatively slow and exhibit short chain lengths. In contrast, tertiary and those acids which yield radicals such as benzyl and allyl, decarboxylate readily and have long chain lengths.[1,4] Generally speaking, primary and secondary alkyl radicals are not readily oxidized by Pb^{IV}, and alkanes (RH) usually result during decarboxylation of such acids by Pb^{IV}. Long chain lengths in decarboxylation are primarily correlated with high yields of oxidation products (R_{ox}).

By the same token, the decarboxylation of primary and secondary acids is markedly catalyzed by copper salts,[2,5] whereas the decarboxylation of tertiary and related acids is little affected under the same conditions.[4] Copper catalysis has been attributed to the efficient interception of alkyl radicals by Cu^{II} (eq 3) and subsequent reduction of Pb^{IV} (eq 4). In this manner,

$$R\cdot + Cu^{II} \longrightarrow R_{ox} + Cu^{I} \quad (3)$$

$$Cu^{I} + Pb^{IV}O_2CR \longrightarrow Cu^{II} + Pb^{III}O_2CR, \text{ etc.} \quad (4)$$

the comparatively slow oxidation of primary and secondary alkyl radicals by Pb^{IV} (eq 1) can be circumvented, and long kinetic chain lengths for decarboxylation and high yields of oxidation products ensue. From these and other observations, it has been concluded that the rates of oxidation of alkyl radicals by Pb^{IV} are roughly in the following order: $Ph_3C\cdot$ > allyl > *t*-alkyl ≫ *sec*-alkyl > primary alkyl.[1,3,4]

The kinetics and products of oxidation of alkyl radicals by Cu^{II} can also be studied by an independent method using diacyl peroxides as the source of radicals.[6] Such measurements have shown that the rates of oxidation of alkyl radicals by Cu^{II} are very fast ($k_2 > 10^8$ l. m^{-1} sec^{-1}) and are generally not highly dependent on structure.[7]

Studies of the oxidation of alkyl radicals by both Pb^{IV} and Cu^{II} using these methods indicate that two princi-

(1) J. Kochi, J. Bacha, and T. Bethea, *J. Amer. Chem. Soc.*, **89**, 6538 (1967).

(2) J. Kochi, *ibid.*, **87**, 3609 (1965).

(3) In the following presentation, coordination around Pb and Cu will not be given explicitly, except where pertinent to the discussion.

(4) J. Bacha and J. Kochi, *J. Org. Chem.*, **33**, 83 (1968).

(5) J. Bacha and J. Kochi, *Tetrahedron*, **24**, 2215 (1968).

(6) J. Kochi, *J. Amer. Chem. Soc.*, **85**, 1958 (1963); J. Kochi and A. Bemis, *Tetrahedron*, in press.

(7) J. Kochi and R. Subramanian, *J. Amer. Chem. Soc.*, **87**, 4855 (1965).

TABLE I

THERMAL AND PHOTOCHEMICAL DECARBOXYLATION OF CYCLOBUTANECARBOXYLIC ACID[a]

Initiation	Solvent PhH/HOAc (v/v)	Cu^{II}, M	Py, M	Products, mole %[b]							Sum of C_4H_7[c]
						Total acetate					
Thermal	95/0	0.0051	0	67	0.5[d]	4	(6)	(43)	(51)	N.D.	72
Photochem	95/0	0.0051	0	75	0.5	3	(6)	(42)	(52)	N.D.	79
Thermal	75/20	0.0051	0	38	0.4[d]	15	(6)	(41)	(53)	N.D.	53
Photochem	75/20	0.0051	0	58	0.4	17	(5)	(41)	(54)	N.D.	75
Thermal	95/0	0	0.10	1	4	37[e]	(5)	(46)	(49)	31	73
Photochem	95/0	0	0.10	4	8	44[f]	(5)	(44)	(51)	19	75
Thermal	15/20[g]	0.0051	0.066	13	2	36	(6)	(42)	(52)	N.D.	51
Photochem	15/20[g]	0.0051	0	2	8	64	(3)	(47)	(50)	N.D.	74

[a] In solutions containing 0.10 M Pb^{IV} and 0.52 M cyclobutanecarboxylic acid (5% by vol.). Thermal at 80°, photochemical at 30°, and 3500 Å. [b] Based on moles/mole of Pb^{IV} irrespective of oxidation state. Values in parentheses represent relative yields. N. D. = not determined. [c] Sum of all C_4H_7 fragments does not represent optimum when all products not analyzed. [d] *Ca.* 0.5% 1,3-butadiene. [e] Includes 15% acetates and 22% cyclobutanecarboxylates (cyclobutyl, 42%, cyclopropylmethyl, 54%, and allylcarbinyl, 4%). [f] Includes 17% acetates and 27% cyclobutanecarboxylates (cyclobutyl, 41%, cyclopropylmethyl, 55%, and allylcarbinyl, 4%). [g] Acetonitrile, 60%.

pal types of products are formed: alkenes and alkyl esters. These products are *formally* derived by 1-equiv oxidation of alkyl radicals according to the standard (half-cell) reactions given by eq 5 and 6, respectively.

I. Oxidative elimination

$$R\cdot \longrightarrow R(-H) + H^+ + \epsilon \qquad (5)$$

II. Oxidative substitution

$$R\cdot + HO_2CR \longrightarrow RO_2CR + H^+ + \epsilon \qquad (6)$$

Oxidation of most primary and secondary alkyl radicals by Cu^{II} usually affords alkene (eq 5).[8] Allylic radicals on oxidation produce only esters (eq 6),[9] but benzylic,[10] homoallylic,[11] and *t*-alkyl radicals usually form a mixture of elimination and substitution products. Furthermore, alkenes generated in the former cases are generally free from rearranged isomers, but esters from oxidative substitution in the second category are often extensively rearranged. The oxidations (I and II) have been classified as *electron-transfer* processes,[12] and two parallel routes have been postulated.[11]

Some preliminary studies (*vide infra*) showed that the copper-catalyzed oxidative decarboxylation of cyclobutanecarboxylic acid by Pb^{IV} was highly dependent on solvent. Thus, in acetonitrile a mixture of homoallylic esters was generated in excellent yields (>70%), but in benzene solutions under similar conditions, cyclobutene was formed in 75% yield. In this paper, we wish to scrutinize the effect of solvents generally on both oxidative decarboxylation of acids by Pb^{IV} and the decarboxylation catalyzed by Cu^{II} salts. Solvent effects are operative in the former through oxidation of alkyl radicals by Pb^{IV} species (eq 1), and in the latter through oxidation by Cu^{II} species (eq 3). The homoallylic carboxylic acids, particularly cyclobutanecarboxylic acid,[13] were especially selected for detailed study because they presented optimum opportunities to examine the effects of solvent on a number of reactions, which often occur concurrently during oxidation of radicals, *viz.*, oxidative elimination I, oxidative substitution II, rearrangement, hydrogen transfer (reduction to alkanes), and aromatic substitution. In addition, various solvents facilitate decarboxylation of acids by Pb^{IV} even at room temperatures (*vide infra*). It is hoped that these studies will shed light on the general mechanism of the oxidation of alkyl radicals by Pb^{IV} as well as Cu^{II} complexes.

Results

A standard procedure was adopted for the study of solvent variation on oxidative decarboxylation. A stock solution of 0.1 M lead(IV) tetraacetate and 0.4 M carboxylic acid (RCO_2H) was made up with acetic acid and the appropriate solvent. In most cases, acetic acid and the other component constituted 10 and 86% by volume, respectively, of the reaction mixture. Small variations in acetic acid concentration had only minor effects on the reaction. Acetic acid served the very useful purpose of diverting the alkyl radical on oxidative substitution to alkyl acetates, which were stable and could be readily analyzed. In general, the ratio of the yields of alkyl acetates and alkyl esters (derived from the parent acid, RCO_2H) were obtained predictably, simply on the basis of the mole fraction of acetic acid and RCO_2H. Competition between acetic acid

$$RCO_2H + Pb^{IV} + HOAc \longrightarrow [ROAc + RO_2CR] + CO_2 + Pb^{II} + 2H^+ \qquad (7)$$

and cyclobutanecarboxylic acid in the decarboxylation step (eq 2) was not serious in 10% (by volume) acetic acid solutions. However, it may have contributed to the low yield of products obtained by the decarboxylation of allylacetic and cyclopropylacetic acids, which as primary acids suffer from this competition.[2,4,5]

Photochemical and Thermal Decarboxylation of Cyclobutanecarboxylic Acid by Pb^{IV}.—Decarboxylation of cyclobutanecarboxylic acid by Pb^{IV} was carried out thermally at 80°[2] in a thermostated bath or photochemically at 30° with irradiation at 3500 Å.[1] These reactions were studied in the presence and absence of Cu^{II} complexes and pyridine after thorough purging with argon. The principal products obtained under these conditions (Table I) were cyclobutane, cyclobutene, and a mixture of homoallylic acetates and cyclo-

(8) H. DeLaMare, F. Rust, and J. Kochi, *J. Amer. Chem. Soc.*, **85**, 1437 (1963).

(9) J. Kochi, *ibid.*, **84**, 774 (1962); **84**, 3271 (1962).

(10) J. Kochi and R. Gilliom, *ibid.*, **86**, 5251 (1964).

(11) J. Kochi and A. Bemis, *ibid.*, in press.

(12) J. Kochi, *Rec. Chem. Progr.*, **27**, 209 (1966).

(13) (a) Oxidative decarboxylation of cyclobutanecarboxylic acid by Pb^{IV} was reported to give a mixture of cyclobutyl, allylcarbinyl, and cyclopropylmethyl acetates. G. Büchi and J. Marvel [quoted in ref 13 of a paper by E. Corey and J. Casanova, *J. Amer. Chem. Soc.*, **85**, 167 (1963)]. (b) For convenience, we describe cyclobutyl, cyclopropylmethyl, and allylcarbinyl as *homoallylic derivatives*.

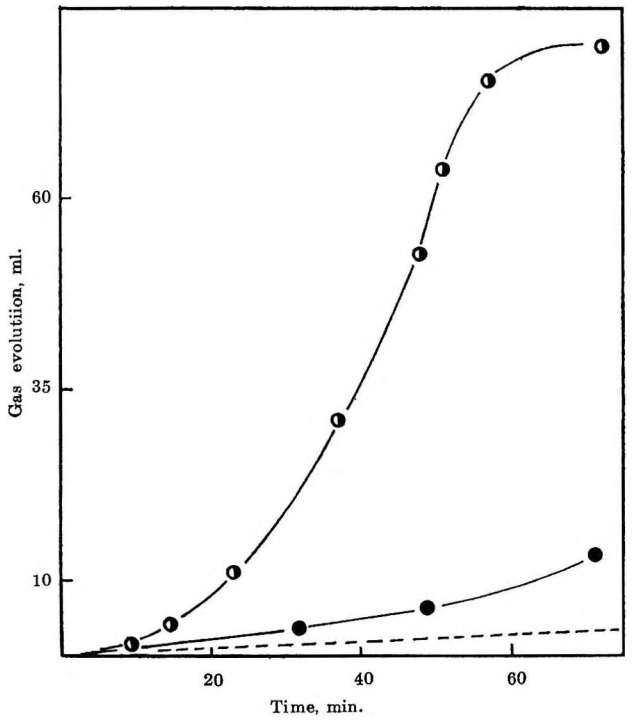
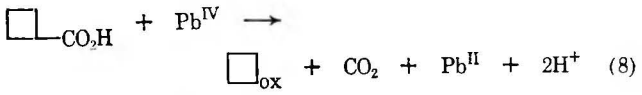
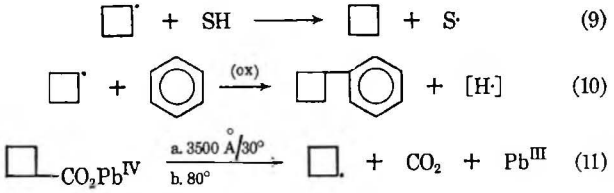


Figure 1.—Thermal decarboxylation of 0.46 *M* cyclobutanecarboxylic acid with 0.10 *M* lead(IV) acetate in benzene at 80°: ◑, 0.0051 *M* copper(II) acetate; ●, 0.10 *M* pyridine; dotted line, no additive.

butanecarboxylates. In most cases, the material balance of the cyclobutyl moiety was greater than 70% based on the stoichiometry given in eq 8. All of these



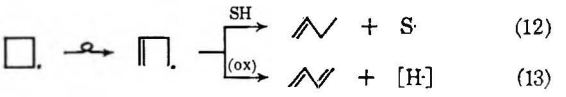
products, with the exception of cyclobutane and cyclobutylbenzene (obtained only in benzene), resulted from oxidation of cyclobutyl radicals. The latter two were formed by attack on solvent by hydrogen abstraction (eq 9)[14] or substitution (eq 10),[2] and were especially



prevalent in photochemical reactions carried out in the absence of Cu^{II}. No doubt, higher steady-state concentrations of radicals result from photochemical (eq 11a) compared with thermal (eq 11b) initiation.[4] Furthermore, the thermal decomposition of cyclobutanecarboxylic acid (0.46 *M*) with 0.10 *M* Pb^{IV} in benzene solutions at 80° was significantly faster in the presence of catalytic amounts (0.0051 *M*) of copper(II) acetate (see Figure 1). Catalysis could be attributed to the more facile oxidation of cyclobutyl radicals by Cu^{II} than by Pb^{IV}.[2,4] The latter is also consistent with the effectiveness of Cu^{II} in reducing the amounts of cyclobutane and cyclobutylbenzene in the photochemical reactions.[15]

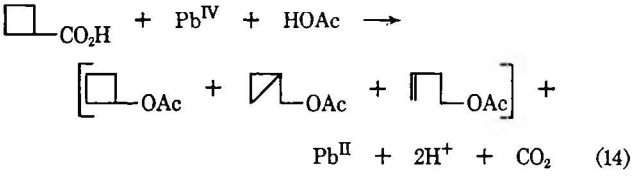
(14) Acetonitrile is a better hydrogen donor than benzene toward alkyl radicals and relatively more cyclobutane was always formed in this solvent.

Small amounts of both 1,3-butadiene and butene-1 were always found as by-products. They did not arise from isomeric impurities in the reactant acid, but were generated *via* rearrangement of cyclobutyl radicals. The latter was never a serious problem under these experimental conditions.[16,17]



If these minor differences are taken into account, examination of Table I shows that oxidation products from reactions carried out thermally and photochemically were equivalent.[1] In both cases decarboxylations carried out with Cu^{II} in benzene solutions afforded excellent yields of cyclobutene, while in acetonitrile the most important products were a mixture of homoallylic esters. Furthermore, the composition of the mixture of rearranged homoallylic esters were invariant with the mode of initiation as well as the solvent.[18] Since the photochemical reaction could easily be carried out under mild conditions, all further studies were carried out in this manner to obviate any further rearrangements and extraneous thermal reactions.[2] The equivalence of products obtained from the photochemical and thermal decarboxylations of cyclobutanecarboxylic acid is consistent with a relatively long kinetic chain length and low activation energies in the propagation sequences (eq 1–2 and 2–4).

Oxidative Decarboxylation of Cyclobutanecarboxylic Acid by Pb^{IV}. Benzene and Acetonitrile.—Previous studies showed that pyridine enhanced the rate of decarboxylation of acids by Pb^{IV} but did not affect the products.[2,4,19] The same effect was observed in the photochemical decarboxylation given in Table II. The quantum yield was not measured quantitatively, but results given in Table II show that products were also largely unaffected by changes in solvent from benzene to acetonitrile. In both solvents, a mixture of homoallylic esters[20] was the major product, together with minor amounts of cyclobutene. Slightly more



(15) Part of this, however, could be due to the filtering of the irradiation by Cu^{II} salts.

(16) (a) J. Roberts and R. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951); (b) E. Renk, P. Shafer, W. Graham, R. Mazur, and J. Roberts, *ibid.*, **83**, 1937 (1961); (c) C. Walling and P. Fredericks, *ibid.*, **84**, 3327 (1962); (d) L. Montgomery and J. Matt, *ibid.*, **89**, 6556 (1967).

(17) No allylcarbinyl chloride has been reported from the photochlorination of cyclobutane by chlorine[16a] or *t*-butyl hypochlorite[16c] which are effective chain-transfer agents. The Hunsdiecker reaction of silver cyclobutanecarboxylate with bromine is also reported to afford only cyclobutyl bromide.[16a] However, further facile additions may have obscured the allylcarbinyl product.

(18) The mixture of homoallylic esters could be analyzed accurately, and there was a consistent but *slight* change in composition from solvent to solvent.

(19) E. Corey and J. Casanova, *J. Amer. Chem. Soc.*, **85**, 167 (1963).

(20) The composition of the cyclobutyl derivative was always slightly greater (47%) in acetonitrile compared to benzene (42%). Other solvents show similar differences, and this has bearing on the solvation of the C_4H_7 cation(s). A nonclassical or three equilibrating homoallylic cations could be consistent with these observations, and we do not wish to pursue this point now.

TABLE II

EFFECT OF COPPER(II) ON THE DECARBOXYLATION OF CYCLOBUTANECARBOXYLIC ACID BY LEAD(IV) IN BENZENE AND IN ACETONITRILE[a]

Solvent[b] (v/v)	Cu^{II}, M	Py, M	Products, mole %										
					Total[c] acetates	AA	CB	CP	Total CB[c,d] carboxylates	AA	CB	CP	Ph	Sum of C_4H_7[e]
PhH (86)	0	0	2	6	49	(4)	(42)	(54)	13	(4)	(39)	(57)	15	85
PhH (86)	0	0.060	2	5	41	(4)	(42)	(54)	11	(4)	(39)	(57)	12	71
CH_3CN (86)	0	0	1	15	49	(2)	(47)	(51)	14	(2)	(47)	(51)	0[f]	79
CH_3CN (86)	0	0.064	1	10	32	(3)	(47)	(50)	9	(2)	(47)	(51)	0[f]	52
PhH (86)	0.0051	0	68	1	12	(5)	(42)	(53)	4	(10)	(41)	(49)	2	87
PhH (86)	0.0051	0.058	78	0	7	(6)	(42)	(52)	2	(13)	(40)	(47)	1	88
PhH (86)	0.0061	0.0074[g]	72	0.2	11	(14)	(36)	(50)	1	N.D.	N.D.	N.D.	1	85
CH_3CN (86)	0.0052	0	3	8	58	(3)	(47)	(50)	12	(4)	(47)	(49)	0	81
CH_3CN (86)	0.0055	0.060	15	1	41	(4)	(47)	(49)	6	(7)	(45)	(48)	0	63

[a] Solutions of 0.10 M Pb^{IV} and 0.42 M cyclobutanecarboxylic acid (4% by vol.) decomposed photochemically at 30°. [b] Contains 10 parts of HOAc in addition. [c] AA = allylcarbinyl, CB = cyclobutyl, CP = cyclopropylmethyl. [d] As cyclobutanecarboxylate esters. [e] Total C_4H_7 fragments in products, does not include cyclobutanecarboxylate moiety. [f] Homoallylic acetamides not analyzed. [g] α,α′-Bipyridine.

TABLE III

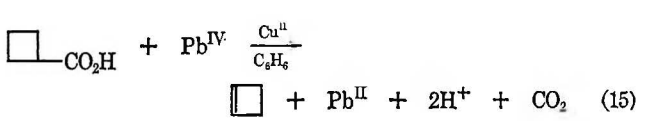
EFFECT OF NITRILE SOLVENTS ON DECARBOXYLATION OF CYCLOBUTANECARBOXYLIC ACID BY LEAD(IV) AND COPPER(II)[a]

Solvent[b] (v/v)	Cu^{II}, M	Products, mole %						
				Total acetates	OAc	OAc	OAc	Sum of C_4H_7
CH_3CN (86)	0.0052	3	8	58	(3)	(47)	(50)	69
CH_3CN (86)	0	1	16	49	(2)	(47)	(51)	66
CH_3CH_2CN (86)	0.0060	7	21	51	(4)	(47)	(49)	79
CH_3CH_2CN (86)	0	4	34	38	(3)	(47)	(50)	76
$CH_3(CH_2)_3CN$ (86)	0.0060	18	13	38	(4)	(47)	(49)	69
$CH_3(CH_2)_3CN$ (86)	0	4	25	35	(3)	(47)	(50)	64
$(CH_3)_2CHCN$ (86)	0.0059	10	26	36	(4)	(47)	(49)	72
$(CH_3)_2CHCN$ (86)	0	4	29	25	(4)	(45)	(51)	58
CH_3CN (0.0 M)[c]	0.0050	68	1[d]	12[e]	(5)	(42)	(53)	87
CH_3CN (0.81 M)[c]	0.0059	67	1[d]	14[e]	(4)	(42)	(54)	88
CH_3CN (1.87 M)[c]	0.0062	60	2[d]	19[e]	(4)	(43)	(53)	87

[a] Solutions of 0.10 M Pb^{IV} and 0.42 M cyclobutanecarboxylic acid (4% by vol.) decomposed at 30° and 3500 Å. [b] In addition to 10 parts of HOAc. [c] In benzene solutions. [d] Cyclobutylbenzene (~2%) also formed. [e] Homoallylic cyclobutanecarboxylates (~4%) formed.

cyclobutane was formed in acetonitrile, probably owing to more facile hydrogen transfer from that solvent compared to benzene; this was compensated, however, by formation of reasonable amounts (12–15%) of cyclobutylbenzene.

Oxidative Decarboxylation of Cyclobutanecarboxylic Acid by Pb^{IV} in the Presence of Cu^{II}. Benzene and Acetonitrile.—A dramatic change in products with solvent was obtained when the decarboxylation of cyclobutanecarboxylic acid by Pb^{IV} was carried out in the presence of catalytic amounts of copper(II) acetate (Table II). In benzene, large amounts of cyclobutene (70–80%) were formed (eq 15). In acetonitrile, ap-



proximately the same amounts of homoallylic esters as that obtained in the absence of Cu^{II} were formed (eq 14). In acetonitrile, cyclobutene was a minor product which increased slightly with addition of pyridine. Cyclobutylbenzene under these conditions was no longer a significant product.

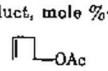
Effect of Nitriles as Solvents for the Oxidation of Cyclobutyl Radicals by Cu^{II}.—The latter two sets of experiments clearly established that it was the oxidation of cyclobutyl radicals by Cu^{II} rather than Pb^{IV} which was affected by a change in solvent from benzene to acetonitrile. Acetonitrile did not affect this change in a stoichiometric manner, since relatively large amounts of acetonitrile were required before its effect was noticeable (Table III). Thus, at low concentrations of acetonitrile the behavior was indistinguishable from a reaction in benzene alone.

Homologating the alkyl chain of acetonitrile had the same effect as dilution with benzene. In the series of equivalent reactions in acetonitrile, propionitrile, valeronitrile, and isobutyronitrile as solvents, the yields of cyclobutene increased at the expense of homoallylic esters only when Cu^{II} was present (Table III). Yields of cyclobutane increased directly with the hydrogen availability in the nitrile solvent; the low concentrations of Cu^{II} employed in these studies were insufficient to cope completely with this side reaction.

Effect of Solvents on the Decarboxylation of Cyclobutanecarboxylic Acid by Pb^{IV}.—A variety of other solvents of different functionality was also employed (Table IV). These could be classified in several categories. (a) Hydrogen donor solvents which afforded cyclobutane in good yield. Chloroform was preeminent, followed by N,N-dimethylacetamide (DMAC) and formamide (DMF), tetrahydrofuran (THF), and hexamethylphosphoramide (HMPA). (b) Solvents in which decarboxylation of cyclobutanecarboxylic acid occurred spontaneously at room temperature. Reaction in hexamethylphosphoramide was complete in

TABLE IV

DECARBOXYLATION OF CYCLOBUTANECARBOXYLIC ACID BY LEAD(IV) AND COPPER(II) IN VARIOUS SOLVENTS[a]

			Product, mole %						
Solvent[b]	Cu^{II}, *M*	Initiation[c]			Total acetates				Sum of C_4H_7
EtOAc	0.0055	Photo.	77	2	11	(4)	(42)	(54)	90
PhCl	0.0054	Photo.	59	1	15	(5)	(42)	(53)	75
$CHCl_3$	0.0055	Photo.	0	65	18	(1)	(38)	(61)	83
$CHCl_3$	0	Photo.	0	64	19	(1)	(39)	(60)	83
$(CH_2)_4SO_2$	0.0068	Photo.	24	5	46	(3)	(47)	(50)	75
$(CH_2)_4SO_2$	0	Photo.	0.3	8	64	(2)	(47)	(51)	73
DMAC	0.0080	R.T.	43	5	10	(1)	(54)	(45)	58
DMAC	0	R.T.	1	15	22	(1)	(56)	(43)	38
DMF	0.0085	R.T.	34	10	15	(2)	(56)	(42)	59
DMF	0	R.T.	1	21	4	(2)	(56)	(42)	26
Pyridine	0.0089	R.T.	1	0.4	~4	...	...	...	5
Pyridine	0	R.T.	0.2	1	~2	...	...	...	3
HMPA	0.0063	R.T.[d]	46	2	4	(2)	(48)	(50)	52
HMPA	0	R.T.[d]	1	19	24	(5)	(48)	(47)	44
DMSO	0.0088	R.T.	34	2	7	...	...	...	41
DMSO	0	R.T.	0.2	2	19	...	...	...	23
THF	0.0088	R.T.	59	7	8	(2)	(50)	(48)	74
THF	0	R.T.	1	17	31	(2)	(50)	(48)	49

[a] In solutions of 0.10 *M* Pb^{IV} and 0.42 *M* cyclobutanecarboxylic acid. [b] Solvent is 86% by vol. component listed and 10% by vol. HOAc. [c] Photo. is irradiation at 3500 Å and 30°. R.T. = initially at room temperature. Solvent added to degassed reaction mixture. [d] Exothermic.

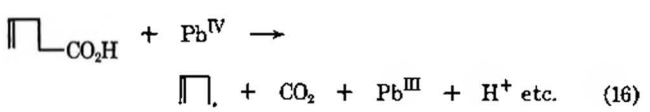
less than 30 min. In tetrahydrofuran[21] and pyridine, decarboxylation was complete within 1 hr, and in dimethylacetamide and dimethyl sulfoxide (DMSO) the reactions took 2 and 4 hr, respectively, under the same conditions. (c) For comparison, reactions in benzene, chlorobenzene, acetonitrile, or ethyl acetate were too slow to measure at room temperature.

In all of these solvents, cyclobutene was never formed in greater than 2% yields. These results were essentially the same as the studies in benzene and acetonitrile described earlier (*vide infra*).

Effect of Solvents on the Decarboxylation of Cyclobutanecarboxylic Acid by Pb^{IV} in the Presence of Cu^{II}.—Reactions examined in the previous section were repeated in the presence of catalytic amounts of Cu^{II}. Under these conditions, differences in the properties among solvents were again quite apparent by the relative amounts of cyclobutene and homoallylic esters produced on decarboxylation of cyclobutanecarboxylic acid. With the exception of the very active hydrogen donor solvent, chloroform, the addition of catalytic amounts of Cu^{II} was sufficient to swamp the hydrogen-transfer reaction (eq 9, SH = $CHCl_3$), and cyclobutane in most cases was a minor product (Table IV).

According to these studies, solvents could be classified into essentially two categories, irrespective of the classification previously made in the absence of Cu^{II}: (i) alkene-producing, and (ii) ester-producing. In the first category (i), ethyl acetate followed by benzene, chlorobenzene, pyridine, and tetrahydrofuran appeared most effective (60–80%, cyclobutene). Other solvents such as N,N-dimethylacetamide and formamide, dimethyl sulfoxide, 1,2-dimethoxyethane, and hexamethylphosphoramide were also conducive to cyclobutene formation (35–45%). The yields of homoallylic esters in these solvents usually amounted to less than 15%. In the second category (ii) of solvents, homoallylic esters were the predominant product (~70%)[22a] and cyclobutene (<10%)[22b] was formed as the minor product. Acetonitrile was rather unique in this regard, although other nitrile solvents had, in degree, similar effects (Table III). Among all other non-nitrile solvents, sulfolane (tetramethylenesulfone) produced exceptional amounts of homoallylic esters. The results in chloroform were somewhat difficult to interpret owing to the overwhelming amount of cyclobutane even in the presence of Cu^{II}.

Decarboxylation of Allylacetic and Cyclopropylacetic Acids.—Essentially the same results were obtained from the decarboxylation of allylacetic acid and cyclopropylacetic acid by Pb^{IV} (Table V). In every case, the products were most readily considered as arising *via* the allylcarbinyl radical. Thus, butene-1 and mixtures of homoallylic and octadienyl acetates were



(16)

the principal products, together with allylcarbinylbenzene when the reaction was carried out in benzene. No methylcyclopropane or other derivatives (such as cyclopropylmethylbenzene) in which the cyclopropylmethyl moiety was intact could be found as products from the decarboxylation of cyclopropylacetic acid. The first-order isomerization of cyclopropylmethyl

(21) Tetrahydrofuran was purified, but, since it is easily autoxidized, adventitious peroxides may have been responsible for this rate effect.[3]

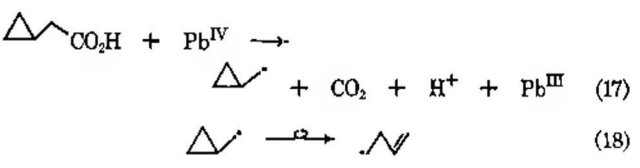
(22) (a) There are small but reproducible changes in the distribution of homoallylic esters in various solvents.[13,16] The distribution in a given solvent, however, is not affected by Cu^{II} (Table IV) despite large changes in total acetate yields. The solvation of C_4H_7 cation(s) appears to be independent of whether they are formed by Cu^{II} or Pb^{IV} oxidation (*cf.* ref 11). (b) It is interesting to note the effect of pyridine on Cu^{II} oxidations in acetonitrile in promoting cyclobutene formation. The effects of pyridine and acetonitrile as ligands appear to be opposed in oxidative eliminations. Slightly better yields of cyclobutene are also obtained by addition of pyridine to the copper-catalyzed decarboxylation in benzene. It has no effect on products in the absence of Cu^{II}.

TABLE V

DECARBOXYLATION OF ALLYLACETIC AND CYCLOPROPYLACETIC ACIDS BY LEAD(IV) AND COPPER(II)[a]

Acid	Solvent[b]	Cu^{II}, *M*	Products, mole %							
					Total acetates				Octadienyl[c] acetates	
Cyclopropylacetic	CH_3CN	0.0062	10	12	20	(11)	(36)	(53)	N.D.	0
Cyclopropylacetic	CH_3CN	0	25	0	10	(8)	(32)	(60)	0	0
Cyclopropylacetic	PhH	0.0064	1	38	~3[d]	...	...	...	20	1
Cyclopropylacetic	PhH	0	24	0	8	(18)	(15)	(67)	0	12
Cyclopropylacetic	$CHCl_3$	0.0060	32	0	N.D.	...	...	...	0	0
Cyclopropylacetic	$CHCl_3$	0	11	0	N.D.	...	...	...	0	0
Allylacetic	CH_3CN	0.0061	6	5	20	(16)	(34)	(50)	0	0
Allylacetic	CH_3CN	0	20	0	~4[d]	...	...	...	0	0
Allylacetic	PhH	0.0062	1	24	~3[d]	...	...	...	10	1
Allylacetic	PhH	0	9	0	~5[d]	...	...	...	0	6

[a] In solutions of 0.10 *M* Pb^{IV} and 0.40 carboxylic acid decomposed photochemically at 30° and 3500 Å. [b] Solvent consists of 86% by vol. component listed and 10% by vol. HOAc. [c] Mixture of 1-acetoxyoctadiene-2,7 and 3-acetoxyoctadiene-1,7. [d] Estimated, ester yields too small to measure.

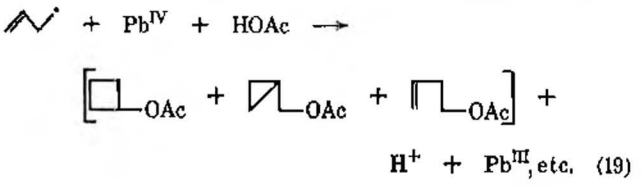


(17)

(18)

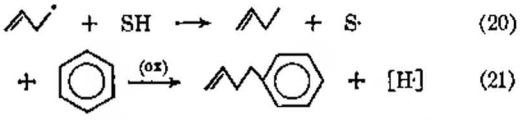
radicals (eq 18)[16,23] under these conditions must have been too rapid[24] compared with other second-order processes, such as hydrogen transfer, oxidation, addition, substitution, etc.

In both benzene and acetonitrile, the allylcarbinyl radicals were oxidized by Pb^{IV} to a mixture of rearranged homoallylic esters in poor yields (5–10%,



(19)

Table V). The principal product was butene-1, which resulted from allylcarbinyl radicals by hydrogen abstraction (eq 20), or allylcarbinylbenzene from substitution on the solvent (eq 21). The over-all material

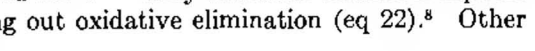


(20)

(21)

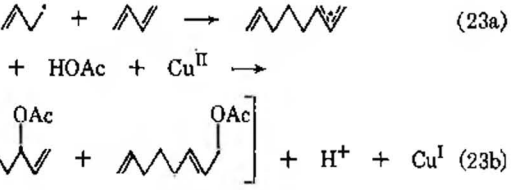
balance of the C_4H_7 alkyl fragments from the decarboxylation of both acids was poor, and it may have been due to competitive decarboxylation of acetic acid since both are primary acids.[2,5]

The decarboxylation of allylacetic and cyclopropylacetic acids by Pb^{IV} in the presence of Cu^{II} afforded two new products: 1,3-butadiene and a mixture of octadienyl acetates. A corresponding reduction in the yields of butene-1 and allylcarbinylbenzene was noted (Table V). Thus, allylcarbinyl radicals, like other primary radicals, show great selectivity toward oxidation by Pb^{IV} and Cu^{II}.[2,5] Only the latter oxidant is capable of carrying out oxidative elimination (eq 22).[8] Other



(22)

independent studies[25] have shown that octadienyl acetates are formed from allylcarbinyl radicals and butadiene by addition (eq 23a) followed by oxidation (eq 23b).



(23a)

(23b)

The contrast in behavior between acetonitrile and benzene as solvents was also evident in the oxidation of allylcarbinyl radical. Thus, homoallylic esters were much more important products in acetonitrile (~20%) than they were in benzene (<3%).[26] Conversely, butadiene and octadienyl acetates were the predominant products in benzene and were less important in acetonitrile. It is significant that homoallylic esters were products even in the absence of Cu^{II}. It indicates that Pb^{IV} was capable of oxidizing the allylcarbinyl radical to substitution products, albeit in low yield, despite its inability to effect oxidative elimination. Changes in solvent did not affect oxidative substitution of allylcarbinyl radicals by Pb^{IV}, similar to observations made with cyclobutyl radicals (*vide supra*).

Discussion

The effects of solvents on the decarboxylation of cyclobutanecarboxylic, allylacetic, and cyclopropylacetic acids, in the presence and absence of Cu^{II} catalyst, have furnished additional insight into the mechanism of electron-transfer oxidation of alkyl radicals by Pb^{IV} and Cu^{II}, respectively. The products of oxidation and the enhanced rate of decarboxylation show clearly that small amounts of Cu^{II} are sufficient to intercept cyclobutyl and allylcarbinyl radicals. Furthermore, hydrogen-transfer reactions in various solvents is a much more serious complication when the Cu^{II} oxidant is absent. Since the rate of oxidation of alkyl radicals by Cu^{II} is also close to diffusion controlled,[7] it is concluded that competition between Cu^{II} and Pb^{IV} for cyclobutyl or allylcarbinyl radicals

(23) C. Walling in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 441 ff.

(24) It is also possible that cyclopropylmethyl radicals are not intermediates and allylcarbinyl radicals are formed directly from decarboxylation (eq 17 + 18).

(25) J. Kochi and H. Maina, *J. Org. Chem.*, **30**, 1862 (1965).

(26) The relative amounts of allylcarbinyl esters in the homoallylic mixture are greater when allylcarbinyl radicals are oxidized compared to cyclobutyl radicals. This distribution of isomers has been discussed previously.[11]

heavily favors the former under these conditions.[27a] In the following discussion, we have attributed all oxidation products[27b] derived from the copper-catalyzed decarboxylation of these acids to oxidation of the relevant alkyl radical by Cu^{II} (eq 3), in preference to oxidation by Pb^{IV} [28] (eq 1).

In these reactions, various amounts of reduced product (cyclobutane, butene-1) are always formed owing to differences in hydrogen donor characteristics of solvents (SH, eq 12 and 20). These products, however, will not enter further in our reckoning, since we now wish to direct our attention to a comparison of Pb^{IV} and Cu^{II} species as electron-transfer oxidants toward alkyl radicals.

The study of cyclobutyl radicals is particularly auspicious since competition between oxidative elimination and oxidative substitution are delicately balanced, and small perturbations in metal oxidant have large effects on the products obtained. When cyclobutanecarboxylic acid is decarboxylated by Pb^{IV} in the absence of Cu^{II} catalyst, the same mixture of oxidation products is obtained in a variety of solvents. In every solvent, oxidation of cyclobutyl radicals by Pb^{IV} produces homoallylic esters as principal products of oxidation, and cyclobutene (*i.e.*, oxidative elimination) is always unimportant. The same is true (in degree) for the oxidation of allylcarbinyl radicals from the decarboxylation of allylacetic and cyclopropylacetic acids by Pb^{IV}.

A major effect of solvent is only observed when Cu^{II} is present during decarboxylation. Thus, in most solvents Cu^{II} prefers to oxidize cyclobutyl radicals by elimination to cyclobutene, despite the thermodynamic instability of the latter. It is only in acetonitrile, its homologs, and to a certain extent sulfolane that Cu^{II} prefers to react with cyclobutyl radicals by oxidative substitution and affords a mixture of homoallylic esters. Under the latter circumstances, Cu^{II} generates the *same mixture* of products as Pb^{IV}, although the rate of oxidation is much faster. The effect of solvent in affecting the course of oxidation cannot be correlated with any general bulk properties of the solvents, such as dielectric constant, ionizing power, or general polar properties (*cf.* Table IV).[29]

The unique effect of acetonitrile is attributed to specific coordination with the Cu^{II} oxidant. Acetonitrile complexes of Cu^{II} are known, although the formation constants are not large.[30] To obtain coordination

$$Cu^{II}(OAc)_2 + n CH_3CN \longrightarrow Cu(NCCH_3)_n(OAc)_2 \quad (24)$$
$$n = 1\text{–}6$$

with Cu^{II} (probably six), acetonitrile must be employed in large excess (solvent).[25,30a] The latter is consistent with the observations on the effects of concentration of acetonitrile and structure of nitrile-type solvents in altering oxidations by Cu^{II} species (Table III).[25,31]

(27) (a) The competition is not always in favor of Cu^{II}, since oxidative decarboxylation of acids which yield easily oxidized radicals such as triphenylmethyl are not affected by Cu^{II}.[1-4] (b) Cyclobutane and butene as reduction products are not included.

(28) This is intended more for illustration rather than to point to exclusiveness, since small contributions from Pb^{IV} oxidation cannot be evaluated. Internal consistency is the most important consideration.

(29) A. Parker, *Advan. Phys. Org. Chem.*, **5**, 173 (1967).

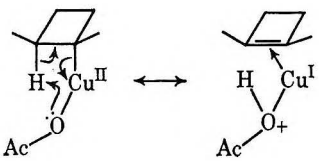
(30) (a) C. Addison, B. Hathaway, N. Logan, and A. Walker, *J. Chem. Soc.*, 4308 (1960); (b) I. Kolthoff and J. Coetzee, *J. Amer. Chem. Soc.*, **79**, 1852 (1957).

Oxidative Elimination.—The formation of cyclobutene generally from reactions of cyclobutyl radicals or cyclobutyl cations (*e.g.*, from solvolysis of cyclobutyl derivatives[32]) is rather unique. Loss of a β-hydrogen atom from the radical or β proton from the carbonium ion is never observed to a significant extent, except on oxidation of the radical by Cu^{II} in non-nitrile solvents. It is concluded from this and previous studies[11] that cyclobutyl cation is not an intermediate in cyclobutene formation. Instead we associate the oxidative elim-



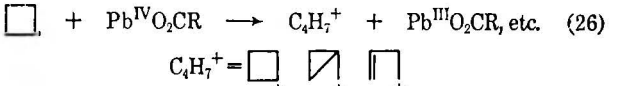
(25)

ination of alkyl radicals by Cu^{II} to a specific intramolecular removal of the β hydrogen synchronously with electron transfer. Part of the driving force for such a process may be derived by synergic bonding between the incipient olefinic bond and Cu^{I}.[33] A transition state for oxidative elimination is represented below.[34]

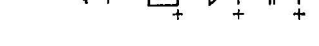


a transition state for oxidative elimination of alkyl radicals by Cu^{II} complexes

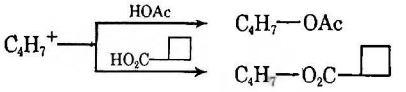
Oxidative Substitution.—A similar process for oxidative elimination by Pb^{IV} and $Cu^{II}(NCCH_3)_n$ complexes does not obtain, since little or no cyclobutene is formed. With these oxidants, a cyclobutyl cation, subject to extensive rearrangement, is an intermediate formed by electron transfer (eq 26 and 27). Oxidative substitution



(26)



via cations as a route to esters has been previously described.[11] A mixture of homoallylic esters is formed by rather indiscriminant solvation of the C_4H_7 cation(s),[35] since homoallylic acetates and cyclobutanecarboxylates are formed in direct proportion to the mole fraction of the parent acids (*cf.* Table II). Cyclobutyl, allylcar-



(31) (a) In the same way, the effect of sulfolane is attributed to sulfolane complexes of Cu^{II}. However, it is also possible to interpret the data in Table IV as indicating that Cu^{II} in sulfolane is a poor oxidant and yields cyclobutene by this route. The homoallylic esters would then be attributed to oxidation by Pb^{IV}. Cu^{II} complexes in sulfolane are under investigation. (b) The stabilization of Cu^{I} by sulfolane has not yet been reported.

(32) (a) J. Roberts and R. Mazur, *J. Amer. Chem. Soc.*, **73**, 2511 (1951); (b) K. Servis and J. Roberts, *ibid.*, **86**, 3773 (1964); **87**, 1331 (1965); *Tetrahedron Lett.*, 1369 (1967); (c) J. Roberts and R. Chambers, *J. Amer. Chem. Soc.*, **73**, 5034 (1951); (d) R. Breslow in "Molecular Rearrangements," P. de Mayo, Ed., part 1, Interscience Publishers, New York, N. Y., 1963, p 233 ff.

(33) (a) O. Chaltykyan, "Copper-Catalytic Reactions," Consultants Bureau, New York, N. Y., 1966. (b) *Cf.* also oxidation of alkyl radicals by Cu^{II}.[25]

(34) Pyridine Cu^{II} complexes are somewhat akin to acetato Cu^{II} oxidant in that they slightly favor oxidative elimination. The basic nitrogen site may aid intramolecular proton transfer.

(35) Reaction of these C_4H_7 cations with acetonitrile also takes place and homoallylic acetamides are formed. This reaction, however, is not so important as it is with *t*-amyl cations.[11]

binyl, and cyclopropylmethyl derivatives comprise the isomeric esters in essentially the same proportion in each fraction. This composition varies only slightly with solvent.[20,22a]

The difference between copper(II) acetate and copper(II) acetonitrile complexes as oxidants may be attributed (to a certain extent) to the higher oxidation potential of the latter. In such a case, greater driving force for electron transfer (eq 27) is derived from the

$$\square + Cu^{II}(NCCH_3)_n \longrightarrow C_4H_7^+ + Cu^{I}(NCCH_3)_n \quad (27)$$

formation of the more stable acetonitrile copper(I) complex.[31b,36] In addition, competition with oxidative elimination (eq 25) is minimized by (a) displacement of the acetato ligands in the Cu^{II} complex by acetonitrile, and (b) reduction of synergic bonding to alkene by the presence of acetonitrile in the copper complex[25] (*cf.* transition state for oxidative elimination).

Cyclobutyl radicals are not unique in undergoing different oxidative processes by various Cu^{II} oxidants. Thus, the dichotomy between oxidative elimination and substitution has also been observed with allylcarbinyl (*vide supra*), α-phenylalkyl,[37] and 2-*p*-methoxyphenethyl[11] radicals. Both oxidative routes (especially cation formation, eq 30) are reasonably accessible in each of these radicals. Furthermore, the behavior of the radicals is not dependent on their mode of formation, since the same results are obtained from the copper-catalyzed decomposition of the corresponding peroxides.[11]

Conclusions.—Oxidative elimination and substitution are not mutually exclusive processes, but under a given set of conditions they are more often competitive. In a previous study the following mechanism[11] was proposed for the oxidation of alkyl radicals by Cu^{II}.

$$R\cdot + Cu^{II} \rightleftharpoons [RCu] \quad (28)$$

$$[RCu] \longrightarrow R(-H) + H^+ + Cu^{I} \quad (29)$$

$$[RCu] \longrightarrow R^+ + Cu^{I} \quad (30)$$

$$R^+ \xrightarrow{HS} RS + H^+ \quad (31)$$

Postulation of an alkyl copper intermediate, formed reversibly, was presented mainly on the basis of kinetic evidence. Such a metastable organocopper intermediate does not materially affect the arguments based on product studies. Equations 29 and 30 are routes *via* an organocopper species for oxidative elimination and substitution, respectively.[38,39] The former path is optimum in noncomplexing solvents, and the latter reaction is aided by acetonitrile and related solvents.

On the basis of these solvent studies, an analogous mechanism is presented for the oxidation of alkyl radicals by Pb^{IV}. However, with Pb^{IV} as oxidant, a route

$$R\cdot + Pb^{IV}O_2CR \rightleftharpoons [RPbO_2CR] \quad (32)$$

$$[RPbO_2CR] \longrightarrow R^+ + Pb^{III}O_2CR, \text{ etc.} \quad (33)$$

for *direct* oxidative elimination similar to eq 29 for Cu^{II} does not appear relevant. We consider most products as stemming from solvation, elimination, rearrangement, etc., of the intermediate alkyl cation, including alkene usually formed in minor amounts.[38b] Pb^{IV} carboxylates do not appear to form complexes with acetonitrile and other ligands of the type that Cu^{II} species do. Thus, the oxidation of alkyl radicals by Pb^{IV} (eq 29) is singularly unaffected by solvents. The latter appear to affect only rates of decarboxylation of acids by Pb^{IV}, when they can exercise nucleophilic properties (*e.g.*, HMPA, DMF, DMAC, etc.) in common with observations of a variety of other bases.[2] Products of oxidation are largely unaffected by changes in solvent in these instances.

These mechanisms help to clarify the earlier observations that oxidations of alkyl radicals by Cu^{II} are much more facile and less selective than analogous oxidations with Pb^{IV}.[2,4,7] In the former, two oxidative paths are available, one (eq 29) of which does not require direct generation of an alkyl cation. The concerted path for oxidative elimination (eq 25) enables Cu^{II} to circumvent carbonium ion formation except when the latter is favorable. Those radicals (*e.g.*, neopentyl,[11] phenyl,[40] benzyl,[4,41] etc.) which neither have β hydrogens nor generate stable cationic species are oxidized only slowly by Cu^{II}. On the other hand, there is one major path (eq 33) available for oxidation of alkyl radicals by Pb^{IV}, and it includes heterolytic dissociation (eq 33). Except for relatively stable cations (*e.g.*, *t*-alkyl, benzylic,[41] allylic, etc.) the latter is an energetically undesirable route and oxidation is generally slow.[4,11] With both Cu^{II} and Pb^{IV}, reversible formation of the alkyl metal intermediate allows alkyl radicals to react by other homolytic processes when electron transfer is reluctant.[42]

Experimental Section

Materials.—Carboxylic acids were purified by distillation and their purity confirmed by gas chromatographic (glpc) analysis of the neat acids and their methyl esters on FFAP (Varian Aerograph) and DEGS (Varian Aerograph) on firebrick. Each was shown to be free of isomeric impurities. Cyclobutanecarboxylic acid was from Columbia Organic Chemicals and allylacetic acid from Peninsular Chemical Co.

Cyclopropylacetic acid was made from ethyl vinylacetate and methylene iodide by the Simmons–Smith procedure.[43]

(36) H. Morgan, *J. Chem. Soc.*, 2901 (1923); B. Hathaway, D. Holah, and I. Postlethwaite, *ibid.*, 3215 (1961); 2444 (1962); W. Schneider and A. v. Zelewsky, *Helv. Chim. Acta*, **46**, 1848 (1963); S. Manahan and R. Iwamoto, *Inorg. Chem.*, **4**, 1409 (1965).

(37) Unpublished results.

(38) (a) It should be emphasized that oxidative elimination and oxidative substitution only represent *categories* of electron-transfer reactions between alkyl radicals and metal oxidant. (b) We do not mean to imply that alkenes can only be formed by the former path and esters can only be formed by the latter. Thus, it is known that carbonium ions do eliminate β protons (E1 reactions) and alkenes are often products from solvolysis and nitrosative deamination.[39] For this reason, the distinction between oxidative elimination and substitution is particularly obscured with *t*-alkyl, benzylic, and similar systems. (c) Furthermore, esters do not always arise *via* a carbonium ion since there is evidence for ligand transfer in the oxidation of allyl[9] and allylcarbinyl[11] radicals. (d) In the absence of nucleophiles such as carboxylates, etc, the carbonium ions can also react with arenes to form aromatic substitution products by electrophilic processes.

(39) C. Bunton, "Substitution Reactions," Elsevier Publishing Co., New York, N. Y., 1964; D. Banthorpe, "Elimination Reactions," Elsevier Publishing Co., New York, N. Y., 1963. See Y. Pocker and D. Kevill, *J. Amer. Chem. Soc.*, **87**, 4771 (1965), for recent discussions of this point.

(40) J. Kochi, *ibid.*, **79**, 2943 (1957).

(41) (a) The oxidation of benzyl radicals shows extremely large polar effects. Although benzyl radical itself is not readily oxidized, the *p*-methoxy isomer is. (b) *Benzylic* radicals (*i.e.*, α-phenylalkyl), which have longer side chains, are readily oxidized by virtue of being secondary radicals and also capable of oxidative elimination as well.

(42) It is not necessary to postulate an alkyllead intermediate. For example, carbonium ions can be formed directly from alkyl radicals by an outer-sphere electron-transfer mechanism. However, we feel that an alkyllead species is generally an intermediate[4] which reacts primarily by eq 33, although *direct* reactions on the alkyllead are also possible (J. Kochi, R. Sheldon, and S. Lande, submitted for publication).

(43) R. Smith and H. Simmons, *Org. Syn.*, **41**, 72 (1961).

Zn–Cu couple was prepared from 81 g (1.24 g-atoms) of Zn powder and 1.25 g of cupric acetate monohydrate in 125 ml of glacial acetic acid by the Le Goff procedure.[44] To this Zn–Cu couple was initially added 100 ml of anhydrous ether and 30 g of methylene iodide with stirring. This was followed by dropwise addition of a mixture of 94 g (0.83 mol) of ethyl vinylacetate and 300 g of methylene iodide (1.24 mol in all) at a rate to maintain gentle reflux. The mixture was then stirred and refluxed for 24 hr under nitrogen. Gas chromatography of the crude reaction mixture showed almost no unreacted ester, and on distillation after work-up afforded 83 g (78%) of ethyl cyclopropylacetate, bp 146–149°. The latter was hydrolyzed by stirring with a solution of aqueous methanolic potassium hydroxide at room temperature for 24 hr. Work-up and distillation yielded cyclopropylacetic acid in 70% yield, bp 86–87° (9 mm).

Lead tetraacetate (G. F. Smith Chemical Co.) was recrystallized from glacial acetic acid (containing 1–2% acetic anhydride) and vacuum desiccated over potassium hydroxide pellets. It was stored at −15° protected from light and moisture. Analysis of the white, free-flowing material by iodometric titration indicated 96–98% $Pb(OAc)_4$. Cupric acetate monohydrate (Mallinckrodt analytical reagent) and 2,2′-bipyridine (Eastman Kodak Co.) were used without further purification.

Benzene and chlorobenzene (Mallinckrodt Chemical Works) were further purified by distillation through a 22-plate Oldershaw column. Glacial acetic acid, ACS reagent (Allied Chemical Corp.) was used as supplied. Acetonitrile (Matheson reagent) was distilled from phosphorus pentoxide. Propionitrile, isobutyronitrile, valeronitrile, and benzonitrile (Eastman Organic Chemicals) and ethyl acetate and tetrahydrofuran (Du Pont Co.) were purified by distillation. Chloroform was purified[45] immediately prior to its use. Vacuum distillation of tetramethylenesulfone (Shell Development Co.) from potassium hydroxide pellets yielded crystalline, odorless material. Dimethylformamide and dimethylacetamide (Du Pont Co.), except for drying over molecular sieves, were used without further purification. Pyridine (Reilly Co.) was distilled from potassium hydroxide. Dimethyl sulfoxide and hexamethylphosphoric triamide were refluxed over calcium hydride and distilled *in vacuo*.

Authentic, characterized samples of cyclobutane and cyclobutene were generouly supplied by Dr. J. Bayless. Other C_4 hydrocarbons, research grade, were supplied by Phillips Petroleum Co. and J. T. Baker Chemical Co. Authentic cyclobutylbenzene, produced by photoisomerization of phenylbutadiene followed by hydrogenation, was generously donated by Dr. M. Pomerantz. Cyclopropylmethylbenzene was from Columbia Organic Chemicals Co. The preparation of 4-phenylbutene-1 has been described elsewhere.[10] *n*-Butylbenzene and *n*-butyl acetate were from Eastman Organic Chemicals.

Cyclopropylcarbinol was prepared from cyclopropanecarboxylic acid (K & K Laboratories) by reduction with lithium aluminum hydride.[46] It was isomerized to cyclobutyl alcohol[47] with hydrochloric acid. Allylcarbinol was from Aldrich Chemical Co. Each of these alcohols was esterified with acetic anhydride and cyclobutanecarbonyl chloride (Kaplop Laboratories) to prepare authentic esters.

Photolysis.—The photolytic decarboxylations were conducted in 40 × 1 cm quartz tubes employing a Rayonet photochemical reactor (The Southern N. E. Ultraviolet Co.) Four 3500-Å lamps (3050–4150 Å) were used. The tubes were placed 10 cm from the nearest light source and the reactor temperature (30–33°) was maintained by air circulation.[1]

Typical Procedure.—A solution of cupric acetate monohydrate (0.0525 g, 0.253 mmol), cyclobutanecarboxylic acid (2.13 g, 21.3 mmol), glacial acetic acid (5 ml), lead tetraacetate (97%) (2.284 g, 5.00 mmol), and benzene (43 ml) was prepared with agitation in a 50-ml volumetric flask. Two 20-ml aliquots were transferred to separate tubes which were flushed free of oxygen with a stream of argon introduced *via* long stainless steel needles. The tubes were closed with rubber serum caps and placed in the photolysis chamber for 1.5 hr. The gaseous products were analyzed qualitatively by glpc for CO_2 and C_4 hydrocarbon, and then quantitatively for cyclobutane and cyclobutene after the introduction of *cis*-butene-2 as internal standard. The reaction mixture was transferred with glacial acetic acid to make a solution of 30-ml total volume. Aliquots of this solution were employed for further analysis. The mixture of homoallylic acetates were analyzed directly without work-up after *n*-butyl acetate was added as internal standard. The acidic nature of the solution in no way interfered with the quantitative distribution of these acetates under analytical conditions. Homoallylic acetates and cyclobutanecarboxylates, together with C_4 benzenes, were also determined after work-up using *n*-butyl acetate, 2-ethylhexyl acetate, and *n*-butylbenzene as internal standards. Work-up consisted of washing twice with water, dilute sodium bicarbonate, and water again and drying of the residual benzene solution over sodium sulfate.

When acetic acid was omitted from the solvent, cupric acetate was dissolved in cyclobutanecarboxylic acid and a small portion of benzene added prior to the addition of lead tetraacetate. A heterogeneous system resulted otherwise, with most of the Cu^{II} salt precipitating.

When pyridine was part of the system, it was added to a mixture of cupric acetate and the carboxylic acid (or directly to the carboxylic acid in those runs without Cu^{II}) prior to the addition of lead tetraacetate. Similarly, the α,α'-bipyridine Cu^{II} complex was initially prepared in the carboxylic acid prior to the addition of lead tetraacetate.

Thermolysis.—The thermal (81°) decarboxylations in benzene, chlorobenzene, and acetonitrile were conducted in an oxygen-free system as described earlier.[2] Solutions for these reactions were prepared in volumetric flasks and transferred to the reaction vessel as described above for photolysis.

Decarboxylations using dimethylformamide (DMF), dimethylacetamide (DMAC), hexamethylphosphoramide (HMPA), dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), or pyridine as solvents were conducted as follows. Cupric acetate (0.0239 g, 0.120 mmol) was dissolved in cyclobutanecarboxylic acid (0.674 g, 6.74 mmol) in a 125-ml erlenmeyer flask. Lead tetraacetate (97%) (0.689 g, 1.51 mmol) and glacial acetic acid (1.5 ml) were added, and the vessel was capped with a rubber septum. The solution and vessel were flushed with argon and 13 ml of DMAC previously flushed with argon was added with a syringe. Some heat was evolved upon mixing. The resulting homogeneous solution was stirred in the dark at 28 ± 1° for 2 hr. Product analysis was then carried out as above.

Analytical Procedures.—Reaction mixtures were analyzed by quantitative gas chromatography (glpc) using various internal standards (*vide supra*) which were previously calibrated against individual reaction products. Identification of gas chromatographic peaks was verified by comparing their retention times with authentic compounds on at least two columns of different polarity. Identification was confirmed by chemical degradation of reaction products (*e.g.*, hydrogenation of olefins and hydrolysis of esters) and comparison of degradation products with authentic samples by glpc.

Gas chromatographic analysis of gaseous hydrocarbons was performed on Case-constructed instruments equipped with thermal conductivity detectors. A 15 ft × 0.25 in. 30% Dowtherm A on firebrick column at 25° was employed for C_4 hydrocarbon analyses.

Other analyses were performed on an Aerograph HiFy (Model 600D) instrument equipped with a flame ionization detector. A 6 ft × 0.125 in. 20% FFAP on acid-washed Chromosorb W column was employed at 85° for acetate analyses and at 150° for the cyclobutanecarboxylates and alkylbenzene analyses.

Registry No.—Cyclobutanecarboxylic acid, 3721-95-7; $Pb(OAc)_4$, 546-67-8; cupric acetate monohydrate, 6046-93-1; allylacetic acid, 591-80-0; cyclopropylacetic acid, 5239-82-7.

Acknowledgment.—The authors wish to thank the National Science Foundation for generous support of this work and Dr. T. Bethea for the preparation of cyclopropylacetic acid.

(44) E. Le Goff, *J. Org. Chem.*, **29**, 2048 (1964).

(45) A. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1951, p 176.

(46) J. Roberts and R. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951).

(47) M. Caserio, W. Graham, and J. Roberts, *Tetrahedron*, **11**, 171 (1960).

Radiation-Induced Substitution of Aromatic Compounds in Dilute Aqueous Solutions.[1] II.[2] Hydroxylation of Anisole

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Received January 15, 1968

Isomeric methoxyphenols and phenol have been quantitatively determined by gas–liquid partition chromatography in irradiated solutions of aqueous anisole. The mechanism for the radiation-induced hydroxylation is discussed in terms of an initially formed methoxy-substituted hydroxycyclohexadienyl radical (I). Two radicals of I subsequently decompose to give one molecule of methoxyphenol, but the obtained G values for methoxyphenols suggest preferential dimer formation. If oxygen is present, in addition to scavenging the solvated electron, it adds to I forming a peroxy radical whose subsequent decomposition alters the isomer distribution of the methoxyphenols. The radiation-induced hydroxylation of anisole is compared with other hydroxylations initiated by γ rays and by chemical reagents.

In the first part of this series we reported the radiation-induced hydroxylation of nitrobenzene in dilute aqueous solution.[2] The initial step of the hydroxylation was found to be the addition of hydroxyl radical to form the nitrosubstituted hydroxycyclohexadienyl radical. The subsequent fate of this radical depended on the presence or absence of hydrated electrons and dissolved oxygen in the system. When essentially all the hydrated electrons had been scavenged by saturating the aqueous solution with nitrous oxide, the total yield of nitrophenols was found to be 0.65, a G value considerably smaller than expected for a stoichiometric conversion of hydroxyl radicals into nitrophenols.[3,4] We rationalized this by postulating that two nitrosubstituted hydroxycyclohexadienyl radicals dismute to one molecule of nitrophenol, but they preferentially form dimers. When the hydrated electrons had not been completely scavenged, additional nitrophenols were formed by a complicated set of reactions involving the nitrosubstituted hydroxycyclohexadienyl radical, dihydroxydinitrophenol and other dimers, and their subsequent products. The isomer distributions and partial rate factors qualitatively indicate that the *ortho* and *para* positions in the radiation-induced hydroxylation of nitrobenzene are activated to a greater extent than the *meta* position.

In electrophilic aromatic substitutions (*e.g.*, chlorination, bromination, acetylation, mercuration, etc.), a methoxyl group is predominantly *para* orienting.[5] The hydroxylation of anisole by Fenton reagent and by several other complex hydroxylating agents[6,7] showed, however, the preferential formation of *o*-methoxyphenol. Although radiation-induced hydroxylations represent simpler systems, since the attacking hydroxyl radical is generated *in situ*, no data are available on the products and their yields for irradiated dilute aqueous anisole. Our purpose was to obtain data for the isomeric distribution of methoxyphenols and to compare the chemical and radiation-induced hydroxylation of this compound. It was of interest also to obtain G values for the hydroxylated products and to compare them with the corresponding values obtained in the irradiation of benzene and other monosubstituted aromatic compounds in dilute aqueous solutions.

Experimental Section

The absorbed dose rate of the cobalt-60 γ irradiation facility used was determined to be 3.16×10^2 rads min^{-1} by the Fricke dosimeter taking $G(Fe^{3+}) = 1.55$.[8]

For the irradiation of air saturated solutions a known quantity, of redistilled reagent grade anisole was added by means of a Hamilton syringe and was dissolved in triply distilled water by vigorous shaking. Argon, oxygen, and nitrous oxide saturated solutions were prepared by bubbling the high purity gas through the triply distilled water in the irradiation cell. The gas was introduced into the irradiation cell by the use of a hypodermic needle which was punched through a silicone septum and pushed close to the bottom of the cell. An outlet for the saturating gas was provided by inserting another needle through a second septum. The duration of the saturation was about 15–20 min and its was enhanced by frequent shaking. After saturation the needles were withdrawn and the required amount of anisole was introduced with a Hamilton gas-tight syringe and dissolved by vigorous shaking.

The conversion of anisole into products was kept at less than 1% to avoid secondary reactions. After the completion of the irradiation, the pH of the irradiated solution was adjusted to 12.5 with sodium hydroxide, and the solution was extracted with ether (200 ml) to remove the unreacted anisole. The pH of the aqueous layer was readjusted to 2.0 with HCl and was extracted with redistilled two 100-ml portions of ether. These ether layers were concentrated by rotary evaporation to 5.0 ml at temperatures not exceeding 20° and were analyzed by gas–liquid partition chromatography. Using a 1-m glass column, 0.25-in. i.d., packed with 2% Versamid 900 (F & M) on Chromosorb W, with temperature programming at 2.5°/min from 25° and at a flow rate of 115 ml of He/min,[9] the following retention times (minutes) were obtained: *o*-methoxyphenol, 25; phenol, 42; *p*-methoxyphenol, 48; *m*-methoxyphenol, 52. Using the same temperature programming, an identical He flow rate, and the same column but packed with a mixture of 2% Versamid on Chromosorb W (75%) and 1% 1,2,3,4-tetrakis(2-cyanoethoxy)butane on C-22 (25%), the following retention times (minutes) were obtained: *o*-methoxyphenol, 22; phenol, 43. A thermal conductivity detector was used at a cell current of 160 or 195 mA. Known concentrations of the methoxyphenols and phenol were used to obtain excellent linear calibrations. Furthermore, using synthetic mixtures of these methoxyphenols and repeating the extraction and concentration techniques used for the analysis of the irradiated samples, the recovery of the compounds was 95–100%.

(1) This research was supported, in part, by the U. S. Atomic Energy Commission.

(2) J. H. Fendler and G. L. Gasowski, *J. Org. Chem.*, **33**, 1865 (1968), is regarded as part I.

(3) The yields of hydroxyl radical and hydrated electron in pure water at pH 7 are: $G_{OH} = 2.4$ and $G_{e_{aq}^-} = 2.8 \pm 0.2$.

(4) E. J. Hart, *Ann. Rev. Nuclear Sci.*, **15**, 125 (1965), and references cited therein.

(5) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).

(6) R. O. C. Norman and J. R. Lindsay Smith, "Oxidases and Related Systems," T. E. King, H. S. Mason, and M. Morrison, Ed., John Wiley and Sons, Inc., New York, N. Y., 1965, p 131, and references cited therein.

(7) G. A. Hamilton, J. W. Hanifin, Jr., and J. R. Friedman, *J. Amer. Chem. Soc.*, **66**, 5266, 5269 (1966).

(8) J. Weiss, A. O. Allen, and H. A. Schwarz, *Proc. Intern. Conf. Peaceful Uses At. Energy, 1st, Geneva, 1955*, **14**, 179 (1956).

(9) T. S. Ma and Donald Spiegel, *Microchem. J.*, **10**, 61 (1966).

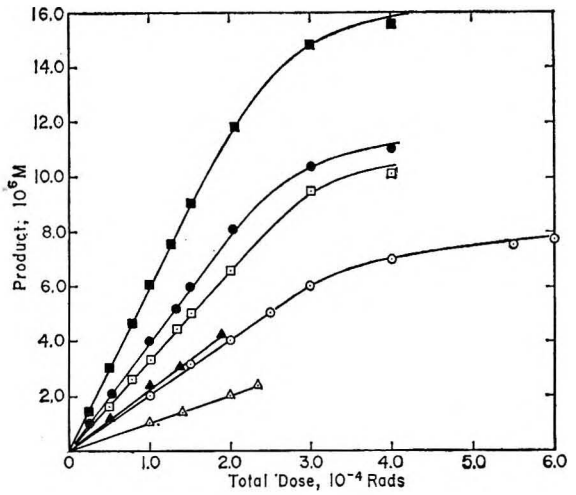


Figure 1.—In air saturated solution ($[O_2] = 1.0 \times 10^{-3}$ M): ⊙, *o*-methoxyphenol; ⊡, *p*-methoxyphenol; △, phenol. In N_2O–O_2 saturated solution ($[N_2O] = 1.45 \times 10^{-2}$ M and $[O_2] = 2.3 \times 10^{-4}$ M): ●, *o*-methoxyphenol; ■, *p*-methoxyphenol; ▲, phenol.

Results

The major products are phenol, and *o*- and *p*-methoxyphenol. The concentrations of these products in air and in nitrous oxide–oxygen saturated solutions at pH 6.5 as a function of total dose are plotted in Figure 1. The concentrations of methoxyphenols increase linearly with the dose up to 2.0×10^4 rads, at which point most of the available oxygen has been used up by its reaction with hydrogen atoms and hydrated electrons. From the initial slopes of the straight lines the G values have been calculated and are given in Table I. At doses of 6–10 $\times 10^5$ rads the irradiated aqueous anisole solution became very dark, presumably owing to the increased formation of dimers, and the methoxyphenol and phenol yields were decreased by a factor of 10. For this reason all the reported G values were obtained from yield–dose plots for doses not exceeding 2×10^4 rads. No postirradiation effects have been found in irradiated solutions of aqueous anisole. We obtained, within experimental error, the same yield of methoxyphenols and phenol in both air and nitrous oxide saturated solutions when we carried out the product analyses 4 weeks after the irradiation.

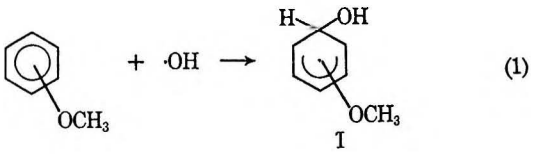
TABLE I
YIELD OF PHENOL AND METHOXYPHENOLS AT pH 6.5 IN 2.0×10^{-4} M AQUEOUS ANISOLE

	G value[a]			
	o-Methoxyphenol	*m*-Methoxyphenol	*p*-Methoxyphenol	Pheno
Air saturated[b]	0.19	None	0.32	0.11
Nitrous oxide and oxygen saturated[c]	0.38	None	0.59	0.23
Nitrous oxide saturated[d]	0.54	None	0.14	0.28
Argon saturated	0.07	None	None	0.46

[a] Estimated error for the methoxyphenol yields are ±5%; for phenol +10%. [b] $[O_2] = 2.30 \times 10^{-4}$ M. [c] $[N_2O] = 1.45 \times 10^{-2}$ M and $[O_2] = 2.3 \times 10^{-4}$ M. [d] $[N_2O] = 2.00 \times 10^{-2}$ M.

Discussion

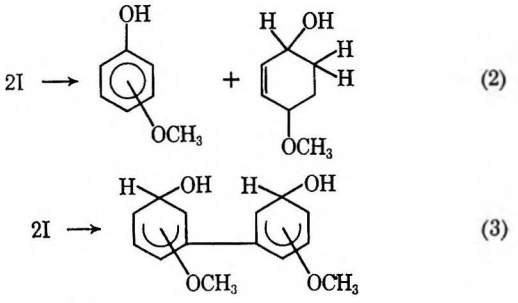
The rate constant for reaction 1 has been determined to be 3.6×10^9 M^{-1} sec^{-1}.[10] Although the rate constant for the reaction of the hydrated electron with anisole is not available, its upper limit can be estimated to be 2×10^9 M^{-1} sec^{-1} from a linear Hammett $\sigma\eta$[11] plot which was recently obtained for the reactivity of hydrated electrons with a number of substituted aromatic compounds.[12] In air, nitrous oxide, and nitrous oxide–oxygen saturated solutions at a 2×10^{-4} M anisole concentration, the reaction of the hydrated electron with anisole is completely suppressed by virtue of its respective reaction with oxygen and nitrous oxide.[13,14]



(1)

I

Since every e_{aq}^- is converted into a ·OH[13] in the nitrous oxide saturated solution, the yield of I is expected to approach the value of 5.2 ± 0.2 ($G_{OH} + G_{e_{aq}^-}$).[3] The total yield of methoxyphenols and phenol in this system is 0.96 (Table I), a G value considerably smaller than expected for a stoichiometric conversion of I into methoxyphenols. A similar situation has been encountered in the irradiation of nitrobenzene in dilute aqueous nitrous oxide saturated solutions[2] and, by analogy, it is plausable to assume that reaction 1 is followed by reactions 2 and 3.



(2)

(3)

Phenol was formed in addition to methoxyphenols in the irradiated aqueous anisole solution (Table I), whereas irradiated aqueous nitrobenzene yielded phenol, in addition to nitrophenols, only at high doses (5–10 $\times 10^5$ rads).[2] In eq 1 we did not specify the point of attack for the hydroxyl radical on anisole. It is conceivable that it not only attacks at the *ortho* and *para* positions but adds also to the C-1 position which carries the methoxyl group. Indeed, in a recent pulse radiolysis study the spectroscopic evidence obtained was found to be compatible with the formation of the 1,1,4-trihydroxycyclohexadienyl radical in irradiated aqueous solutions of hydroquinone.[15] The resulting 1-methoxy-1-hydroxycyclohexadienyl radical would then react according to reaction 2 with elimination of ·OCH_3 which would lead to phenol formation. Phenol

(10) M. Anbar, D. Meyerstein, and P. Neta, *J. Phys. Chem.*, **70**, 2660 (1966).

(11) $\eta = \log k(C_6H_5X + e_{aq}^-)/k(C_6H_6 + e_{aq}^-)$.

(12) M. Anbar and E. J. Hart, *J. Amer. Chem. Soc.*, **86**, 5633 (1964).

(13) The rate constants for these reactions[14] are

$$e_{aq}^- + N_2O \xrightarrow[k = 9 \times 10^9\ M^{-1}\ sec^{-1}]{} \cdot OH + N_2O + OH^-$$

$$e_{aq}^- + O_2 \xrightarrow[k = 1.9 \times 10^{10}\ M^{-1}\ sec^{-1}]{} O_2^-$$

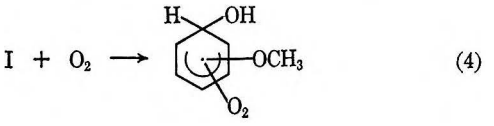
and the concentrations of the gases in the saturated solutions are given in the footnote of Table I.

(14) M. Anbar and P. Neta, *Int. J. Appl. Radiat. Isotopes*, **18**, 493 (1967), and references cited therein.

(15) G. E. Adams and B. J. Michael, *Trans. Faraday Soc.*, **63**, 1171 (1967).

could also be formed if radical I eliminated methanol to yield a phenoxyl radical. Unfortunately we did not find a sensitive analytical technique to detect methanol in the low concentrations in which it might be present, but the presence of nitrate[2,16] and chloride[17] ions in irradiated aqueous solutions of nitro and chlorobenzene tend to support this mechanism. Furthermore, in a recent pulse radiolysis study of aqueous phenol the initially formed dihydroxycyclohexadienyl radical was demonstrated to form phenoxyl radical either by OH^- or H^+ removal.[18] Naturally we were unable to distinguish between these modes of phenol formation which might concurrently or competitively occur. Regardless of the mechanism, the formation of phenol from nitrobenzene is considerably less favorable than it is from chloro[17] or fluorobenzene,[19] which emphasizes the differences that monosubstituted aromatic compounds exhibit in radiation-induced hydroxylations.

When oxygen is present in the aqueous anisole solution, it not only scavenges the hydrated electron[13] but reacts with I to give a peroxy radical (eq 4) which then



(4)

presumably decomposes by a first-order process[20] to yield methoxyphenols and $HO_2\cdot$ or O_2^-.

The reactivity of oxygen with the nitrosubstituted hydroxycyclohexadienyl radical[21] was found to be some 200 times less than with the unsubstituted hydroxycyclohexadienyl radical.[20] It was suggested that the reactivity of monosubstituted hydroxycyclohexadienyl radicals toward oxygen decreases with the increasing electronegativity of the substituents.[21] Since a methoxy group is considerably less electronegative than a nitro group, it is expected that the rate constant for reaction 4 is several times higher than it is for the reaction of oxygen with nitro or even unsubstituted hydroxycyclohexadienyl radicals. In agreement with this expectation is the dramatic change in the isomer distributions of the methoxyphenols in the presence of oxygen compared with those in its absence (Tables I and II). Since in the nitrous oxide–oxygen saturated solution the isomer distribution is the same as in the air saturated solution (Table II) but the total yield of hydroxylated products is twice as great in the former system as in the latter (Table I), the same mechanism must prevail in these two systems.

TABLE II

ISOMER DISTRIBUTION OF METHOXYPHENOLS AND PARTIAL RATE FACTORS FOR THE HYDROXYLATION OF ANISOLE

Conditions	Isomer distribution, % ortho	meta	para	Partial rate factors[a] o_f^R	m_f^R	p_f^R
Radiation induced[b]	37	0	63	0.93	...	3.15
Radiation induced[c]	39	0	61	0.96	...	3.06
Radiation induced[d]	80	0	20	2.01	...	1.02
Fenton reaction	86	0	14	2.16	...	0.70
Ferric–catechol system[e]	64	3	33	1.61	0.08	1.66
Ferric–hydroquinone system[e]	65	<5	35	1.64	0.12	1.76
Udenfriend system[e]	88	0	12	2.20	...	0.60

[a] $o_f^R = [k(C_6H_5OCH_3 + \cdot OH)/(1/6)k(C_6H_6 + \cdot OH)][\%\ o\text{-methoxyphenol}/(2 \times 100)]$; $m_f^R = [k(C_6H_5OCH_3 + \cdot OH)/(1/6)[k(C_6H_6 + \cdot OH)][\%\ m\text{-methoxyphenol}/(2 \times 100)]$; $p_f^R = [k(C_6H_5OCH_3 + \cdot OH)/[(1/6)k(C_6H_6 + \cdot OH)][\%\ p\text{-methoxyphenol}/100]$. [b] $[C_6H_5OCH_3] = 2.0 \times 10^{-4}\ M$, $[O_2] = 2.30 \times 10^{-4}\ M$. [c] $[C_6H_5OCH_3] = 2.0 \times 10^{-4}\ M$, $[N_2O] = 1.45 \times 10^{-2}\ M$, $[O_2] = 2.3 \times 10^{-4}\ M$. [d] $[C_6H_5OCH_3] = 2.0 \times 10^{-4}\ M$, $[N_2O] = 2.00 \times 10^{-2}\ M$. [e] Isomer distributions taken from ref 6 and 7.

In argon saturated solution anisole competitively reacts both with hydrated electrons and with hydroxyl radicals. The over-all result of these and the subsequent set of complex reactions is the significant decrease in methoxyphenol formation which is paralled by an increase in phenol (Table I). Although a similar situation has been encountered in the radiation chemistry of aqueous argon saturated fluorobenzene,[19] the present data are insufficient for any detailed mechanistic interpretation in this system.

Assuming that the isomer distribution of methoxyphenols reflects the extent of hydroxyl radical attack on the different ring positions of anisole, the partial rate factors (Table II) show some selectivity indicating that the attacking hydroxyl radical is, at least partially, electrophilic. A qualitative comparison of the partial rate factors for chemical and radiation induced hydroxylations of anisole (Table II) tends to indicate that they follow different mechanisms and therefore the attacking species for the former is not likely to be a simple uncomplexed hydroxyl radical. Alternatively it might indicate that in chemical hydroxylations oxygen may be rapidly depleted and therefore the hydroxylation mechanism resembles that observed for the radiation-induced hydroxylation in nitrous oxide saturated solutions.

Registry No.—Anisole, 100-66-3; phenol, 108-95-2; *o*-methoxyphenol, 90-05-1; *p*-methoxyphenol, 150-76-5.

Acknowledgments.—Helpful discussions with Drs. K.-D. Asmus, E. J. Fendler, and I. A. Tabu are gratefully acknowledged.

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(18) E. J. Land and M. Ebert, *Trans. Faraday Soc.*, **63**, 1181 (1967).
(19) J. H. Fendler, unpublished results.
(20) L. M. Dorfman, I. A. Taub, and R. E. Bühler, *J. Chem. Phys.*, **36**, 3051 (1962).
(21) K.-D. Asmus, B. Cercek, M. Ebert, A. Henglein, and A. Wigger, *Trans. Faraday Soc.*, **63**, 2435 (1967).

Relative Rates of Addition of Iodine Isocyanate to Unsaturated Compounds[1]

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Received July 5, 1967

The relative rates of addition of iodine isocyanate (generated *in situ* from iodine and silver cyanate) to unsaturated compounds was studied with 18 unsaturated compounds at a temperature range from −80 to 3°, over a range of concentrations, and at various ratios of reactants. Rates of reaction decrease with decreasing temperature and concentration of unsaturated compound and also when excess olefin is used. Vinyl and isopropenyl acetates react very rapidly whereas alkynes react slowly. When an electron-withdrawing carbonyl group or chlorine atom is attached to the double bond, essentially no reaction occurs. The relative rates of addition of *in situ* generated iodine isocyanate to unsaturated compounds follows a series typical of an electrophilic reaction.

The pioneering work of Birckenbach and Linhard[3] showed that iodine isocyanate adds to olefinic double bonds in a manner typical of pseudo-halogens. Recently Drefahl and Ponsold[4] showed that the isocyanate group becomes attached to the more alkyl- (or aryl-) substituted olefinic carbon in substituted cyclohexenes, and Hassner and Heathcock[5] obtained a similar result in acyclic systems. Both groups demonstrated that the reaction occurs in a stereospecific *trans* manner, and suggested that an iodonium ion is involved as an intermediate.[4,5] The addition products are vicinal iodoisocyanates.

While iodine isocyanate appears to behave as an electrophilic agent, there is little information available concerning its relative reactivity with olefins of varying nucleophilic character. Birckenbach and Linhard[3] had qualitatively noted that the addition of iodine isocyanate to ethylene was much slower than to either cyclohexene or 2-methyl-2-butene. Experimentally, this problem can be studied with solutions of preformed iodine isocyanate or by generating this reagent *in situ* from silver cyanate and iodine in the presence of the olefin. The use of preformed iodine isocyanate solutions offers certain obvious advantages over the heterogeneous *in situ* method and some preliminary studies have been reported.[6] Nonetheless, the *in situ* method is more commonly used in synthetic procedures and a detailed knowledge of the relative reactivities under these experimental conditions is highly desirable.

In a preliminary communication[1b] we reported that there is a strong similarity among the relative electrophilicities of iodine isocyanate (generated *in situ*), dibromocarbene, and bromine. We now wish to report the relative rates of the addition of iodine isocyanate, generated *in situ* under heterogeneous conditions, to a wide variety of unsaturated compounds and to assess the synthetic utility of this reaction.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord 137 and were run as Nujol mulls. Kinetic results were monitored with an F & M scientific model 500 gas chromatograph equipped with a disk integrator using columns and conditions appropriate to the compounds studied. Microanalyses were performed by Microanalysis Laboratories, Wilmington, Del.

Unsaturated compounds and internal standards were shown to be pure by glpc analysis. The iodine was Fisher or Baker resublimed grade; silver cyanate was from Eastman Organic Chemical Co.

General Procedure.—Reactions were run in a semimicro, four-necked flask fitted with a condenser and/or drying tube, an electrically driven stirrer with a Teflon blade, a thermometer, and a rubber septum through which samples could be removed for analysis. The entire apparatus was wrapped in aluminum foil to exclude light.

The requisite amounts of anhydrous ether, iodine, olefin, and an internal standard were placed in the flask which was then sealed and immersed in a dewar flask containing a freezing methanol–water solution. About four–eight replicate samples (~3 μl) of this solution were removed through the rubber septum *via* a hypodermic syringe and the glpc areas of the unsaturated compound and internal standard were computed. The use of the internal standard (generally this was approximately 40% by weight, based on unsaturated compound, of benzene, toluene, or a suitable saturated aliphatic hydrocarbon) permitted ready determination of unreacted unsaturated compound during the course of the reaction. Column conditions and stationary phases chosen depended on the compounds studied; however, most unsaturated hydrocarbons were monitored using a 20-ft column with 15% Apiezon L on Anakrom ABS 70/80 mesh. The more polar unsaturated compounds were monitored with silicone SE 30 or Carbowax 20M–terephthalate columns. Ordinarily, good agreement was found between the initial ratio of internal standard and that computed from glpc curves.

After the iodine–unsaturate–ether solution had attained thermal equilibrium, dry silver cyanate was added in one portion with stirring. Samples for glpc analysis were removed periodically through the rubber septum. (During sampling, stirring was discontinued for approximately 30 sec to permit the insoluble silver salts to settle.) Whenever possible, reactions were followed until over 90% of the unsaturated compound had disappeared. Nonreactive compounds were run for at least 24 hr.

The reaction conditions for the kinetic runs are summarized in Table I. Figures 1–5 show plots of the extent of reaction (measured by disappearance of unsaturated compound) against time in minutes. The rate data are reproducible and have been repeated many times.

General Isolation Procedure.—In most cases, after completion of the kinetic runs the solutions were filtered and the bulk of the ether was removed by evaporation. At this point, infrared spectra showed a strong band at 2250 cm^{-1} due to the presence of an organic isocyanate. In some cases, the vicinal iodoisocyanates were converted into methyl iodocarbamates by refluxing in methanol (30–45 min for secondary isocyanates and 5–6 hr for tertiary isocyanates) until that infrared band had disappeared. The bulk of the methanol was then evaporated and the residual sample was treated with a large quantity of dilute aqueous sodium sulfite to remove traces of iodine and to precipitate the iodocarbamate which was then filtered off, if solid, or extracted with ether. These compounds could usually be further purified by recrystallization from methanol or acetone. Infrared spectra of vicinal methyl iodocarbamates showed N—H bands at about 3200 and 1500 cm^{-1} and a C=O band at about 1650 cm^{-1}.

(1) (a) Pseudo-Halogens. II. (b) For part I, see C. G. Gebelein and D. Swern, *Chem. Ind.* (London), 1462 (1965). (c) Presented in part at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965. (d) This work was partially supported by Public Health Service Research Grants No. CA-07803 and CA-07174.

(2) Work submitted in partial fulfillment of the requirements for the Ph.D. degree, Temple University, Feb 1967.

(3) L. Birckenbach and M. Linhard, *Ber.*, **63**, 2544 (1930); **64**, 961, 1076 (1931).

(4) G. Drefahl and K. Ponsold, *Chem. Ber.*, **93**, 519 (1960); G. Drefahl, K. Ponsold, and G. Köllner, *J. Prakt. Chem.*, **28**, 136 (1964).

(5) A. Hassner and C. C. Heathcock, *Tetrahedron Lett.*, 1125 (1964).

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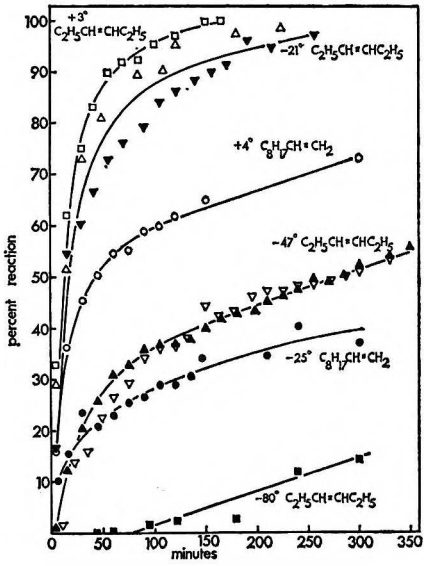

Figure 1.—Effect of temperature on the reaction rate of 0.25 *M* 1-decene and 0.15 *M* *trans*-3-hexene with iodine isocyanate: 1-decene at 4°, ○; 1-decene at −25°, ●; *trans*-3-hexene at 3°, □; *trans*-3-hexene at −21°, △▼; *trans*-3-hexene at −47°, ▲▽; *trans*-3-hexene at −80°, ■.

TABLE I

ADDITION OF IODINE ISOCYANATE, GENERATED *in situ*, TO UNSATURATED COMPOUNDS

Unsaturated compound	Molarity	Molar ratio, AgOCN/I_2/ unsaturate	Reacn temp, ±1°C	Figure
1-Hexene	0.500	1.33/1.00/1.00	4[a]	2
1-Decene	0.262	1.31/1.00/1.03	−25	1
1-Decene	0.246	1.30/1.00/0.96	4	1
Vinyl acetate	0.137	1.30/1.00/1.67	−47	4
Vinyl acetate	0.135	1.29/1.00/0.65	−48	4
Vinyl acetate	0.500	1.33/1.00/1.00	−20[b]	
Isopropenyl acetate	0.145	1.28/1.00/0.70	−47	4
Isobutyl vinyl ether	0.139	1.28/1.00/0.67	−48	
Methyl vinyl ketone	0.500	1.33/1.00/1.00	1[c]	
Methyl methacrylate	0.500	1.33/1.00/0.50	−25[c]	
2-Methyl-1-pentene	0.137	1.29/1.00/0.66	−47	3
2-Methyl-1-pentene	0.500	1.33/1.00/1.00	3[a]	2
trans-3-Hexene	0.146	1.28/1.00/0.70	−80	1
trans-3-Hexene	0.137	1.29/1.00/0.66	−48	1, 3, 4
trans-3-Hexene	0.145	1.28/1.00/0.70	−22	1, 3
trans-3-Hexene	0.150	1.32/1.00/0.73	3	1
trans-3-Hexene	0.500	1.33/1.00/1.00	1[a]	2
Ethyl crotonate	0.500	1.33/1.00/1.00	4[c]	
2,3-Dimethyl-2-butene	0.137	1.29/1.00/0.66	−47	3
2,3-Dimethyl-2-butene	0.142	1.29/1.00/0.68	−47	3
3-Hexyne	0.500	1.33/1.00/1.00	4	2
Cyclopentene	0.141	1.28/1.00/0.67	−22	5
Cyclohexene	0.135	1.33/1.00/0.67	−22	3, 5
Cyclohexene	0.500	1.33/1.00/1.00	1[a]	2
Cycloheptene	0.136	1.29/1.00/0.66	−23	5
Cycloheptene	0.500	1.33/1.00/1.00	−19[a]	
Cycloheptene	0.500	1.33/1.00/1.00	2[a]	2
Cyclooctene	0.134	1.28/1.00/0.64	−23	5
Norbornene	0.141	1.28/1.00/0.67	−21	5

[a] In these more concentrated solutions, an exotherm of 4–6° was noted. [b] An exotherm of 22° occurred in this run. The solvent was tetrahydrofuran. [c] When no reaction was observed after 5 hr, the reaction system was allowed to warm to room temperature and was monitored for at least 24 hr.

In certain cases, the vicinal iodoisocyanates were converted into the corresponding iodoamine hydrochlorides by adding concentrated aqueous hydrochloric acid to the ethereal solution and stirring sevaral hours. After evaporation to dryness, the iodoamine hydrochloride was recrystallized from ethanol. The ir spectra showed the typical NH_3^+ bands at 2400–2600 cm^{-1}.

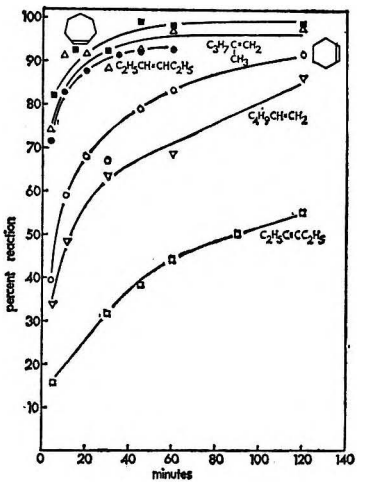

Figure 2.—Rate of addition of iodine isocyanate to various unsaturated compounds at 1–4°, 0.50 *M* unsaturate, and a molar ratio of AgOCN/I_2/unsaturate of 1.33/1.00/1.00: ■, cycloheptene; △, 2-methyl-1-pentene; ●, *trans*-3-hexene; ○, cyclohexene; ▽, 1-hexene; □, 3-hexyne.

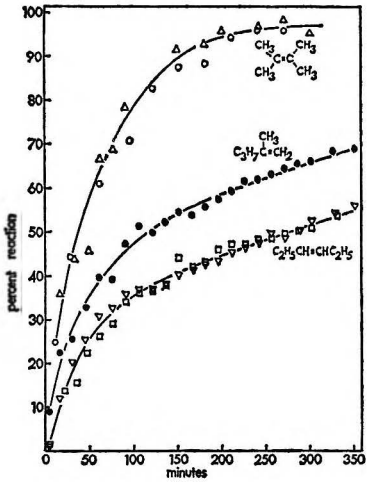

Figure 3.—Rate of addition of iodine isocyanate to *trans*-3-hexene, 2-methyl-1-pentene, and 2,3-dimethyl-2-butene at −47°, 0.14 *M* olefin, and an average AgOCN/I_2/olefin ratio of 1.29/1.00/0.67.

Preparative Runs.—Preparative runs were made in several cases using the general procedure described by Hassner and Heathcock.[7,8] Iodoisocyanates were converted into the corresponding carbamates or amine hydrochlorides in the usual fashion.

Methyl (*trans*-2-iodocyclohexyl)carbamate was prepared from cyclohexene, mp 133.0–133.7° from acetone (lit.[3] mp 135°).

Methyl (*trans*-2-iodocyclopentyl)carbamate was prepared from cyclopentene, mp 81–83° from methanol (lit.[7,8] mp 85–87°).

Anal. Calcd for $C_7H_{12}NO_2I$: C, 31.25; H, 4.50; N, 5.21; I, 47.16. Found: C, 31.39; H, 4.64; N, 4.79; I, 46.05.

4,5-Trimethylene-2-oxazolidone was prepared from methyl (*trans*-2-iodocyclopentyl)carbamate by mild heating in a manner similar to that described by Heathcock and Hassner,[9] mp 87–88° from acetone.

Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.75; H, 6.90; N, 10.98.

Methyl (*trans*-2-iodocycloheptyl)carbamate was prepared from cycloheptene, mp 103.5–104.5° from methanol (lit.[7,8] mp 103–104°).

Anal. Calcd for $C_9H_{16}NO_2I$: C, 36.38; H, 5.43; N, 4.71; I, 42.71. Found: C, 36.36; H, 5.28; N, 4.61; I, 42.55.

(7) A. Hassner and C. Heathcock, *Tetrahedron*, 1037 (1964).

(8) A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967).

(9) C. Heathcock and A. Hassner, *Angew. Chem. Intern. Ed. Engl.*, **2**, 213 (1963).

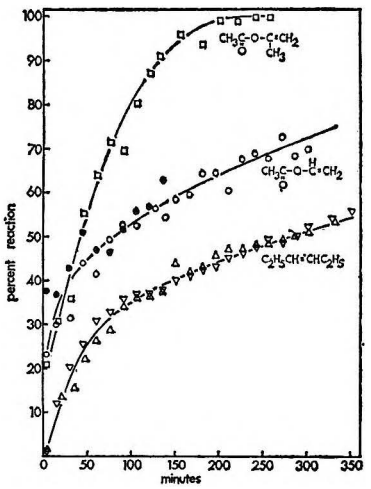

Figure 4.—Rate of addition of iodine isocyanate to *trans*-3-hexene, vinyl acetate, and isopropenyl acetate at −47°, 0.14 *M* of unsaturate, and an average AgOCN/I_2/unsaturate ratio of 1.29/1.00/0.67.

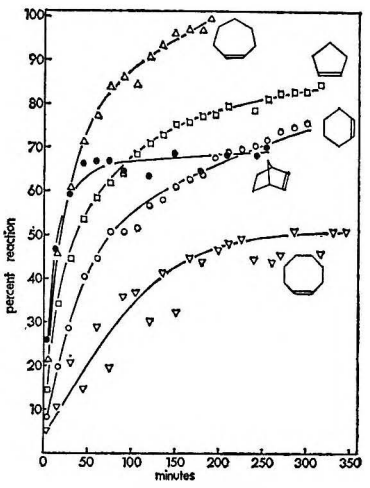

Figure 5.—Rate of addition of iodine isocyante to cyclic olefins at −22°, 0.14 *M* olefin, and an average AgOCN/I_2/olefin ratio of 1.29/1.00/0.66: □, cyclopentene; ○, cyclohexene; △, cycloheptene; ▽, cyclooctene; ●, norbornene.

Methyl (*trans*-2-iodocyclooctyl)carbamate was prepared from cyclooctene, mp 117.8–118.4° from methanol (lit.[7,8] 115–116.5°).

Anal. Calcd for $C_{10}H_{18}NO_2I$: C, 38.60; H, 5.83; N, 4.50; I, 40.78. Found: C, 38.77; H, 5.78; N, 4.48; I, 40.85.

Methyl (2-iodocyclododecyl)carbamate was prepared from cyclododecene (33% *cis*- and 67% *trans*-), mp 103.8–104.9° from methanol (lit.[7,8] mp 102–104°).

Anal. Calcd for $C_{14}H_{25}NO_2I$: C, 45.79; H, 7.14; N, 3.81; I, 34.55. Found: C, 45.95; H, 7.24; N, 3.76; I, 34.29.

Methyl [1-(iodomethyl)heptyl]carbamate was prepared from 1-octene, mp 48.0–48.9° from methanol.

Anal. Calcd for $C_{10}H_{20}NO_2I$: C, 38.35; H, 6.44; N, 4.47; I, 40.52. Found: C, 38.41; H, 6.42; N, 4.47; I, 40.69.

4-Iodo-3-aminohexane hydrochloride was prepared from *trans*-3-hexene, mp 147.5–149.0 from ethanol.

Anal. Calcd for $C_6H_{15}NICl$: C, 27.35; H, 5.74; N, 5.32. Found: C, 27.58; H, 5.66; N, 5.12.

3-Iodo-2-amino-2,3-dimethylbutane hydrochloride was prepared from 2,3-dimethyl-2-butene, mp >330° from ethanol.

Anal. Calcd for $C_6H_{15}NICl$: C, 27.35; H, 5.74; N, 5.32. Found: C, 26.93; H, 5.99; N, 5.43.

Results

Figures 1–5 summarize the results of heterogeneous kinetic studies on the addition of iodine isocyanate, generated *in situ*, to a variety of unsaturated compounds at different temperatures, concentrations, and reactant ratios. In all figures, the extent of reaction is expressed as the per cent of unsaturated compounds consumed in a given time interval.

Figure 1 shows that *in situ* generated iodine isocyanate reacts faster with *trans*-3-hexene than with 1-decene, even though the latter was employed at a higher molarity. Figure 1 also shows that the rate of reaction decreases with decreasing temperature.

The effects of structure of the unsaturated compound is seen in Figure 2 which shows the reaction of five olefins and one acetylene with iodine isocyanate at 1–4°. The disubstituted 1-olefin, 2-methyl-1-pentene, reacts faster than the internal *trans* olefin, *trans*-3-hexene, and the monosubstituted olefin, 1-hexene. Internal olefins show considerable variation in rate. The difference in reactivity of the fastest reacting olefins can not be ascertained accurately at this temperature and concentration, however. The internal acetylene, 3-hexyne, was slower than 1-hexene.

When the temperature is lowered still further to −47°, as shown in Figure 3, the difference between 2-methyl-1-pentene and *trans*-3-hexene becomes evident. Under these conditions, the very reactive 2,3-dimethyl-2-butene can be studied. This last olefin is the most reactive olefin studied.

Iodine isocyanate also adds to unsaturated compounds other than olefins and acetylenes. Vinyl and isopropenyl acetates both react rapidly. At −47° and 0.14 *M*, the rates of reaction of vinyl and isopropenyl acetates can be conveniently studied, as shown in Figure 4. Isopropenyl acetate reacts faster than vinyl acetate and about as fast as 2,3-dimethyl-2-butene. Vinyl acetate reacts slightly more slowly than 2-methyl-1-pentene, but faster than *trans*-3-hexene.

Figure 5 shows the reaction of five cyclic olefins with iodine isocyanate at −22°. The order of increasing rate of reaction is cyclooctene < cyclohexene < cyclopentene < cycloheptene = norbornene (initial rate).

Methyl oleate and methyl elaidate (*cis*- and *trans*-methyl-9-octadecenoate, respectively) both react about as rapidly as *trans*-3-hexene at 3° and 0.15 *M*.

Unsaturated compounds, such as methyl vinyl ketone, methyl methacrylate, ethyl crotonate, and vinylidene chloride do not appear to react with iodine isocyanate. Polyunsaturated. compounds, such as dienes, do react with iodine isocyanate. Preliminary results indicate that dienes do not always react with 2 mol of iodine isocyanate; this is in agreement with Birckenbach's[3] observation that isoprene reacts with only 1 mol of iodine isocyanate.

Discussion

Figures 1–5 show that different unsaturated compounds display widely different reactivity with iodine isocyanate under the reaction conditions studied. While a qualitative ranking can readily be made on the basis of these data, a quantitative approach offers several advantages. These include the possibility of assessing the effect of alkyl group loading on the reactivity of the double bond, the effect of ring size in cyclic systems, and a comparison of the iodine isocyanate reactions with other electrophilic reactions.

Relative Reactivity Determinations.—The most direct method of obtaining a quantitative series is to

compare the specific rate constants for the individual systems. The heterogeneous system, however, does not lend itself to a true kinetic study. The results obtained do not follow first-, second-, or third-order kinetics.

The addition reaction does not depend primarily on the rate of generation of iodine isocyanate from iodine and silver cyanate. Solutions of iodine isocyanate react very rapidly with many olefins.[6] If generation of iodine isocyanate were the controlling factor, there should be less marked differences observed among the various unsaturated compounds studied; this is in contrast to the results in Figures 1–5. In addition, many olefins (for example, *trans*-3-hexene at −22°) add iodine isocyanate faster than it is generated in solutions containing no olefin.[6]

Table II summarizes the results of four different sets of reaction conditions that had been used to span the wide reactivity range of compounds studied. The agreement between the value of 570 for *trans*-3-hexene at −22° and 580 for this olefin at +1° indicates that the method used here is at least internally consistent. The most important conclusion from Table II is that the presence of an electron-withdrawing group adjacent to the double bond retards the reaction while electron-donating groups accelerate it. Thus, the electron-withdrawing carbonyl groups in methyl vinyl ketone, methyl methacrylate, and ethyl crotonate, and the chlorine atoms in vinylidene chloride effectively preclude addition of iodine isocyanate to these compounds. On the other hand, the reactivity shows a pronounced increase as the number of electron-donating alkyl groups about the double bond increases. These results are typical of an electrophilic reaction, and are consistent with the proposals of Drefahl and Ponsold[4] and of Hassner and Heathcock.[5]

TABLE II

RELATIVE REACTIVITIES OF UNSATURATED COMPOUNDS WITH IODINE ISOCYANATE (GENERATED *in Situ* UNDER HETEROGENEOUS CONDITIONS) AT VARIOUS TEMPERATURES AND CONCENTRATIONS[a,b]

	Molarity of unsaturated compd				
Compound	0.14[b,c]	0.15[d]	0.50[e]	0.15[b,f]	Average rel reactivity
2,3-Dimethyl-2-butene	3800				3800
Isopropenyl acetate	3700				3700
Vinyl acetate	1950				1950
2-Methyl-1-pentene	1250				1250
Methyl oleate				570	570
trans-3-Hexene		570	580		570
Methyl elaidate				500	500
Norbornene		440			440
Cycloheptene		430			430
Cyclopentene		220			220
Cyclohexene		100	100		100
1-Hexene			50		50
Cyclooctene		35			35
3-Hexyne			8.0		8
Methyl vinyl ketone			0		0
Vinylidene chloride			0		0
Methyl methacrylate			0		0
Ethyl crotonate			0		0

[a] Since a comparison of the relative reactivities could not be made using specific kinetic rate constants, an alternate procedure was used. We have computed the reciprocal time in minutes to achieve equivalent extents of reaction and normalized these data on a scale in which cyclohexene is assigned the arbitrary value of 100. These normalized reciprocal times were computed at intervals of 5% reaction and were averaged to yield the relative reactivity values for the unsaturated compounds studied. [b] The base point for these conditions was *trans*-3-hexene = 570. Reaction temperatures were as follows: [c] −47°, [d] −22°, [e] 1–4°, [f] 2°.

Like *trans*-3-hexene, the five cyclic olefins are all disubstituted olefins but the relative reactivity for the slowest, cyclooctene, is only about one-twelfth that of the fastest, norbornene, and all are less reactive than *trans*-3-hexene.

The reactivity range from the slowest to the fastest in the cyclic and acyclic, disubstituted internal olefins is a factor of about 16. The major cause of this large spread appears to be complexation with iodine. These complexation phenonema are beyond the scope of the present paper but will be considered in detail in a subsequent article. We will also consider relative reactivities derived from competitive reactions of pairs of olefins with preformed solutions and with *in situ* generated iodine isocyanate. The present paper is concerned only with the relative reactivity encountered in the heterogeneous, *in situ* systems.

Surprisingly, vinyl acetate is almost 40 times as reactive as 1-hexene. The difference must reflect the effect of the acetoxy group compared with the *n*-butyl group. Vinyl acetate, however, is known to react slowly with electrophilic reagents. Hanna and Siggia[10] noted that bromination of vinyl acetate in acetic acid is much slower than that of 1-octene. Vinyl acetate also reacts slowly with iodine monochloride[11] and peroxyacetic acid.[12] These results suggest that the acetoxy group is less electron-donating than is an alkyl group. On the other hand, the acetoxy group is known to be activating in electrophilic aromatic substitution.[13,14]

If electrophilic attack on vinyl acetate is actually involved here, we would expect to observe an additional increase in rate with isopropenyl acetate since it could form the more highly stabilized tertiary carbonium ion. Isopropenyl acetate reacts about twice as fast as vinyl acetate (Table II). We must conclude that the acetoxy group is able to stabilize a positive charge effectively in the enol esters studied.

Alkynes, such as 3-hexyne, react very slowly with iodine isocyanate generated *in situ*. The slowness of this reaction, as compared with similar alkene reactions, may be due to the difficulty of forming the unsaturated iodonium ion, or that iodine adds to the triple bond to form a vinylic diiodide that reacts slowly.

The relative reactivity of iodine isocyanate with unsaturated compounds agrees fairly well with electrophilic reactivity orders shown in the literature but not

(10) J. G. Hanna and S. Siggia, *Anal. Chem.*, **37**, 690 (1965).
(11) D. Swern and E. F. Jordan, Jr., *J. Amer. Chem. Soc.*, **70**, 2334 (1948).
(12) L. S. Silbert, Z. B. Jacobs, W. E. Palm, J. P. Witnauer, W. S. Port, and D. Swern, *J. Polym. Sci.*, **21**, 161 (1956).
(13) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 430.
(14) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p 627.

with the reactivity orders of reagents that react *via* a cyclic or free-radical mechanism. These observations support the conclusion that iodine isocyanate behaves as an electrophilic reagent.

The relative reactivities also show that it is advantageous to use the *in situ* method to prepare iodine isocyanate adducts of internal olefins since the total reaction time (INCO generation plus addition) is less than that required to perform iodine isocyanate and add it to the double bond. With terminal olefins, dienes, or alkynes, the use of performed solutions of iodine isocyanate is the method of choice.[15]

Registry No.—Iodine isocyanate, 3607-48-5; methyl [1-(iodomethyl)heptyl]carbamate, 16666-25-4; 4-iodo-3-aminohexane hydrochloride, 16666-26-5; 3-iodo-2-amino-2,3-dimethylbutane hydrochloride, 16666-27-6.

(15) B. Grimwood and D. Swern, *J. Org. Chem.*, **32**, 3665 (1967).

Some Rate Studies and Their Mechanistic Implications for the Reaction of 2-Methylquinoline 1-Oxide and Acetic Anhydride[1]

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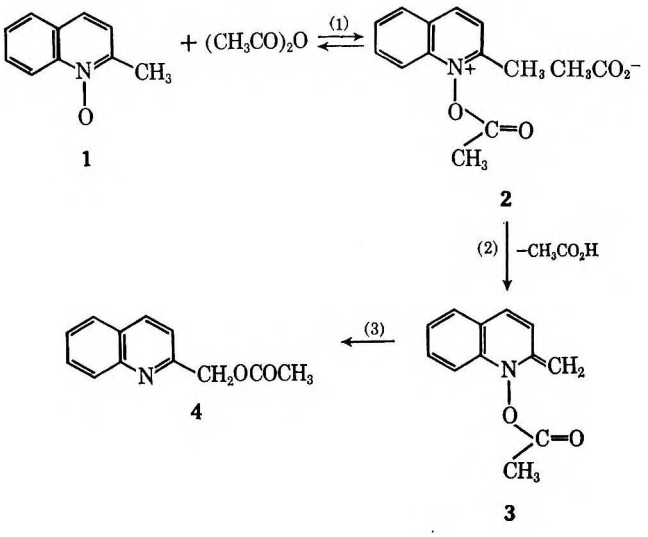
Received January 9, 1968

The rate of reaction of 2-methylquinoline 1-oxide (**1**) with acetic anhydride has been measured by three methods which gave similar results. The rate constants are believed to be a product of the equilibrium constant for reaction of **1** with acetic anhydride to form 1-acetoxy-2-methylquinolinium acetate (**2**) and of a rate constant for the latter to yield 2-quinolylmethyl acetate (**4**). α,α,α-Trideuterio-2-methylquinoline 1-oxide was found to react one-half as rapidly as the undeuterated derivative. This, plus the fact the product (**4**) formed at about the same rate as the equilibrium mixture of **1** and **2** disappeared, indicates that removal of a methyl hydrogen is the rate-determining step. Also it can be seen that any intermediate between **2** and **4** must have a very fleeting existence.

The reaction of 2- and 4-alkylaromatic N-oxides has been the subject of many synthetic and mechanistic studies; however, only one report,[3,3a] is available on the reaction kinetics of an alkylaromatic N-oxide, 2-methylquinoline 1-oxide, with acetic anhydride. Kinetic studies have been made on the reaction of pyridine N-oxide[4,5] and of acridine N-oxide[6] with acetic anhydride.

The following is a brief summary of some of the facts about the mechanism of the reaction of 2-alkylaromatic N-oxides and acetic anhydride. The example being cited is 2-methylquinoline 1-oxide (Scheme I) which is known to differ from 2-methylpyridine 1-oxide only in a slower rate of reaction and in more products for the latter. The first step is reversible based on C^{14} labeling and product studies.[7] 1-Acetoxy-2-methylquinolinium perchlorate undergoes reaction with acetate ion, trimethylamine, or cyanide ion to yield **4**.[7] This indicates that it is possible for **2** to be an intermediate in the reaction of **1** with acetic anhydride to yield **4** and also it can be seen from the results of the reactions with trimethylamine and with cyanide that the product (**4**) has the same acetoxy group which **2** had. The reaction of **2** to yield **4** involves scrambling of the oxygens of the acetoxy group as

SCHEME I



shown by O^{18}-labeling studies.[8] The fact that the reaction of 1-acetoxy-2-(α,α-dideuteriobenzyl)pyridinium perchlorate with sodium acetate when carried to half-completion showed no deuterium decrease in starting material[9] indicates by analogy that any intermediate or product formed after **2** is not in equilibrium with **2**. This implicates the removal of a proton as the rate-determining step. Compound **3**, an anhydro base, is a reasonable intermediate which has often been postulated, but its presence has not been detected.[10]

Much of the recent effort in this area has been to determine whether the N–O bond undergoes homolytic or

(1) Presented in part before the Division of Organic Chemistry of the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

(2) (a) Based in part on the Ph.D. Dissertation, 1964, of R. S. Darlak who was a NDEA Fellow, 1960–1963. This assistance is gratefully acknowledged. (b) Based in part on the Ph.D. Dissertation, 1966, of M. L. DeMatte who had a West Virginia University Senate Research Grant during the summer of 1965. This assistance is also gratefully acknowledged.

(3) S. Furukawa, *Yagkugaku Zasshi*, **79**, 492 (1959); *Chem. Abstr.*, **53**, 18029 (1959).

(3a) NOTE ADDED IN PROOF—See S. Oae, S. Tamagaki, T. Negoro, K. Ogino, and S. Kozuka, *Tetrahedron Lett.*, No. 8, 917 (1968), for a preliminary report on kinetic studies of 2- and 4-alkyl-substituted heteroaromatic N-oxides with acetic anhydride.

(4) J. H. Markgraf, H. B. Brown, S. C. Mohr, and R. G. Peterson, *J. Amer. Chem. Soc.*, **85**, 958 (1963).

(5) S. Oae and S. Kozuka, *Tetrahedron*, **21**, 1972 (1965).

(6) J. H. Markgraf and M.-K. Ahn, *J. Amer. Chem. Soc.*, **86**, 2699 (1964); J. H. Markgraf and C. G. Carson, *J. Org. Chem.*, **29**, 2806 (1964).

(7) C. W. Muth and R. S. Darlak, *ibid.*, **30**, 1909 (1965).

(8) S. Oae, T. Kitao, and Y. Kitaoka, *J. Amer. Chem. Soc.*, **84**, 3359 (1962); S. Oae and S. Kozuka, *Tetrahedron*, **20**, 2671 (1964).

(9) V. J. Traynelis and P. L. Pacini, *J. Amer. Chem. Soc.*, **86**, 4917 (1964).

(10) V. J. Traynelis, private communication. Spectral evidence for an anhydro base in the reaction of 1-acetoxy-4-benzylpyridinium perchlorate with acetate ion has been obtained.

heterolytic cleavage enroute to product.[11-13] The results point to heterolytic cleavage as the major pathway to product.

The present kinetic study was designed to determine whether 2 is a kinetically allowable intermediate in the foregoing reaction and to determine whether the proton abstraction in this reaction is the rate-determining step. 2-Methylquinoline 1-oxide was chosen for study rather than 2-methylpyridine 1-oxide because the former can be studied by ultraviolet spectroscopy in 100% acetic anhydride which is the solvent used in the synthesis of products such as **4**.

Experimental Section

Materials.—2-Methylquinoline 1-oxide hydrate, mp 77–78° (lit.[14] mp 77–78°), was distilled to yield anhydrous 2-methylquinoline 1-oxide (43% over-all yield) as a pale yellow liquid, bp 125–128° (0.2–0.3 mm). Upon standing the liquid solidified to a white solid, mp 44–45.4°. Both the hydrated and anhydrous N-oxides were stored in the dark, and the latter was stored over P_2O_5.

The nmr spectra ($CDCl_3$) of the hydrated and anhydrous N-oxides were the same except for the lack of a band at τ 7.0 for the anhydrous material which was present for hydrated N-oxide. The neutralization equivalent[15] for 2-methylquinoline 1-oxide was found to be 159.5 (calcd, 159.2).

α,α,α-Trideuterio-2-methylquinoline 1-oxide was prepared in the following manner under an atmosphere of nitrogen. To a solution made from 0.3 g (0.013 g-atom) of sodium and 10 ml of deuterium oxide (99.7%), Merck Sharp and Dohme, Canada Ltd, was added 5.0 g (0.031 mol) of 2-methylquinoline 1-oxide. The mixture was refluxed for 24 hr. The white solid which separated on cooling was distilled to give 4.2 g of pale yellow oil. The same procedure was repeated twice to yield 2.0 g (40%) of α,α,α-trideuterio-2-methylquinoline 1-oxide as a white solid: bp 137–139° (0.8–0.9 mm); mp 43–44.5°; ir (KBr) 2250 (C-D stretch), 1060 cm^{-1} (CD_3 bending); negligible absorption ($CDCl_3$) at τ 7.3 where 2-methyl hydrogens of 2-methylquinoline 1-oxide absorb.

Anal.[16] Calcd for $C_{10}H_6D_3NO$: 33.3 atom % excess D. Found: 34.2 atom % excess D.

1-Acetoxy-2-methylquinolinium perchlorate was prepared as follows. To 20 ml of acetic anhydride, cooled in an ice bath, was added 4.0 g (0.024 mol) of 60% perchloric acid at such a rate that the temperature did not exceed 25°. This solution was allowed to warm to room temperature and then to stand for 0.5 hr at room temperature before use.

To 10 ml of glacial acetic acid was added 4.0 g (0.021 mol) of 2-methylquinoline 1-oxide hydrate. After this solution had been cooled to ice temperature, 5 ml of acetic anhydride was added with stirring. To the resulting solution was added the foregoing perchloric acid–acetic anhydride solution; the temperature of the reaction was maintained between 0–10°. A white precipitate formed as the perchloric acid–acetic anhydride was added and redissolved before addition was complete. The white crystals were removed by filtration under nitrogen and washed with anhydrous ether to yield 4.6 g (73%) of 1-acetoxy-2-methylquinolinium perchlorate, mp 150–152° dec (lit.[15] mp 152–153°). The product was hygroscopic and was stored over phosphorus pentoxide.

Acetic anhydride (Eastman Kodak, White Label) was distilled through a 2-ft Vigreux column. The 139–139.5° fraction was used in the rate determinations.

Tetra-*n*-butylammonium acetate, mp 115–117° (lit.[17] mp 118 ± 2°), was used.

(11) T. Cohen and J. H. Fager, *J. Amer. Chem. Soc.*, **87**, 5701 (1965).
(12) T. Koenig, *ibid.*, **88**, 4045 (1966).
(13) R. Bodalski and A. R. Katritzky, *Tetrahedron Lett.*, No. 3, 257 (1968).
(14) I. J. Pachter, *J. Amer. Chem. Soc.*, **75**, 3026 (1953).
(15) C. W. Muth, R. S. Darlak, W. H. English, and A. T. Hammer, *Anal. Chem.*, **34**, 1163 (1962).
(16) Analysis was performed by Josef Nameth, 303 W. Washington St., Urbana, Ill. 61801.
(17) W. E. Thompson and C. A. Kraus, *J. Amer. Chem. Soc.*, **69**, 1016 (1947).

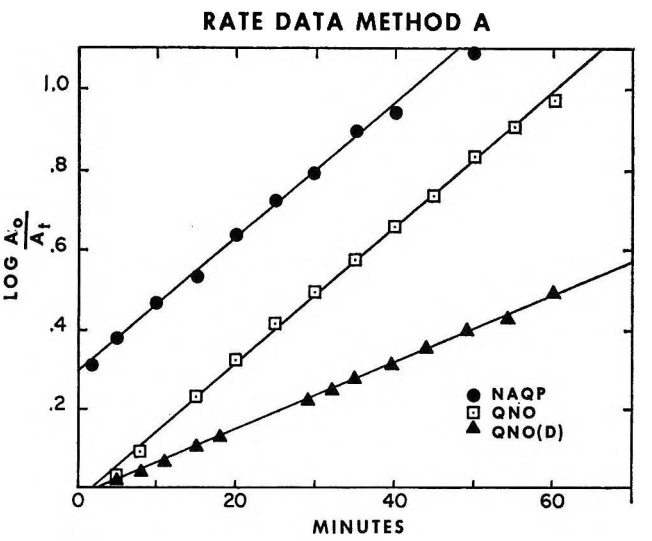


Figure 1.—Pseudo-first-order rates of reaction for (a) N-acetoxy-2-methylquinolinium perchlorate (●) with tetra-*n*-butylammonium acetate at 24.5 ± 0.1°, (b) 2-methylquinoline 1-oxide (⊡) at 25.1 ± 0.1°, and (c) α,α,α-trideuterio-2-methylquinoline 1-oxide at 25.2 ± 0.1 (▲) all in acetic anhydride by method A; data for a and b are from Tables I and II, respectively.

The dioxane used was purified according to the method of Wiberg.[18]

Methods for Determining Rates of Reaction. A. Monitoring Decrease of Absorbance of a Mixture of 2-Methylquinoline 1-Oxide and Acetic Anhydride or a Mixture of 1-Acetoxy-2-methylquinolinium Perchlorate and Acetate Ion in Acetic Anhydride. Apparatus.—A Beckman Model DU spectrophotometer, equipped with a cooling cell box which was attached to a Sargent S-84880 thermostat bath, was employed. The temperature was maintained at ±0.1° over the range 5–47°.

Rate Measurement.—As an example, 0.00309 g (1.94×10^{-5} mol) of 2-methylquinoline 1-oxide was dissolved and mixed well in 100 ml of acetic anhydride which had been thermostated to the temperature of the kinetic run. In all cases, no more than 2 min elapsed between the time of initial mixing of the reagents and the first reading which was made in a 1-cm cell. Null readings were obtained using acetic anhydride.

For studies with 1-acetoxy-2-methylquinolinium perchlorate a weighed amount of the latter was dissolved in acetic anhydride, and this solution was diluted with acetic anhydride containing the other reactants so the resulting concentration of 1-acetoxy-methylquinolinium perchlorate was $1\text{–}2 \times 10^{-4}$ *M*. Each day a fresh solution was prepared.

Tetra-*n*-butylammonium acetate was dissolved in acetic anhydride and, the resulting solution was standardized by titration with perchloric acid in acetic acid.

Plots of the log of the absorbance at time zero divided by the absorbance at time *t* at 331 and 340 mμ *vs.* time indicated that the reaction being followed was pseudo first order. It was established that 2-quinolylmethyl acetate, the only product that has been isolated from the reaction, does not absorb appreciably at these wavelengths. With the exception of a few of the reactions conducted at lower temperatures, all reactions were followed to a minimum of 60% completion; nine or more points were plotted for each run.

Results of typical kinetic runs are given in Tables I and II and plotted in Figure 1.

Identification of 2-Methylquinolylmethyl Acetate under Conditions of the Kinetic Experiments.—The ultraviolet spectra of solutions of both 2-methylquinoline 1-oxide in acetic anhydride and 1-acetoxy-2-methylquinolinium perchlorate plus tetra-*n*-butylammonium acetate in acetic anhydride became on standing nearly superimposable on the spectrum of 2-quinolylmethyl acetate. The latter was isolated in 71% yield when the reaction was carried out on a synthetic scale and nmr analysis indicated the yield was about 90%.

(18) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 245.

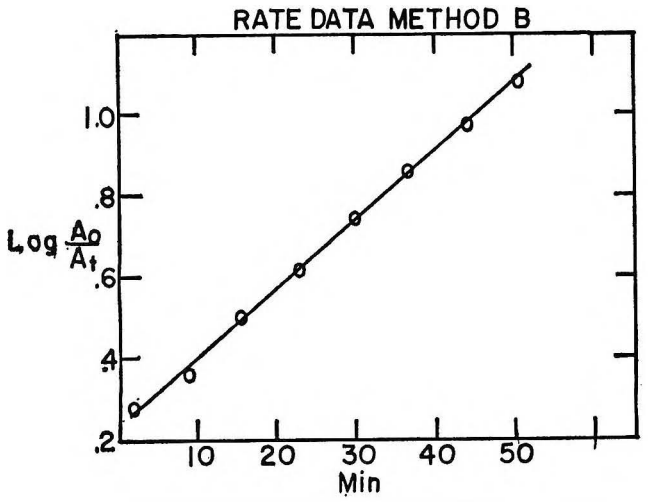


Figure 2.—Pseudo-first-order rate of reaction of 2-methylquinoline 1-oxide with acetic anhydride at 25.1 ± 0.1° by method B; data are from Table III.

TABLE I
RATES OF REACTION OF 2-METHYLQUINOLINE 1-OXIDE WITH ACETIC ANHYDRIDE[a] BY METHOD A

Time, sec	Absorbance at 331 mμ	Log $\frac{A_{t=0}}{A_{t=n}}$
120	0.995	
300	0.930	0.0294
480	0.800	0.0947
900	0.582	0.2329
1200	0.475	0.3211
1500	0.383	0.4146
1800	0.318	0.4954
2100	0.267	0.5713
2400	0.218	0.6594
2700	0.183	0.7354
3000	0.147	0.8305
3300	0.124	0.9044
3600	0.106	0.9725

[a] Initial concentration, 1.96×10^{-4} *M* 2-methylquinoline 1-oxide in acetic anhydride; temperature 25.1 ± 0.1°.

TABLE II
RATES OF REACTION OF 1-ACETOXY-2-METHYLQUINOLINIUM PERCHLORATE WITH ACETATE ION IN ACETIC ANHYDRIDE BY METHOD A[a]

Time, sec	Absorbance at 331 mμ	Log $\frac{A_{t=0}}{A_{t=n}}$
0	0.850	...
120	0.408	0.3187
300	0.353	0.3816
600	0.288	0.4700
900	0.246	0.5385
1200	0.195	0.639[illegible]
1500	0.163	0.7273
1800	0.136	0.795[illegible]
2100	0.1085	0.894[illegible]
2400	0.097	0.9427
3000	0.069	1.0906

[a] Initial concentrations of 1-acetoxy-2-methylquinolinium perchlorate and tetra-*n*-butylammonium acetate, 2.00×10^{-4} and 2.57×10^{-4} *M*, respectively; temperature 24.5 ± 0.1°.

B. Interrupting the Reaction of 2-Methylquinoline 1-Oxide and Acetic Anhydride by Adding Water. Determination of 2-Methylquinoline 1-Oxide by Ultraviolet Spectroscopy.—This method is similar to that used by Markgraf, *et al.*[4,6]

The rate of reaction of 2-methylquinoline 1-oxide with acetic anhydride was determined by measuring the absorbance at 340 mμ of reaction mixtures which had been quenched with water and diluted with dioxane. Since the product was found not to absorb at 340 mμ, the absorbance was taken as a measure of the starting material which remained.

For measuring reaction rates the reaction vessel, containing a known amount of 2-methylquinoline 1-oxide, was placed in a Fisher Unitized bath. A known weight of acetic anhydride, which had been previously thermostated at the temperature of the kinetic run, was then added to the reaction vessel. Timing was started upon addition of acetic anhydride. At various times, an aliquot was removed from the reaction vessel with a 2-ml pipet. The aliquot was immediately added to a preweighed 50-ml volumetric flask containing 2 ml of water and 2 ml of dioxane. The volumetric flask was then shaken for 2 min and reweighed. The sample was then diluted to 50 ml with dioxane, and the optical density of the solution was determined at 340 mμ. In all cases, no more than 5 min elapsed from the initial quenching of an aliquot to the time the optical density was determined. The null reading was obtained with a solution of all components except the 2-methylquinoline 1-oxide. The concentration of 2-methylquinoline 1-oxide in an aliquot was determined by comparing the optical density of an aliquot of the solution in dioxane with the optical densities of the Beer's law curve of 2-methylquinoline 1-oxide. The Beer's law curve was determined at 340 mμ for absorbance *vs.* concentration over a fivefold change in concentration. Excellent linearity was obtained; the intercept was zero.

A decrease in absorbance of the solution was found to occur if the solution were allowed to stand in the light. The same decrease in absorbance was observed with a solution of 2-methylquinoline 1-oxide in dioxane. To obtain accurate values of absorbance, red-tinted glass volumetric flasks were employed. In all cases, the absorbances of the solution were found to be constant over a 1-hr period.

Results of a typical kinetic run are given in Table III and plotted in Figure 2. All reactions were followed to at least 60% completion; six to eight points were plotted for each run.

TABLE III
RATES OF REACTION OF 2-METHYLQUINOLINE 1-OXIDE WITH ACETIC ANHYDRIDE BY METHOD B AT 25.1 ± 0.1°

Time, sec	Calcd N-oxide molarity,[a] $M \times 10^4$	Absorbance of aliquot[b] at 340 mμ	Obsd[c] N-oxide molarity, $M \times 10^4$	Log $\frac{C_{t=0}}{C_{t=n}}$
120	3.584	1.37	1.898	0.2760
540	3.584	1.12	1.551	0.3595
930	3.656	0.840	1.163	0.4975
1380	3.572	0.620	0.859	0.6189
1800	3.626	0.472	0.654	0.7438
2200	3.660	0.365	0.506	0.8593
2640	3.608	0.277	0.384	0.9729
3030	3.540	0.213	0.295	1.079

[a] Molarity of solution resulting after quenching and dilution to 50 ml with dioxane. The original reaction mixture from which the aliquots were taken had 1.358×10^{-3} g of N-oxide per 1.000 g of acetic anhydride. [b] After quenching and diluting to 50 ml with dioxane. [c] Extinction coefficient of 2-methylquinoline 1-oxide under these conditions is 7.22×10^3.

Since the concentrations of the N-oxide for the kinetic study were quite low no effort was made to isolate the N-oxide or the product; however, from 1.31 g of 1-acetoxy-2-methylquinolinium perchlorate stirred in 40 ml of acetic anhydride which was shaken with 40 ml of water for 10 min there was isolated 0.18 g (14%) of starting material, 0.22 g (25%) of 2-quinolylmethyl acetate, and 0.30 g (35%) of 2-methylquinoline 1-oxide.

C. Monitoring Nmr Signal for Disappearance of Methyl Hydrogens and for Appearance of Methylene Hydrogens from Reaction of 2-Methylquinoline 1-Oxide (1) with Hexadeuterioacetic Anhydride.—Solutions of 0.050–0.075 g of 1 in 0.5 ml of hexadeuterioacetic anhydride (99% isotopic purity, Stohler Isotope Chemicals, Rutherford, N. J.) containing 0.062–0.085 g of 1,1,2,2-tetrachloroethane as a standard were studied. Integrations at τ 3.8 (standard), 4.65 (methylene hydrogens), and 7.3 (methyl hydrogens) were made ten or more times during 1320 sec using a Varian Associates HA-60 nuclear magnetic resonance spectrometer. Hexadeuterioacetic anhydride was used in place

of nondeuterated acetic anhydride in order to minimize the absorption of the solvent at τ 7.3.

The pseudo-first-order rate constant (k_d) for the disappearance of the signal due to methyl hydrogens was found from the slope of the line from a plot of the log of the integration of the methyl signal *vs.* time. The pseudo-first-order rate constant (k_g) for the appearance of the signal for the methylene hydrogens was found from the slope of the line from a plot of log $(a_0 - x)$ *vs.* time, where a_0 is two-thirds of the integration of the signal of the methyl hydrogens at time zero and x is the integration of the signal of the methylene hydrogens at time t. The slopes of the lines from which the rate constants were determined were calculated by a computer. A least-squares program was used.

2-Quinolylmethyl acetate in acetic anhydride was found to show a singlet at τ 4.65.

The results are summarized in Table IV.

Table IV

Rates of Reaction of 2-Methylquinoline 1-Oxide with Hexadeuterioacetic Anhydride Using Nmr (Method C) at 35 ± 0.5°

	Decay of CH_3, $k \times 10^4$, sec^{-1}	Growth of CH_2 (product), $k \times 10^4$, sec^{-1}
	13.1 ± 0.7	12.2 ± 0.7
	12.5 ± 0.6	14.5 ± 1.0
	12.7 ± 0.6	10.1 ± 0.7
	12.0 ± 0.7	11.3 ± 0.7
	17.9 ± 0.4	13.1 ± 0.9
	14.7 ± 0.9	15.3 ± 0.2
Av	13.8 ± 2.0	12.8 ± 2.0

Results

The decrease of absorbance of a mixture of 2-methylquinoline 1-oxide and acetic anhydride at both 331 and 340 mμ (method A) has been found to obey pseudo-first-order kinetics at 8.2, 25.1, and 36.2°. It was determined that 2-quinolylmethyl acetate, the only product isolated, does not absorb appreciably at these wavelengths. The k values from this method (Table V) are in satisfactory agreement with those of methods B and C.

Table V

Rates of Reaction of 2-Methylquinoline 1-Oxide and Acetic Anhydride by Method A[a]

Temp, °C	A_0,[b] $M \times 10^4$	$k \times 10^4$, sec^{-1}
8.2	1.64	1.5[c]
25.1	2.38	6.5
36.2	2.21	14

[a] Rate constants from absorbances at 331 mμ. [b] Average initial concentration of 2-methylquinoline 1-oxide. [c] Average of six determinations; others are the average of four determinations.

Likewise the decrease in absorbance of a mixture α,α,α-trideuterio-2-methylquinoline 1-oxide and acetic anhydride at both 331 and 340 mμ (method A) has been found to obey pseudo-first-order kinetics at three temperatures (Table VI).

Table VI

Rates of Reaction of α,α,α-Trideuterio-2-methylquinoline 1-Oxide and Acetic Anhydride by Method A[a]

Temp, °C	A_0,[b] $M \times 10^4$	$k \times 10^4$, sec^{-1}
8.4	1.62	0.8[c]
25.2	2.27	3.3
36.2	1.28	8.1

[a] Rate constants from absorbances at 331 mμ. [b] Average initial concentration of α,α,α-trideuterio-2-methylquinoline 1-oxide. [c] Average of six determinations; others are the average of four determinations.

By comparing the k values in Table V and VI it can be seen the kinetic isotope effects at approximately 8, 25, and 36° are 1.9, 2.0, and 1.7, respectively.

Method A was also used to follow the reaction of 1-acetoxy-2-methylquinolinium acetate in acetic anhydride at five temperatures. The k values (Table VII) are in good agreement with those obtained from the reaction of the N-oxide with acetic anhydride.

Table VII

Rates of Reaction of 1-Acetoxy-2-methylquinolinium Perchlorate with Tetra-*n*-butylammonium Acetate in Acetic Anhydride by Method A

A_0,[a] $M \times 10^4$	B_0,[b] $M \times 10^4$	Temp, °C	$k \times 10^4$, sec^{-1}
1.45	2.57	5.5	1.6
1.52	2.57	15.2	3.9[c]
2.00	2.57	24.5	6.7
1.49	2.57	33.6	14
1.49	2.57	47.0	34

[a] Initial concentration of 1-acetoxyquinaldinium perchlorate. [b] Initial concentration of tetra-*n*-butylammonium acetate. [c] Average value for three runs while remainder of values are the average value for four runs.

The change in rate caused by added substance to both 2-methylquinoline 1-oxide hydrate in acetic anhydride and to 1-acetoxy-2-methylquinolinium perchlorate plus tetra-*n*-butylammonium acetate in acetic anhydride were studied. The results are given in Tables VIII and IX. In both systems acetic acid decreased the rates and a large excess of tetra-*n*-butylammonium acetate only slightly increased the rates.

Table VIII

Rates of Reaction of 1-Acetoxy-2-methylquinolinium Perchlorate with Tetra-*n*-butylammonium Acetate in Acetic Anhydride with Added Substances at 24.5° by Method A

A_0,[a] $M \times 10^4$	B_0,[b] $M \times 10^4$	Added substance		$k \times 10^4$, sec^{-1}
		Identity	M	
2.00	2.57	None		6.7
2.00	2.57	HOAc	0.348	4.1
2.99	2.99	HOAc	1.374	2.1
2.00	2.57	$NaClO_4$	1.99×10^{-3}	7.4
1.53	2.57	$NaClO_4$	3.29×10^{-3}	9.8
1.66	23.1	None		7.5

[a] Initial concentration of 1-acetoxy-2-methylquinolinium perchlorate. [b] Initial concentration of tetra-*n*-butylammonium acetate.

Table IX

Rates of Reaction of 2-Methylquinoline 1-Oxide Hydrate with Added Substances in Acetic Anhydride at 24.5° by Method A

A_0,[a] $M \times 10^4$	B_0,[b] $M \times 10^4$	Added substance		$k \times 10^4$, sec^{-1}
		Identity	M	
2.59	None	...	...	6.4
2.99	3.11	HOAc	0.229	4.9
3.11	3.11	HOAc	0.488	4.1
3.23	2.57	$NaClO_4$	3.37×10^{-3}	8.8
2.50	None	Et_4NClO_4	3.29×10^{-4}	6.7
1.95	23.1	None	...	7.0

[a] Initial concentration of 2-methylquinoline 1-oxide hydrate. [b] Initial concentration of tetra-*n*-butylammonium acetate.

The rate of reaction of 2-methylquinoline 1-oxide with acetic anhydride has been studied by quenching aliquots of the mixture with water and analyzing for 2-methylquinoline 1-oxide (method B). The pseudo-

first-order k values as determined from an average of three experiments at 25.2 and three experiments at 8.2° were 6.3×10^{-4} and 1.6×10^{-4} sec^{-1}, respectively. These values are in satisfactory agreement with those from method A.

From the kinetic data of Tables V and VI the thermodynamic activation parameters were calculated.[19] The enthalpies of activation, $\Delta H^{\pm}$, obtained from the slope of the line from a plot of log k/T *vs.* $1/T$ were 13.4 and 14.1 kcal/mol, respectively, for 2-methylquinoline 1-oxide and its α,α,α-trideuterio derivative. The entropies of activation, $\Delta S^{\pm}$, at 25.1° were calculated to be −28.3 and −27.5 eu, respectively.

Table IV gives a summary of the results obtained by method C.

Discussion

The fact that both mixtures of 2-methylquinoline 1-oxide (**1**) and acetic anhydride and of N-acetoxy-2-methylquinolinium perchlorate, tetra-*n*-butylammonium acetate and acetic anhydride showed only one absorption band in the τ 7.0–7.5 region, whereas N-acetoxy-2-methylquinolinium perchlorate in acetonitrile showed singlet absorptions at both τ 7.0 and 7.2 is further support[7] of the postulate that equilibrium for step 1 in Scheme I is rapidly obtained. It is assumed that exchange is occurring so rapidly that the nmr signal of the acetoxy methyl of N-acetoxy-2-methylquinolinium ion and of acetic anhydride are found in a weighted average which is indistinguishable from the signal for acetic anhydride.

The rate constants for the reaction of 2-methylquinoline 1-oxide (**1**) and acetic anhydride as determined by three methods are in satisfactory agreement. Apparently these constants are a product of the equilibrium constant for step 1 and of the rate constant for the reaction of N-acetoxy-2-methylquinolinium ion with acetate ion to form product **4**. Furukawa's ultraviolet studies[3] of **1** with varying amounts of acetic anhydride in dioxane can be interpreted to mean that the equilibrium constant for step 1 is important in determining the rate of formation of product **4**.

A kinetic isotope effect of 1.9 for the reaction for the reactions of **1** and of 2-α,α,α-trideuterio-2-methylquinoline 1-oxide with acetic anhydride is interpreted to mean that proton abstraction from the 2-methyl group by acetate ion is the rate-determining step. Since the concentrations of the two N-oxides were about the same and since the kinetic isotope effect is believed to be the ratio of K_1k_H to K_1k_D the influence of K_1 is probably cancelled. Any secondary isotope effect on this equilibrium would be expected to be smaller than 1.9.[20] If the reaction of **2** to form **4** is nonreversible as is the reaction of 1-acetoxy-2-(α,α-dideuteriobenzyl)-pyridinium perchlorate with sodium acetate,[9] then the isotope effect is not on an equilibrium between **2** and a later intermediate, for example, **3**. The removal of the proton in the rate-determining step probably has an early transition state.

The rate of reaction of N-acetoxy-2-methylquinolinium perchlorate with tetra-*n*-butylammonium acetate was found to be nearly the same as the rate of reaction of 2-methylquinoline 1-oxide with acetic anhydride. This is as expected if the foregoing mixture is reacting as shown in Scheme I. The very large drop in absorbance initially after mixing N-acetoxy-2-methylquinolinium perchlorate and tetra-*n*-butylammonium acetate is believed to be due to the rapid formation of product **4** while the equilibrium of step 1 is being established.

As can be seen from Table VIII and IX the presence of acetic acid slowed both the reaction of 2-methylquinoline 1-oxide hydrate with acetic anhydride and the reaction of N-acetoxy-2-methylquinolinium perchlorate with tetra-*n*-butylammonium acetate in acetic anhydride. Acetic acid possibly reacts with N-oxide **1** to alter the position of equilibrium in step 1 of Scheme I.

The addition of a 23-fold excess of tetra-*n*-butylammonium acetate caused only a moderate increase in rates in both systems. This can be explained by assuming as is shown in Scheme I that the added acetate ion is involved in competing reactions, the formation of **1** and **4**.

From method B, in which aliquots of 2-methylquinoline 1-oxide (**1**) in acetic anhydride were quenched with water, the amounts of **1** in the quenched aliquots were lower than would have been predicted if one assumes that all of the N-acetoxy-2-methylquinolinium acetate in the mixture before water is added is hydrolyzed to **1**. Apparently water underwent reaction with N-acetoxy-2-methylquinolinium ion to form the product **4** as well as **1**. The water may have served as a base to cause rearrangement to product or maybe it promoted ionization of a tight ion pair so that acetate ion could be a more effective base to cause rearrangement to product.

The pseudo-first-order rate constant for the decrease in N-oxide concentration as determined by this method was similar to that obtained by methods A and C. This agreement can be explained by assuming that any N-acetoxy-2-methylquinolinium acetate reacts with water to give a constant ratio of N-oxide and product. From a larger scale experiment in which N-acetoxy-2-methylquinolinium perchlorate was shaken with a mixture of acetic anhydride and water, the yields of N-oxide, N-acetoxy-2-methylquinolinium perchlorate, and 2-quinolylmethyl acetate isolated were 35, 14, and 25%, respectively.

By monitoring the growth of the signal at τ 4.65 of a mixture of 2-methylquinoline 1-oxide (**1**) in hexadeuterioacetic anhydride the rate of product formation was determined. This rate of product formation was found to be approximately the same as the rate of disappearance of the signal at τ 7.3 which was assumed to be due to 2-methyl groups of the equilibrium mixture of **1** and N-acetoxy-2-methylquinolinium acetate (see Table IV). This of course means that product is formed at about the same rate as the equilibrium mixture of the former reagents is disappearing. Consequently if N-acetoxy-2-methylquinolinium acetate is reacting to form an anhydro base (**3**), which in turn forms product **4**, the anhydro base must have a very fleeting existence. No appreciable color was observed which one would expect from an anhydro base. Also from the nmr spectrum of the reaction mixture there was no evidence for vinyl hydrogens which the anhydro base would possess.

(19) A. Frost and R. F. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1963, p 99.

(20) E. R. Thornton, *Ann. Rev. Phys. Chem.*, **17**, 349 (1966).

The high negative entropy of activation (−28 eu) as determined from the rate constants for method A is believed to be due to both the entropy of activation for the removal of a proton from the 2-methyl group of N-acetoxy-2-methylquinolinium ion and to the entropy for the reaction which results in the formation of N-acetoxy-2-methylquinolinium acetate. Separation of these entropy factors will be necessary before their individual evaluation can be made.

Registry No.—**1**, 1076-28-4; acetic anhydride, 108-24-7; α,α,α-trideuterio-2-methylquinoline 1-oxide, 16649-54-0; N-acetoxy-2-methylquinolinium perchlorate, 1658-39-5; tetra-*n*-butylammonium acetate, 10534-59-5; hexadeuterioacetic anhydride, 16649-49-3.

Acknowledgments.—The authors are indebted to Dr. George A. Hall, Jr., Dr. C. Gordon McCarty, and Dr. Vincent J. Traynelis for valuable discussions during this investigation. We thank Miss Evie Pakas, who, as a 1967 National Science Foundation Summer Research Participant, carried out the rate studies involving nmr spectroscopy. We also acknowledge with pleasure the technical assistance which Mr. Robert Smith gave us in connection with the nmr studies and to Mr. David Chapman for his assistance with the computer programming.

Lead Tetraacetate Oxidation of 4,4,4-Triphenyl-1-butanol, 3,3,3-Triphenyl-1-propanol, and 4,4,4-Triphenylbutyric Acid

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Received February 26, 1968

Lead tetraacetate oxidations of 4,4,4-triphenyl-1-butanol (**1**), 3,3,3-triphenyl-1-propanol (**2**), and 4,4,4-triphenylbutyric acid (**3**) were carried out in benzene solution at 70°. In the absence of oxygen the major products obtained from **1** were 1,1-diphenylindan (**8**), 2,3,4,5-tetrahydro-5,5-diphenyl-1-benzoxepin (**9**), and 4,4,4-triphenyl-1-butyl acetate (**4**); from **2**, 4,4-diphenylchroman (**18**) and 3,3,3-triphenyl-1-propyl acetate (**5**); and from **3**, indan **8** exclusively. In the presence of oxygen little (if any) **8** was formed from alcohol **1** or acid **3**, and in both of these cases the cyclic ether, **18**, was shown to be a major product. On the basis of these results and other supporting evidence, it is argued that 3,3,3-triphenylpropyl radical (**19**) is a prime intermediate in the lead tetraacetate oxidations of **1** and **3**, that anchimeric assistance due to phenyl participation is not involved in the oxidative deformylation of **1** or in the oxidative decarboxylation of **3**, and that relief of steric compression provides a driving force for the unexpectedly facile deformylation of **1**. The data are shown to be consistent with a radical chain mechanism previously proposed for the lead tetraacetate oxidation of monohydric alcohols. Possible reasons are considered for the apparent absence of carbon–oxygen phenyl migration in the lead tetraacetate oxidations of **1**–**3**, and independent methods of synthesis for several of the possible oxidation products (including the novel cyclic ether, **9**) are described.

Because of its unusually high tendency to undergo homolytic rearrangement, the trityl function has received extensive study as a neighboring group[1] in homolytic and quasihomolytic reactions.[2] We previously demonstrated the occurrence of trityl group rearrangements in the lead tetraacetate oxidations of 3,3,3-triarylpropionic acids[2s] and triarylmethanols[2t] and performed quantitative migratory aptitude measurements on these reactions. On the basis of results obtained with the latter system, a chain sequence involving the successive formation of alkoxy radicals, carbon radicals, and carbonium ions (either actual or incipient) was proposed as a general mechanism for the oxidation of most types of monohydric aliphatic alcohols with lead tetraacetate.[2t] In a continuation of our studies of the properties of trityl as a neighboring group in lead tetraacetate oxidations, we now report work dealing with the oxidation of alcohols **1** and **2** and the acid **3**. These oxidations, particularly that of **1**, exhibit certain unusual features that are not predictable from the results of previous studies on related systems. Most significantly, this work has provided additional strong evidence for the involvement of radicals in the lead tetraacetate oxidation of monohydric alcohols.

$Ph_3C(CH_2)_nX$

1, $n = 3$; X = OH
2, $n = 2$; X = OH
3, $n = 2$; X = CO_2H
4, $n = 3$; X = OAc
5, $n = 2$; X = OAc
6, $n = 2$; X = CHO

(1) As used here, the term "neighboring group" does not necessarily imply the involvement of anchimeric assistance in bond-breaking processes.

(2) For representative examples, see (a) H. Wieland, *Ber.*, **44**, 2550 (1911); (b) M. A. Spielman, *J. Amer. Chem. Soc.*, **57**, 1117 (1935); (c) M. S. Kharasch, A. Fono, and W. Nudenberg, *J. Org. Chem.*, **15**, 763 (1950); (d) M. S. Kharasch, A. C. Poshkus, A. Fono, and W. Nudenberg, *ibid.*, **16**, 1458 (1951); (e) P. D. Bartlett and J. D. Cotman, Jr., *J. Amer. Chem. Soc.*, **72**, 3095 (1950); (f) R. M. McNeer, Ph.D. Thesis, University of Chicago, 1953; (g) S. J. Cristol and J. E. Leffler, *J. Amer. Chem. Soc.*, **76**, 4468 (1954); (h) D. Y. Curtin and T. C. Miller, *J. Org. Chem.*, **25**, 885 (1960), and earlier papers by Curtin, *et al.*; (i) L. Kaplan, *J. Amer. Chem. Soc.*, **88**, 4531 (1966); (j) D. B. Denney and N. F. Newman, *ibid.*, **89**, 4692 (1967); (k) H. Breederveld and E. C. Kooyman, *Rec. Trav. Chim.*, **76**, 297 (1957); (l) J. W. Wilt and D. D. Oathoudt, *J. Org. Chem.*, **23**, 218 (1958); (m) J. W. Wilt and J. L. Finnerty, *ibid.*, **26**, 2173 (1961); (n) J. W. Wilt and J. A. Lundquist, *ibid.*, **29**, 921 (1964); (o) W. Rickatson and T. S. Stevens, *J. Chem. Soc.*, 3960 (1963); (p) D. B. Denney, R. I. Ellsworth, and D. Z. Denney, *J. Amer. Chem. Soc.*, **86**, 1116 (1964); (q) C. Rüchardt and R. Hecht, *Ber.*, **98**, 2460 (1965); (r) W. H. Starnes, Jr., *J. Amer. Chem. Soc.*, **85**, 3708 (1963); (s) W. H. Starnes, Jr., *ibid.*, **86**, 5603 (1964); (t) W. H. Starnes, Jr., *ibid.*, **89**, 3368 (1967), and **90**, 1807 (1968).

Results and Discussion

Oxidation of 4,4,4-Triphenyl-1-butanol (1).—Alcohol **1** was synthesized in two ways. The preferred method involved hydroboration–oxidation of the olefin, **7**,

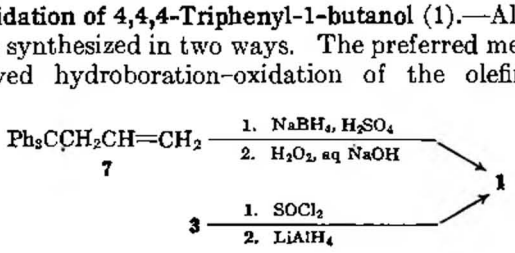


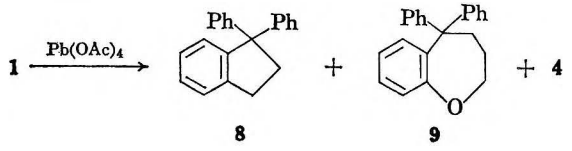
TABLE I
LEAD TETRAACETATE OXIDATIONS[a]

		Yield,[b] %									
Expt	Compd	1	2	3	4	5	6	8	9	18	21
1[c]	1	20 ± 1	...	...	35 ± 2	...	*d*	5 ± 1	9 ± 2	...	...
2[e]	1	19 ± 7	...	7 ± 5	14 ± 2	...	...	<1[f]	16 ± 2	11 ± 1	...
3	2	...	14	...	...	39	...	...	...	24	<1
4[g]	3	...	...	78	...	...	...	8	...	...	...
5[e,g]	3	...	...	82	...	...	...	<1[f]	...	1	...

[a] 1.62 mmol of compd, 3.25 mmol of $Pb(OAc)_4$, 5.0 mmol of $CaCO_3$, 15 ml of benzene, 70 ± 1°, 21.0 hr, He atmosphere. [b] Deviations refer to duplicate runs. [c] Ethylene yield, 1.5%; identification tentative. [d] Trace detected by nmr spectroscopy. [e] Run under O_2 atmosphere. [f] Identification uncertain. [g] Reaction time, 95.0 hr.

which is easily obtained from trityl and allyl chlorides in a Grignard coupling reaction.[3] An alternative procedure involving lithium aluminum hydride reduction of the acyl chloride corresponding to acid **3** also gave good results but was considerably less convenient owing to the rather lengthy sequence of reactions required for the preparation of **3** according to a published method.[2n]

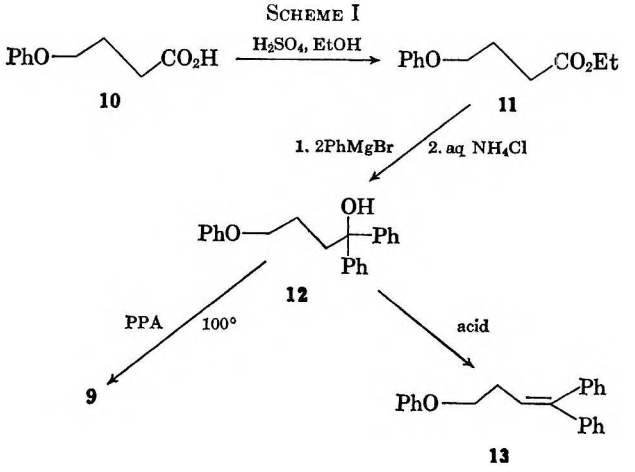
Oxidation of **1** with 2 mol of lead tetraacetate in an oxygen-free atmosphere (expt 1, Table I) gave as principal products 1,1-diphenylindan (**8**), 2,3,4,5-tetrahydro-5,5-diphenyl-1-benzoxepin (**9**), and the acetate



8 9

(**4**) of the starting alcohol, together with appreciable amounts of unchanged **1** and some minor products. Structures of the three major products were confirmed by comparing their properties with those of authentic, independently synthesized specimens. The previously unreported acetate, **4**, was easily secured by acetylation of **1** with acetic anhydride, while **8** was readily obtained from 3,3-diphenyl-1-indanone by Wolff–Kishner reduction (Huang-Minlon modification). Ether **9**, a novel representative of a relatively rare ring system, was prepared by a sequence starting with 4-phenoxybutyric acid (**10**) and proceeding *via* ester **11** and alcohol **12** in the manner depicted in Scheme I. Closure of the seven-membered ring oc-

SCHEME I



curred to the extent of 30% when the heterogeneous reaction of **12** and polyphosphoric acid (PPA) was carried out with very efficient stirring. When performed with inefficient stirring, this reaction gave excellent yields of the new olefin, **13**, a product which was also recovered in high yields after exposure of **12** to the action of certain other acidic reagents (see Experimental Section).

A possible outcome of the lead tetraacetate oxidation of **1** is stepwise or concerted decomposition of the alcohol into three stable fragments: trityl radical (or cation), ethylene, and formaldehyde. Indeed, the probable formation of ethylene in expt 1 suggests that this type of process did occur to some extent. However, the very low yield of ethylene and the absence of appreciable amounts of trityl acetate (or its hydrolysis product, tritanol) indicate that multiple fragmentation was a minor reaction path, at most.

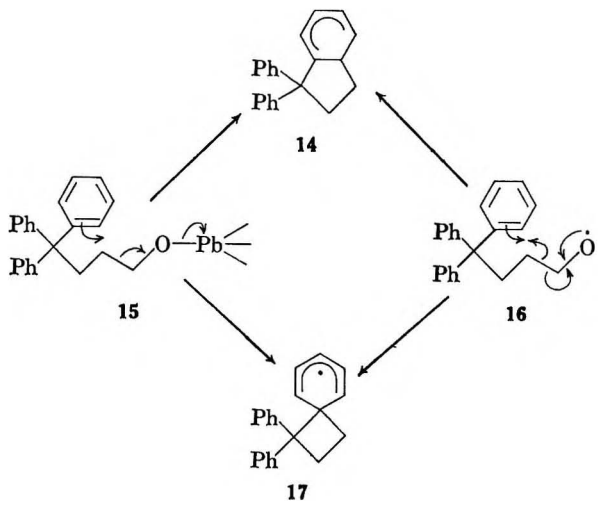
Formation of **8** in the lead tetraacetate oxidation of **1** was quite unexpected, since no β-scission products had previously been obtained from lead tetraacetate oxidations of other primary aliphatic alcohols having the general structure RCH_2CH_2OH (R = alkyl or substituted alkyl),[4] even in cases where competing processes leading to saturated cyclic ethers were strongly disfavored by structural factors (*e.g.*, 1-propanol,[4b,i] 4,4-dimethyl-1-pentanol,[4d] 4,4-dimethyl-1-hexanol[4d]). Consideration was given to the possibility that deformylation of **1** was facilitated by a release of steric compression on going from the ground state to the transition state for cleavage, but this explanation seemed unlikely *a priori* in view of the rather large distance between the trityl group and the reaction site, the absence of cleavage in the oxidation of alcohols having similar structures (4,4-dimethyl-1-pentanol,[4d] 4,4-dimethyl-1-hexanol[4d]), and the general lack of evidence for steric acceleration of alkoxy radical fragmentations.[5] On the other hand, the possible occurrence of a concerted deformylation process leading directly to **14** (radical or cation) *via* a cyclic transition state such as **15** or **16** (either homolytic or heterolytic in the case of **15**) was suggested by the structure of the deformylation product (**8**) and by the known formation of major amounts of cleavage products in lead tetraacetate oxidations of other primary alcohols capable of yielding resonance-

(3) A. N. Nesmeyanov and E. G. Perevalova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1002 (1954); *Chem. Abstr.*, **49**, 6892 (1955).

(4) (a) V. M. Mićović, R. I. Mamuzić, D. Jeremić, and M. L. Mihailović, *Tetrahedron*, **20**, 2279 (1964); (b) M. L. Mihailović, Z. Maksimović, D. Jeremić, Ž. Čeković, A. Milovanović, and L. Lorenc, *ibid.*, **21**, 1395 (1965); (c) M. L. Mihailović, Ž. Čeković, Z. Maksimović, D. Jeremić, L. Lorenc, and R. I. Mamuzić, *ibid.*, **21**, 2799 (1965); (d) M. L. Mihailović, Ž. Čeković, and D. Jeremić, *ibid.*, **21**, 2813 (1965); (e) M. L. Mihailović, J. Bošnjak, Z. Maksimović, Ž. Čeković, and L. Lorenc, *ibid.*, **22**, 955 (1966); (f) M. L. Mihailović and M. Miloradović, *ibid.*, **22**, 723 (1966); (g) M. L. Mihailović, L. Živković, Z. Maksimović, D. Jeremić, Ž. Čeković, and R. Matić, *ibid.*, **23**, 3095 (1967); (h) D. Hauser, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **47**, 1883 (1964); (i) R. E. Partch, *J. Org. Chem.*, **30**, 2498 (1965); (j) S. Moon and P. R. Clifford, *ibid.*, **32**, 4017 (1967).

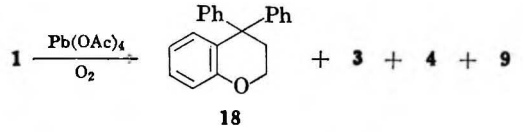
(5) J. D. Bacha and J. K. Kochi, *J. Org. Chem.*, **30**, 3272 (1965); F. D. Greene, M. L. Savitz, F. D. Osterholtz, H. H. Lau, W. N. Smith, and P. M. Zanet, *ibid.*, **28**, 55 (1963).

SCHEME II



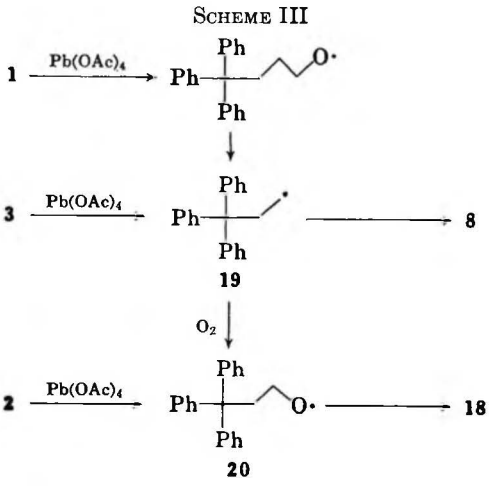
stabilized cleavage fragments (benzyl[4g,6] or allyl[6]) (see Scheme II).

In an attempt to decide among these various mechanistic possibilities, the lead tetraacetate oxidation of **1** was repeated under an atmosphere of pure oxygen (expt 2, Table I). Under these conditions little (if any) **8** was formed, and a new cleavage product, 4,4-diphenylchroman (**18**), was produced, together with acid **3** (presumably arising *via* autoxidation of aldehyde **6**) and the other anticipated products.



Compound **18** is undoubtedly formed by a mechanism involving entrapment of 3,3,3-triphenylpropyl radical (**19**) by molecular oxygen. The peroxy radical produced in this way could be converted into a number of possible intermediates capable of yielding **18** directly; however, we prefer to formulate the cyclizing intermediate as the alkoxy radical, **20** (see Scheme III).[7] The formation of **18**, coupled with the essentially complete absence of **8** from the products of expt 2, strongly suggests that radical **19** (or the cation resulting from its subsequent oxidation)[8] is also the precursor of **8** and militates against formation of **8** *via* the concerted pro-

SCHEME III



cesses considered above. Consideration must also be given, of course, to the possibility that a concerted process leading directly to **14** is followed by a rapid conversion of this species to radical **19**. However, **14** must be more stable than **19** if formation of **14** is to provide a driving force for deformylation. Conversion of **14** into **19** would then have to be an endothermic process requiring a significant energy of activation.[9] This type of process would not be expected to compete effectively with relatively rapid reactions such as the oxidation of **14** by Pb^{IV} or oxygen.[10] A similar argument can be made against alternative concerted mechanisms involving the direct production of radical **17**. It should also be noted that formation of **17** would require an energetically unfavorable four-membered cyclic transition state, and that this radical would be expected to yield appreciable amounts of product(s) resulting from phenyl migration, which could occur either before or after rapid radical oxidation.

If the foregoing arguments are accepted, one is forced to conclude that the driving force for oxidative deformylation of **1** is provided by rather subtle structural factors. Unlikely though it appeared at the outset, we now suspect that release of ground-state compression is, in fact, the correct explanation. The basis for this supposition is provided by certain unusual features appearing in the 100-MHz nmr spectra of compounds **1**–**6** and several related substances currently under study in this laboratory. In all of these cases we have found that the protons of the methylene group α to the trityl function exhibit complex splitting patterns due to magnetic nonequivalence. Similar behavior is observed with the β-methylene protons, and comparisons of the spectra of homologous pairs of compounds show that deviations from first-order splitting are more pronounced when $n = 3$ rather than 2 (see general structure for **1**–**6**). When $n = 1$, the methylene protons

(6) S. Moon and J. M. Lodge, *J. Org. Chem.*, **29**, 3453 (1964).

(7) (a) Possible reactions leading to the alkoxy radical are $2RO_2\cdot \rightarrow 2RO\cdot + O_2$; and $RO_2\cdot$ + H donor $\rightarrow RO_2H$, followed by $RO_2H \rightarrow RO\cdot + HO\cdot$. Any ROH formed by H abstraction might be reconverted into RO· by reaction with Pb(IV); a similar reconversion of RO_2H into $RO_2\cdot$ also seems possible [*cf.* P. D. Bartlett and P. Günther, *J. Amer. Chem. Soc.*, **88**, 3288 (1966)]. However, extensive formation of alcohol **2** seems unlikely, since this should have led to the production of an appreciable amount of acetate **5** (see expt 3, Table I). Direct (concerted) cyclization of RO_2H has no well-established analogies. (b) Direct cyclization of a Pb(IV) alcoholate is disfavored by the lack of evidence for neighboring phenyl participation in the lead tetraacetate oxidation of triphenylmethanol.[2t] Intramolecular addition followed by radical oxidation is clearly the preferred route from RO· to ethers such as **9** and **18**. An alternative sequence involving H abstraction, aryl radical oxidation, and internal solvation seems highly unlikely in view of the high strengths of aryl C–H bonds [J. A. Kerr, *Chem. Rev.*, **66**, 465 (1966)] and the high energy of the phenyl cation [I. P. Fisher, T. F. Palmer, and F. P. Lossing, *J. Amer. Chem. Soc.*, **86**, 2741 (1964)]. For another argument against the latter type of mechanism, see ref 4g.

(8) (a) Both intermediates could be involved, since the oxidation of primary alkyl radicals by Pb(IV) is relatively slow: (b) J. K. Kochi, *J. Amer. Chem. Soc.*, **87**, 3609 (1965); (c) J. K. Kochi, J. D. Bacha, and T. W. Bethea, III, *ibid.*, **89**, 6538 (1967); (d) J. D. Bacha and J. K. Kochi, *J. Org. Chem.*, **33**, 83 (1968).

(9) Reversible addition of simple primary aliphatic radicals to aromatic nuclei has apparently never been observed. In this connection it also seems pertinent to note that the additions of trifluoromethyl or chlorodifluoromethyl radicals to benzene have been shown to be essentially irreversible in the vapor phase at temperatures below 100° [G. E. Owen, Jr., J. M. Pearson, and M. Szwarc, *Trans. Faraday Soc.*, **61**, 1722 (1965); J. R. Majer, D. Phillips, and J. C. Robb, *ibid.*, **61**, 110 (1965)].

(10) Although rate constants are not available for the oxidation of cyclohexadienyl-type radicals by Pb(IV), the structural correlations of Kochi[8b-d] suggest that these oxidations are probably faster than the rapid competing processes of dimerization and disproportionation. For examples and a discussion of the rapid oxidation of cyclohexadienyl-type radicals with oxygen, see D. H. Hey, "Advances in Free-Radical Chemistry," Vol. II, G. H. Williams, Ed., Logos Press Ltd., London, England, p 65 ff.

appear as a sharp singlet. Although a complete explanation of these observations is lacking, they clearly suggest the presence of rotational restrictions (steric compressions) which become less pronounced as the length of the alkyl chain is decreased. We hope that a fuller analysis of these spectra[11] will lead to a rigorous explanation of the observed nonequivalences and permit a firm decision regarding their possible connection with the relatively facile deformylation of **1**.

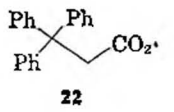
Oxidation of 3,3,3-Triphenyl-1-propanol (2).—Lead tetraacetate oxidation of alcohol **2** gave results that were consistent with the mechanistic scheme presented in Scheme III. The identified products of this reaction (expt 3, Table I) were cyclic ether **18** (isolated in a preparative run and shown to be identical with the product from expt 2), acetate **5**, unchanged starting alcohol, and a trace of 3,3,3-triphenylpropionic acid, **21** (probably formed by autoxidation of the corresponding aldehyde during work-up). Here again we prefer to formulate the cyclizing species as radical **20**, although direct cyclization of a Pb^{IV} alcoholate is not completely ruled out.[7b]

Oxidation of 4,4,4-Triphenylbutyric Acid (3).—Lead tetraacetate oxidations of acid **3** were carried out under conditions strictly analogous to those used with alcohols **1** and **2**. In the absence of oxygen (expt 4, Table I) **3** reacted very slowly to give the indan, **8**. In the presence of oxygen (expt 5, Table I) the extent of conversion of the acid was even less, and the only identifiable product of the reaction was the ether, **18**. These results, summarized in Scheme III, are consistent with previous observations in support of a radical chain mechanism for the oxidative decarboxylation of primary aliphatic acids with lead tetraacetate,[8b,d] and they provide strong evidence for the presence of a common intermediate, radical **19**, in the oxidations of **1** and **3**. In accordance with the arguments presented above regarding the mechanism of deformylation of **1**, we therefore conclude that the oxidative decarboxylation of **3** is not anchimerically assisted by phenyl participation. Also consistent with this conclusion is the very slow rate of reaction of **3**, since in this respect **3** behaves like the primary aliphatic acids studied by Kochi under similar conditions.[8b]

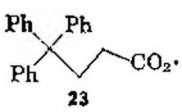
Rearrangements and Cyclizations Involving the Trityl Group.—A further point of interest concerning the oxidation of acid **3** is the apparent absence of products (phenyl esters) resulting from intramolecular migration of a phenyl group to carboxyl oxygen. In this respect the oxidation resembles the Hunsdiecker reaction of **3** and the thermal decomposition of the corresponding diacyl peroxide.[2n] On the other hand, carbon–oxygen phenyl migration is a major process in the lead tetraacetate oxidation of acid **21** and in other reactions which are potential sources of radical **22**.[2k-s] The reason for the different rearrangement tendencies of radicals **22** and **23** (or structurally related intermediates) is a rather intriguing question,[2n] and in the case of the anomalous Hunsdiecker reaction of acid **21** it has been suggested that development of the highly conjugated system of the rearrangement product, phenyl 3,3-diphenylacrylate, may provide a driving force for phenyl migration.[2n] However, this explanation requires that the aryl shift proceed entirely *via* an extraordinary bimolecular mechanism involving abstraction of methylene hydrogen in a preliminary step or in the slow step of the rearrangement, and it does not account for the formation of phenyl 3,3-diphenylpropionate upon thermal decomposition of the *t*-butyl perester of acid **21**.[2r] Denney, *et al.*,[2p] have discussed the possible effects of conformation, decarboxylation rate, and other factors on the facile rearrangement of radical **22**. The present work leads to one further suggestion regarding the problem in question, namely, that the conformational changes required to reach a cyclic transition state are more extensive in the case of **23** and may be subject to a steric retardation (see above) which is absent or attenuated in the case of the smaller radical (**22**).

$Ph_3CH_2CO_2H$

21



22



23

$Ph_2\dot{C}(CH_2)_nOPh$

24a, $n=2$

b, $n=3$

In view of the facile 1,4-phenyl migration observed with **22** and its potential precursors, the complete absence of 1,4-rearrangement products from the lead tetraacetate oxidation of alcohol **2** is quite surprising. We have no convincing explanation for this result and can only suggest that perhaps the branched structure of the carboxyl group exerts a special conformational bias in favor of the five-membered cyclic transition state[2k,m,r,s] responsible for rearrangement and allows the process to occur with a minimal loss of rotational entropy. Since the ring formed from **2** is actually six membered, one might expect the occurrence of 1,5-phenyl migration *via* a cyclic six-membered transition state in the lead tetraacetate oxidation of alcohol **1**, but this prediction also seems to be contradicted by experiment. However, interpretation of these results is complicated by the possibility that the cyclic ethers, **9** and **18**, are actually formed in a *two-stage* process which includes phenyl migration as the *initial step*. Cyclization of the rearranged radicals formed in this way (**24a** and **b** or the analogous cations produced by subsequent oxidation) could lead to the observed products, if only in theory.[12] This type of mechanism cannot be ruled out completely, though it does seem unlikely in view of the apparent absence of noncyclized products (phenyl ethers) derived from radicals **24a** and **b**. Moreover, formation of six-membered cyclic ethers (chroman[4g,i] and 1,4-benzodioxan[4f]) in the lead tetraacetate oxidations of other phenyl-substituted alcohols whose structures supply no strong driving force for rearrangement suggests that phenyl migration is not involved in the oxidation of alcohol **2**, at least.[7b]

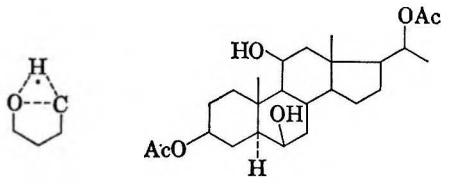
Mechanism of the Lead Tetraacetate Oxidation of Monohydric Alcohols.—The demonstrated presence of radical **19** in the lead tetraacetate oxidation of alcohol **1** constitutes conclusive evidence for a homolytic β-scission process and is consistent with the general mechanism previously proposed for such oxidations.[2t] This

(11) Work with Dr. J. J. R. Reed of this laboratory is currently in progress. It is interesting to note that similar magnetic nonequivalences are also observed with alcohol **12** (see Experimental Section).

(12) In principle, *all* intramolecular cyclizations involving the trityl group can be accounted for in terms of similar two-stage mechanisms.

result also provides good indirect evidence for operation of a radical chain mechanism in the Pb^{IV} oxidation of alcohols to saturated cyclic ethers, since previous studies have strongly suggested that this mode of reaction and the β-scission process are mechanistically similar.[4e,13] In these systems the presence of efficient radical scavengers should decrease the yields of products formed *via* the general chain mechanism and increase the yields of products (*e.g.*, acetates of starting alcohols[14]) formed by competing nonradical processes. However, Table I shows that the lead tetraacetate oxidation of alcohol **1** gives increased yields of cyclized products and a lower yield of acetate **4** when oxygen is added to the system. This result suggests that short kinetic chains are involved in the formation of the cyclized materials, and that the rate of chain initiation is faster when oxygen is present. The latter effect may be connected with the formation of oxidation products such as water and methanol (from oxygen and methyl radicals). Coordination or metathetical reactions of these products with a Pb^{IV} alcoholate of **1** might have produced new Pb^{IV} species capable of undergoing more rapid homolysis. Under these conditions it is also possible that partial hydrolysis or methanolysis of the product acetate (**4**) occurred, making more of the starting alcohol available for reaction by the homolytic path.

The possible intervention of a bridged radical species, **25**, has been considered in connection with the lead tetraacetate oxidation of monohydric alcohols.[15]



25 **26**

It has been suggested that, in sterically constrained systems, tetrahydrofuran formation may occur *via* direct oxidation of **25**, rather than by a more conventional mechanism involving intramolecular hydrogen abstraction by an alkoxy radical, followed by oxidation of the resulting carbon radical to a carbonium ion (or ion pair).[15] Thus, the fact that lead tetraacetate oxidation of the 6β,11β-dihydroxy steroid, **26**, gives 6β,19-oxide exclusively, even though the two hydroxyl groups are equidistant from C-19, is said to rule out the presence of an ion-pair intermediate.[15] However, this argument fails to consider the possibility that steric interaction of the counteranion with the axial hydrogen at C-4 might have kept an intimate ion pair from attaining the optimum conformation needed for internal solvation by the 11β-hydroxyl.[16] Oxidation of steroidal alcohols by the "hypoiodite" method (photolysis in the presence of lead tetraacetate and iodine) occasionally yields products that appear to have been formed from carbonium ion intermediates. These products sometimes differ from those obtained upon oxidation of the same alcohols with lead tetraacetate alone, and in certain instances the differences have been used to make a case against carbonium ions in the lead tetraacetate reaction.[15,17] This type of argument also seems tenuous at best, since the detailed mechanism of the "hypoiodite" reaction has not been established, and since the partitioning of ion-pair intermediates among competing reaction paths might be influenced to a considerable degree by the nature of the counteranions, which could easily be different for the two reactions in question. In view of these considerations, we conclude that the involvement of a transition state or intermediate symbolized by **25** requires further experimental verification.

(13) K. Heusler, *Tetrahedron Lett.*, 3975 (1964).

(14) M. L. Mihailović, R. I. Mamuzić, L. Žigić-Mamuzić, J. Bošnjak, and Ž. Čeković, *Tetrahedron*, **23**, 215 (1967), and references cited therein.

(15) K. Heusler and J. Kalvoda, *Angew. Chem. Intern. Ed. Engl.*, **3**, 525 (1964).

(16) *Cf.* the discussion of the structures of intimate ion pairs by S. Winstein and G. C. Robinson, *J. Amer. Chem. Soc.*, **80**, 169 (1958).

Experimental Section[18]

Materials.—Lead tetraacetate (Matheson) was dried in a vacuum desiccator containing sodium hydroxide. Anhydrous calcium carbonate (Matheson, A.C.S. reagent) was stored in a vacuum oven at 60° under 5–10-mm pressure. Benzene (Baker reagent) was dried over sodium ribbon. All other chemicals used were either highly purified commercial products or compounds prepared in this laboratory by the indicated literature procedures. Purities were verified by spectral measurements, determinations of appropriate physical constants, and, where possible, by vpc analysis.

4,4,4-Triphenylbutyric Acid (3).—Acid hydrolysis of 4,4,4-triphenylbutyronitrile[2n] according to a published procedure,[2n] followed by recrystallization of the crude product from aqueous ethanol, gave **3** in 90% yield: mp 155–157° (lit.[2n] mp 159–160°); ir (CS_2) 1704 (strong, carboxyl C=O, lit.[2n] for **3**, 1712) and 2550–2700 cm^{-1} (broad and weak, carboxyl OH); nmr (CCl_4), δ 11.62 (broad s, 1, CO_2H), 7.0–7.3 (m, 15, three C_6H_5), 2.75–3.03 (m resembling t, 2, Ph_3CCH_2), and 1.95–2.23 ppm (m resembling t, 2, CH_2CO_2H).

4,4,4-Triphenyl-1-butanol (1). A. From 4,4,4-Triphenylbutyric Acid (3).—Acid **3** (3.00 g, 9.48 mmol) was stirred under reflux with thionyl chloride (10 ml) for 2.3 hr. Evaporation of the mixture gave a residue which was freed of excess reagent by repeated dissolution in benzene followed by reevaporation. The solid thus obtained (mp 87–89°, presumably the acyl chloride) was taken up in dry ether (50 ml), and the solution was stirred under nitrogen while a large excess of lithium aluminum hydride (0.72 g, 19 mmol) in dry ether (20 ml) was added dropwise during 10 min. After 1.7 hr of refluxing, followed by cautious treatment with excess water and 10% hydrochloric acid, the ether layer was separated, washed with 1 *N* sodium carbonate solution, dried, and evaporated to give 2.75 g (96%) of alcohol **1**, mp 120–122°. Two recrystallizations from cyclohexane gave slender, snow-white needles: mp 122–123°; ir (CS_2) 3584 cm^{-1} (medium, OH), no carbonyl absorption; nmr (CCl_4, 60°), δ 6.9–7.3 (m, 15, three C_6H_5), 3.48 (t, 2, J = 6 Hz, CH_2OH), 2.53–2.70 (m, 2, Ph_3CCH_2), 1.13–1.44 (m, 2, CH_2CH_2OH), and 1.04 ppm (s, 1, OH); mass spectrum (70 eV) *m/e* 302.1670 (weak; calcd for $C_{22}H_{22}O$, 302.1670), 284.1557 (medium; calcd for $C_{22}H_{20}$, 284.1565), and 243.1185 (strong; calcd for $C_{19}H_{15}$, 243.1174).

(17) D. Hauser, K. Heusler, J. Kalvoda, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **47**, 1961 (1964).

(18) Boiling points and melting points are uncorrected. The melting points were determined with a Fisher-Johns apparatus. Elemental microanalyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., or by Galbraith Laboratories, Inc., Knoxville, Tenn. Evaporations were carried out at ambient temperature under 5–10 mm pressure on rotary evaporators. Infrared, 100-MHz nmr, and high resolution mass spectra were obtained with a Perkin-Elmer instrument (Model 21), a Varian Associates instrument (Model HA-100), and an AEI MS-9 spectrometer, respectively. Unless noted otherwise, nmr measurements were made at room temperature using dilute solutions that contained TMS for internal standardization. Nmr peak multiplicities are abbreviated as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), qr (quartet), qn (quintet), and m (multiplet). Exact mass measurements are referred to C = 12 μ. Programmed temperature vpc analyses were done with an F & M instrument (Model 500) equipped with a 6 ft × 0.25 in. (o.d.) stainless steel column containing SE-30 (15%) on 45–60 mesh Chromosorb W. The carrier gas was helium; column temperature was increased from 100 to 350° at the rate of 8°/min. Various instrumental analyses were performed by Miss T. Reid and Messrs. B. R. Coltharp, T. J. Denson, J. Dzilsky, T. Hines, H. W. Kinsey, R. J. LeCompte, G. C. McCollum, A. C. Raymer, V. H. Rushing, G. R. Taylor, and J. L. Taylor.

Anal. Calcd for $C_{22}H_{22}O$: C, 87.37; H, 7.33. Found: C, 87.68; H, 7.42.

A compound that melted at 240° and was assigned the structure of **1** has been reported to result from reaction of trityl Grignard reagent with trimethylene oxide.[19] In the present work no attempts were made to resolve this discrepancy, since the structure of our sample of **1** was conclusively established by the foregoing observations and by the following independent synthesis.

B. From 4,4,4-Triphenyl-1-butene (7).—A solution of the olefin[3] (15.38 g, 54.1 mmol) and sodium borohydride (0.784 g, 20.7 mmol) in 40 ml of purified, anhydrous diglyme was prepared in a dry apparatus under nitrogen (inert atmosphere was maintained during entire reaction period) and stirred at 24–25° (water bath cooling) while a solution of concentrated sulfuric acid (0.581 ml, 10.4 mmol) in dry ether (14 ml) was added dropwise during 10 min. After 3.5 hr of stirring at ambient temperature and 1.5 hr at 70–75°, the mixture was cooled to 32°, treated rapidly in succession with 1.5 ml of water and 6.8 ml of 3 *N* sodium hydroxide, and kept at 33–35° by means of an ice-water bath while 6.8 ml of 30% aqueous hydrogen peroxide was introduced during 15 min with continued stirring. The cooled mixture was stirred at 27–33° for 20 min; then the cooling bath was removed; and stirring was continued for an additional 6.5 hr at ambient temperature. Removal of the product was accomplished by extraction with three 30-ml portions of ether; and, after dilution with a large additional quantity of ether in order to prevent precipitation of the alcohol during subsequent operations, the combined extracts were washed five times with ice water, dried, and evaporated. Recrystallization of the solid residue from cyclohexane afforded 10.58 g of alcohol **1**, mp 120–121°; a second crop weighing 0.81 g (total yield, 70%) and, melting at 118–120° was also recovered. A further recrystallization from cyclohexane gave a product that melted at 122–123° and was identical in every respect [vpc, ir, mass spectrometry (ms), nmr] with a sample of **1** prepared according to procedure A, above.

3,3,3-Triphenyl-1-propanol (2).—Wilt and Lundquist[2n] described the preparation of this alcohol from 3,3,3-triphenylpropionic acid *via* lithium aluminum hydride reduction of the corresponding acyl chloride. Their method was employed in the present work, using a detailed procedure analogous to method A for alcohol **1**. From 42.7 g (0.141 mol) of the acid and 100 ml of thionyl chloride there was obtained 45.1 g of crude acyl chloride; this afforded 39.7 g (98%) of **2** upon reduction with 10.70 g (0.282 mol) of lithium aluminum hydride. The crude alcohol was actually quite pure: it melted at 108.5–110° (lit.[2n] mp 107.5–108°) and showed no change in melting point after recrystallization from cyclohexane; ir (CS_2) 3610 cm^{-1} (medium, OH), no carbonyl absorption; nmr (CCl_4), δ 6.91–7.24 (m, 15, three C_6H_5), 3.29 (distorted t, 2, $J \approx 7$ Hz, CH_2OH), 2.77 (distorted t, 2, $J \approx$ Hz, Ph_3CCH_2), and 2.18 ppm (s, 1, OH); mass spectrum (70 eV) *m/e* 288.1522 (weak; calcd for $C_{21}H_{20}O$, 288.1514), 270.1406 (medium; calcd for $C_{21}H_{18}$, 270.1408), and 243.1174 (strong; calcd for $C_{19}H_{15}$, 243.1174).

Reactions of 4,4,4-Triphenyl-1-butanol (1), 3,3,3-Triphenyl-1-propanol (2), and 4,4,4-Triphenylbutyric Acid (3) with Lead Tetraacetate. A. 4,4-Diphenylchroman (18) from 2.—A well-stirred mixture of alcohol **2** (1.44 g, 4.99 mmol), lead tetraacetate (4.44 g, 10.0 mmol), and anhydrous benzene (50 ml) was heated in a dry atmosphere at 70 ± 1° for 48 hr. Work-up according to a procedure previously described[2t] gave 1.72 g of semisolid material containing the neutral organic products. Brief extraction of this fraction with a small amount of petroleum ether (bp 30–60°) at room temperature, followed by evaporation of the extract, afforded 1.28 g of solid, which was taken up in a minimum amount of benzene–chloroform. Slow evaporation of the solution at room temperature caused the deposition of 0.35 g (24%) of **18** in the form of large, colorless prisms, mp 172–176°. Recrystallization from methanol gave a product melting at 174–175.5°: ir (CS_2) 1225 cm^{-1} (strong, =CO–), no OH or C=O absorption; nmr ($CDCl_3$), δ 6.5–7.4 (m, 14, C_6H_4 and two C_6H_5), 4.02 (distorted t, 2, $J \approx 5$ Hz, CH_2O), and 2.76 ppm (distorted t, 2, $J \approx 5$ Hz, CH_2CH_2O); mass spectrum (70 eV) *m/e* 286.1364 (strong; calcd for $C_{21}H_{18}O$, 286.1357), 257.0972 (strong; calcd for $C_{19}H_{13}O$, 257.0966), and 209.0962 (strong; calcd for $C_{15}H_{13}O$, 209.0966).

Anal. Calcd for $C_{21}H_{18}O$: C, 88.08; H, 6.34. Found: C, 88.01; H, 6.47.

B. 4,4,4-Triphenylbutyraldehyde (6) from 1.—A mixture of alcohol **1** (2.00 g, 6.61 mmol), lead tetraacetate (3.08 g, 6.95 mmol), and pyridine (35 ml) was stirred at room temperature for 33 hr (final color, pale orange)[20] and then evaporated. The residue was extracted thoroughly with several portions of benzene at room temperature, and the combined extracts were washed twice with 4% aqueous HCl and once with 1 *N* sodium carbonate solution. Evaporation of the dried organic moiety afforded 2.03 g of brownish solid which yielded only small amounts of impure solid materials (<0.1 g) upon attempted recrystallization from cyclohexane or methanol–water. The remaining material was dissolved in boiling methanol (25 ml), and the solution was stirred vigorously while a solution of sodium metabisulfite (3 g) in water (15 ml) was added rapidly. After 6.7 hr of stirring at ambient temperature, the mixture was filtered, and the recovered solid was washed several times on the filter with methanol and then with ether. An aqueous solution of the solid yielded no organic products after basification with a large excess of 3 *N* sodium carbonate. The filtrate and washings were combined, evaporated to remove the methanol, and extracted once with ether. Addition of a large excess of 3 *N* sodium carbonate to the aqueous phase, followed by extraction with ether and evaporation of the dried ether solution, afforded 0.43 g (22% yield) of crude **6** as a viscous oil that slowly solidified, mp 96–108°. Two recrystallizations of the product from petroleum ether (bp 30–60°) at −10° gave snow-white microcrystals: mp 109.5–110.5°; ir (CS_2) 1735 (strong, C=O), 2720, and 2820 cm^{-1} (both medium, CH of CHO), no OH; nmr (CS_2), δ 9.52 (distorted s, 1, CHO), 7.0–7.2 (m, 15, three C_6H_5), 2.80 (distorted t, 2, $J \approx 7$ Hz, Ph_3CCH_2), and 2.15 ppm (distorted t, 2, $J \approx 7$ Hz, CH_2CHO); mass spectrum (70 eV) *m/e* 300 (too weak for exact mass measurement; calcd for $C_{22}H_{20}O$, 300), 244.1249 (strong; calcd for $C_{19}H_{16}$, 244.1252), and 243.1172 (strong; calcd for $C_{19}H_{15}$, 243.1174).

Anal. Calcd for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 88.07; H, 6.68.

C. Other Reactions (Table I).—These reactions were run under pure helium or oxygen after freeze–thaw degassing, using the apparatus and procedures already described.[2t] Conversions of Pb^{IV} were incomplete in all experiments except expt 2. Reaction mixtures were worked up by a method used previously[2a] to obtain three fractions: **A**, the solids removed by an initial filtration; **B**, the organic acid fraction; and **C**, the neutral organic products. Acidification of the **A** fractions with excess hydrochloric acid, followed by thorough extraction with ether, gave no organic products except acetic acid. Compositions of the **B** fractions were established by melting point determinations and spectral comparisons. The **C** fractions were analyzed quantitatively by programmed temperature vpc[18] (internal standard method) using pure reference compounds for calibration. Products in **C** were identified by retention times and by comparing the spectral properties (ir, nmr, ms) of trapped vpc peaks with those of authentic specimens. Rough analyses of the **C** fractions by nmr gave results that were in satisfactory agreement with the results obtained by vpc. The total gas evolved during one of the duplicate runs of expt 1 was analyzed by isothermal vpc, using a standard procedure developed by the Analytical Research Section of this laboratory. On the basis of retention times the gaseous products were tentatively identified as carbon dioxide (the major constituent), ethylene, methane, and carbon monoxide.

Several unidentified peaks were detected in the chromatograms of the **C** fractions obtained from alcohol **1**; however, these peaks amounted to only about 4–5% (expt 1) or 12–13% (expt 2) of the total peak area. No minor peaks were detected in the chromatogram of the **C** fraction from expt 3. On the basis of retention times, two of the minor products from **1** could have been acetate **5** and olefin **13**; however, trapped vpc fractions supposedly corresponding to these compounds were shown to be complex mixtures by spectral analyses. In any event, the yields of **5** and **13** could have been no more than 1–2%. The presence of a trace of aldehyde **6** among the products of expt 1 was suggested by a small nmr peak at the correct position for the CHO proton. Mass spectral analysis of the total **C** fraction from expt 1 gave no evidence for the presence of appreciable amounts of materials with molecular weights higher than those of the identified products.

(19) T. Cuvigny and H. Normant, *Compt. Rend.*, **254**, 318 (1962).

(20) *Cf.* R. E. Partch, *Tetrahedron Lett.*, 3071 (1964).

Small amounts (2–3% yield) of the ethyl ester of **3** were detected in the C fractions from expt 4 and 5. This ester is not considered to be a product of the lead tetraacetate oxidation, since its formation is believed to have been due to the presence of a small amount of ethanol (the recrystallization solvent) in the sample of **3** used for these experiments (nmr analysis of **3** supported this hypothesis). Acetate **5** and ester **27** (see below) were shown to be absent from the products of expt 4 and 5, although a few minor products (unidentified, total yield <1%) were detected in the chromatograms of the C fractions.

In a preliminary experiment, 5.00 mmol each of acid **3**, lead tetraacetate, and pyridine were refluxed in dry benzene (25 ml) for 93.5 hr. Approximately 40% of **3** was converted into indan **8** under these conditions.

In order to confirm the absence of phenyl esters formed by intramolecular rearrangement, the C fractions from two experiments with acid **3** (the run with pyridine just described and a large-scale run similar to expt 4) were "saponified" by boiling for several hours with large excesses of potassium hydroxide in aqueous ethanol. Work-up by a procedure described previously[21] gave only traces of phenol, which could have come from phenyl acetate (an expected minor by-product derived from the solvent)[4b] rather than from rearrangement products.

In view of the foregoing observations, it is believed that no important products escaped detection in expt 1–5. Mechanical losses during work-up could have had a major effect on the material balances, since the amounts of **1–3** used for these experiments were always quite small (*ca.* 0.5 g).

1,1-Diphenylindan (8).—A mixture of 3,3-diphenyl-1-indanone[21] (1.48 g, 5.21 mmol), 85% hydrazine hydrate (3 ml), sodium hydroxide (1.0 g), and ethylene glycol (15 ml) was stirred and heated under a water-cooled condenser for 4 hr at 140–159°. Low-boiling constituents were then allowed to distil, and the temperature was kept at 200° for 9.5 hr while stirring was continued. The mixture was cooled, poured into water (100 ml), and extracted with three 20-ml portions of ether. Evaporation of the dried extracts gave a residue, which was boiled with methanol and filtered to remove a small amount of impure, high-melting solid. Stepwise concentration and cooling of the filtrate yielded more of this solid and eventually caused precipitation of **8** as snow-white crystals, 0.83 g (59%), mp 68–69°. Recrystallization from methanol gave a product melting at 70–70.5° (lit.[22] mp 67–68°): ir (CS_2), no OH or C=O; nmr (CCl_4), δ 6.80–7.24 (m, 14, C_6H_4 and two C_6H_5) and 2.81 ppm (distorted s, 4, CH_2CH_2); mass spectrum (70 eV) *m/e* 270.1424 (strong; calcd for $C_{21}H_{18}$, 270.1408) and 193.1024 (strong; calcd for $C_{15}H_{13}$, 193.1017).

3,3,3-Triphenyl-1-propyl 4,4,4-Triphenylbutyrate (27).—The crude acyl chloride obtained in the usual way from 0.50 g (1.58 mmol) of acid **3** (see method A for the preparation of alcohol **1**) was dissolved in dry benzene (5 ml) and added dropwise during 18 min to an ice-cold, stirred solution of alcohol **2** (0.45 g, 1.56 mmole) in pyridine (4 ml). The reaction vessel was stoppered with a Drierite tube, and after an additional 30 min of stirring in the cold the mixture was allowed to stand at room temperature for 18.5 hr. Water (20 ml) was added, and the product was extracted with 20 ml of benzene in two portions. The combined extracts were washed in succession with cold 5% hydrochloric acid (40 ml in three portions), saturated sodium bicarbonate solution, and water. Evaporation of the dried benzene solution gave 0.91 g of waxy, white solid, which afforded 0.32 g (35%) of ester **27**, mp 170–172°, upon recrystallization from methanol. A further recrystallization (hexane) produced tiny, snow-white crystals: mp 172–173°; ir (CS_2) 1740 (strong, ester C=O), 1186, 1173, 1161 (all strong, individual components of a single broad band, ester C–O–C), and 1035 cm^{-1} (medium, broad, ester C–O–C); nmr (CCl_4), δ 6.9–7.3 (m, 30, six C_6H_5), 3.74 (distorted t, 2, $J \approx 8$ Hz, CH_2O), 2.69–2.96 (m, 4, two Ph_3CCH_2), and 1.93 ppm (highly distorted t, 2, $J \approx 8$ Hz, CH_2CO).

Anal. Calcd for $C_{43}H_{38}O_2$: C, 88.02; H, 6.53. Found: C, 87.98; H, 6.54.

3,3,3-Triphenyl-1-propyl Acetate (5).—In accordance with a procedure similar to that described in the literature,[23] heating of a stirred mixture of alcohol **2** (1.00 g, 3.47 mmol) and acetic anhydride (10 ml) for 110 min at reflux temperature gave ester **5** in essentially quantitative yield, mp 119–119.5°. A single recrystallization from ethanol afforded 0.98 g (85%) of short, flat, almost colorless needles: mp 120.7–121.5° (lit.[23] mp 114–115°); ir (CS_2) 1735 (strong, ester C=O), 1230, and 1031 cm^{-1} (both bands strong and broad, ester C–O–C); nmr ($CDCl_3$), δ 7.04–7.33 (m, 15, three C_6H_5), 3.90 (distorted t, 2, $J \approx 8$ Hz, CH_2O), 2.93 (distorted t, 2, $J \approx 8$ Hz, Ph_3CCH_2), and 1.97 ppm (s, 3, CH_3CO).

4,4,4-Triphenyl-1-butyl Acetate (4).—Reaction of alcohol **1** (1.00 g, 3.31 mmol) with acetic anhydride (10 ml) in the manner just described yielded 1.12 g (98%) of crude **4** in essentially pure form, mp 73.5–75.0°. Recrystallization from petroleum ether (bp 30–60°) gave clusters of white needles that melted at 75–76°; continued heating transformed the melt into a second crystalline modification melting at 95–96°. A further recrystallization of the low-melting form from petroleum ether, using the high-melting form for seeding, gave white platelets: mp 95.5–96.5°; nmr (CCl_4), δ 7.0–7.3 (m, 15, three C_6H_5), 4.03 (t, 2, $J = 7$ Hz, CH_2O), 2.55–2.73 (m, 2, Ph_3CCH_2), 2.03 (s, 3, CH_3CO), and 1.26–1.60 ppm (m, 2, CH_2CH_2O). The ir spectra (CS_2) of the two forms of **4** were identical in every respect; they exhibited strong bands at 1739 (ester C=O) and 1235 cm^{-1} (ester C–O–C), as well as a broad doublet of medium intensity at 1043–1035 cm^{-1} (one band due to ester C–O–C, assignment of other band obscure).

Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.87; H, 7.23.

Ethyl 4-Phenoxybutyrate (11).—A stirred mixture of 4-phenoxybutyric acid[24] (50.0 g, 0.277 mol), absolute ethanol (150 ml, 2.56 mol), and concentrated sulfuric acid (5.0 g) was refluxed for 3.0 hr, cooled, concentrated to a volume of approximately 100 ml, and diluted with water (300 ml). The lower (ester) layer was separated, and the aqueous phase was extracted with three 50-ml portions of ether. All organic phases were combined, washed twice with 5% sodium bicarbonate solution, dried, concentrated, and then fractionated through a short spinning-band column to recover 51.5 g (89%) of the desired ester as a colorless oil: bp 112° (1.4 mm) [lit.[25] bp 170–173° (25 mm)]; ir (neat) 1740 (strong, ester C=O), 1247 (strong, broad, =CO–), and 1174 cm^{-1} (strong, broad, ester C–O–C); nmr (CCl_4), δ 7.03–7.27 (m, 2, *m*-H of C_6H_5O), 6.66–6.91 (m, 3, *o*- and *p*-H of C_6H_5O), overlapping 4.05 (qr, $J = 7$ Hz) and 3.92 (t, $J = 6$ Hz) (4, CH_2CH_2 and CH_2OPh, respectively), 2.42 (t, 2, $J = 6$ Hz, CH_2CO), 2.02 (qn, 2, $J = 6$ Hz, CH_2CH_2CO), and 1.20 ppm (t, 3, $J = 7$ Hz, CH_3).

1,1-Diphenyl-4-phenoxy-1-butanol (12).—This experiment was performed under nitrogen. A solution of phenylmagnesium bromide was prepared in the usual way from 4.86 g (0.200 g-atom) of magnesium and 33.40 g (0.213 mol) of bromobenzene in 110 ml of dry ether. Ethyl 4-phenoxybutyrate (20.82 g, 0.100 mol) in dry ether (200 ml) was added to the stirred solution at a rate such that gentle refluxing occurred, and the mixture was stirred and heated under reflux for 1.0 hr after addition was complete. A saturated aqueous solution of ammonium chloride (36 ml) was then added slowly (exothermic reaction caused refluxing) with efficient stirring. When coagulation of the precipitate appeared to be complete, the clear ether layer was separated by decantation, and the precipitate was extracted twice with fresh portions of ether. The ether solutions were combined, dried, and evaporated to give an oil that crystallized and then dissolved upon stirring with boiling hexane. Concentration and cooling of the solution gave two crops of alcohol **12** as clusters of white prisms: mp 87–88° (26.35 g) and 86–87.5° (2.76 g, total yield 91%); mp 88–88.5° after a further recrystallization from petroleum ether (bp 30–60°); ir (CS_2) 3584 (medium, sharp, free OH), 3460 (weak, H-bonded OH), and 1244 cm^{-1} (strong, =CO–); nmr (CCl_4), δ 6.6–7.4 (m, 15, three C_6H_5), 3.81 (t, 2, $J = 6$ Hz, CH_2O), 2.25–2.45 (m, 2, CH_2CPh_2OH), 2.21 (s, 1, OH), and 1.55–1.85 ppm (m, 2, CH_2CH_2O).

Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.98; H, 6.96. Found: C, 82.93; H, 6.98.

In another experiment, crystallization of the crude alcohol from petroleum ether (bp 30–60°) gave a product that melted at 68–69° (fairly rapid heating), solidified upon further heating, and remelted at 87–88°. When heated very slowly this material melted only at the higher temperature, and its nmr spectrum was identical with that of the product having a single melting point.

(21) C. F. Koelsch and C. D. LeClaire, *J. Org. Chem.*, **6**, 516 (1941).

(22) P. Gagnon, *Ann. Chim.* (Paris), **12**, 296 (1929); *Chem. Abstr.*, **24**, 4027 (1930).

(23) C. B. Wooster, H. D. Segool, and T. T. Allan, Jr., *J. Amer. Chem. Soc.*, **60**, 1666 (1938).

(24) W. Reppe, *Ann.*, **596**, 158 (1955).

(25) S. G. Powell and R. Adams, *J. Amer. Chem. Soc.*, **42**, 646 (1920).

2,3,4,5-Tetrahydro-5,5-diphenyl-1-benzoxepin (9).—Polyphosphoric acid (100 g) was placed in a 500-ml indented (Morton) flask equipped with an efficient cone drive stirrer (Teflon paddle). The acid was preheated to 100 ± 1° and stirred very vigorously at this temperature while 10.0 g (31.4 mmol) of finely powdered **12** was added in small portions over a period of 15 min. Rapid stirring at 100 ± 1° was continued for an additional 110 min. The hot, brownish yellow mixture was then poured into 700 ml of ice water, made strongly basic (pH 10) with excess 50% sodium hydroxide solution, and extracted twice with benzene. Evaporation of the dried extracts gave 8.48 g of pale yellow solid, which was mixed well with a minimum amount of petroleum ether (bp 30–60°), cooled to −10°, and filtered to recover 5.24 g of solid. (Work-up of the filtrate yielded none of the desired product.) The solid was boiled and stirred for 3 hr with approximately 2 l. of methanol; and after filtering to remove a small amount of insoluble material, the solution was concentrated to the cloud point and cooled. Small white crystals of **9** precipitated (2.50 g, mp 180–182°); a second crop melting at 179–182° (0.31 g, total yield 30%) was obtained in the usual way. Recrystallization of the first crop from methanol gave tiny, snow-white needles: mp 182.0–182.3°; ir (CS_2) 1220 cm^{-1} (strong, =CO–), no OH or C=O; nmr (CCl_4), δ 6.6–7.3 (m, 13, two C_6H_5 and 7, 8, and 9 H of C_6H_4), 6.28 (dd, 1, J_{ortho} = 8 Hz, J_{meta} = 2 Hz, 6 H of C_6H_4),[26] 3.83 (t, 2, J = 6 Hz, CH_2O), 2.66 (distorted t, 2, $J \approx 6$ Hz, CH_2CPh_2), and 1.87 ppm (distorted qn, 2, $J \approx 6$ Hz, CH_2CH_2O); mass spectrum (70 eV) *m/e* 300.1541 (strong; calcd for $C_{22}H_{20}O$, 300.1514), 223.1122 (medium; calcd for $C_{16}H_{15}O$, 223.1123), and 181.0650 (weak; calcd for $C_{13}H_9O$, 181.0653).

Anal. Calcd for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 88.06; H, 6.75.

(26) This assignment is based on (a) an examination of a molecular model, which indicates that the proton in question lies near the periphery of the shielding cone of one of the phenyl groups, and (b) a comparison with the nmr spectrum reported for 2,3,4,5-tetrahydro-5,5-dimethyl-1-benzoxepin [H. Hart, J. L. Corbin, C. R. Wagner, and C. Wu, *J. Amer. Chem. Soc.* **85**, 3269 (1963)], which exhibits no aromatic peaks at δ <6.8.

4,4-Diphenyl-3-butenyl Phenyl Ether (13).—Treatment of benzene solutions of alcohol **12** with dry HCl or phosphorus pentoxide produced **13** in essentially quantitative yield. Very high yields of **13** also resulted from reactions of **12** with polyphosphoric acid (see above) which were performed with inefficient stirring. In an experiment typifying the most convenient method of synthesis, a solution of **12** (0.50 g, 1.57 mmol) in benzene (10 ml) was placed over Drierite (0.5 g), saturated with dry hydrogen chloride, allowed to stand at room temperature in a stoppered flask for 6 hr, filtered, and evaporated, The nmr spectrum of the crude liquid residue (0.47 g, 100%) was identical with the spectrum of an analytical sample of **13** prepared by distillation of the crude product through a short spinning-band column. The pure material was obtained as a straw-colored oil: bp 179° (0.7 mm); ir (neat) 1243 cm^{-1} (strong, =CO–), no OH; nmr (CCl_4), δ 7.0–7.4 (m, 12, two C_6H_5C and *m*-H of C_6H_5O), 6.68–6.89 (m, 3, *o*- and *p*-H of C_6H_5O), 6.14 (t, 1, J = 7 Hz, CH_2CH=C), 3.91 (t, 2, J = 7 Hz, CH_2O), and 2.54 ppm (qr, 2, J = 7 Hz, CH_2CH=C); mass spectrum (70 ev) *m/e* 300.1491 (weak; calcd for $C_{22}H_{20}O$, 300.1514), 207.1174 (medium; calcd for $C_{16}H_{15}$, 207.1174), and 193.1017 (medium; calcd for $C_{15}H_{13}$, 193.1017).

Anal. Calcd for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 87.94; H, 6.77.

Registry No.—**1**, 16778-07-7; **2**, 15070-88-9; **3**, 16778-09-9; **4**, 16778-10-2; **5**, 16778-11-3; **6**, 16778-12-4; **8**, 16778-13-5; **9**, 16778-14-6; **11**, 2364-59-2; **12**, 16778-16-8; **13**, 16778-17-9; **18**, 16778-18-0; **27**, 16778-19-1; lead tetraacetate, 546-67-8.

Acknowledgment.—The author is indebted to Mr. H. J. Tarski for excellent technical assistance, and to numerous colleagues in the Analytical Research Section of this laboratory for stimulating discussions.

Mechanisms of Photochemical Reactions in Solution. LIII.[1] Cycloaddition of Carbonyl Compounds to Allenes

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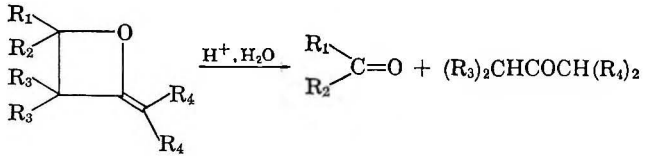
Received January 22, 1968

Adlehydes and ketones undergo photochemical cycloaddition reactions to allenes to form oxetanes. The latter will in turn react with the carbonyl compounds forming 1,5- and 2,5-dioxaspiro[3.3]heptane derivatives. In some cases the oxetanes undergo photoisomerization to cyclobutanones. The quantum yield for disappearance of acetophenone in the presence of tetramethylallene was found to be 0.59. A mechanism is proposed involving the addition of carbonyl triplets to the allenes.

Preliminary reports of studies of photochemical cycloaddition of ketones to allenes have recently been reported by Arnold and Glick[2] and by ourselves.[3] The principal products formed in the reactions are shown in Table I along with analytical data and key spectroscopic characteristics. In some instances pinacols derived from the ketones were also isolated. The structures of the addition compounds are indicated by their spectra and by hydrolysis in aqueous acid.



Hydrolytic cleavage of monoadducts (**1**, **4**, **7**, **9**, **11**, **12**, and **17**) gives the original ketone and the ketone that is formally derived by addition of the elements of water to the allene.

The spiro ketal, **8**, is easily cleaved to acetophenone and diisopropyl ketone.

$$8 \xrightarrow{H^+,\ H_2O} 2C_6H_5COCH_3 + (CH_3)_2CHCOCH(CH_3)_2$$

The 2,5-dioxaspiro[3.3]heptanes (**5**, **13**, **14**, and **15**) are not cleaved to ketones by aqueous acid at room temperature.

All of the monoadducts have strong infrared absorption bands at or close to 1735 cm^{-1}. We believe that the band is analogous to absorption of enol ethers found between 1633 and 1712 cm^{-1}.[4] The very high frequency of the absorption is reminiscent of the

(1) Part LII: B. M. Monroe, S. A. Weiner, and G. S. Hammond, *J. Amer. Chem. Soc.*, **90**, 1913 (1968).

(2) D. A. Arnold and A. H. Glick, *Chem. Commun.*, 813 (1966).

(3) H. Gotthardt, R. Steinmetz, and G. S. Hammond, *ibid.*, 480 (1967).

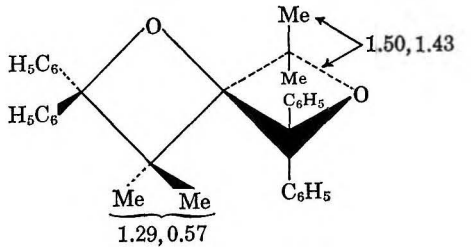
(4) S. M. McElvain and R. E. Starn, *J. Amer. Chem. Soc.*, **77**, 4571, 5601 (1955).

high carbonyl stretching frequencies in cyclobutanones,[5] and to the high frequency band assigned to the double stretch in β-isopropylidene-β-butyrolactone.[6]

A troublesome discrepancy between our work and that of Arnold and Glick[2] appeared in the study of the reaction of benzophenone with tetramethylallene. A single, noncrystalline monoadduct has been isolated in both laboratories and we agree in assigning structure **4** to the compound. The carbide group have isolated two bis adducts melting at 150.5–152.5° and at 152–154°. Structure **5** was assigned to the former material and the latter was believed to be the spiro ketal, **6**.

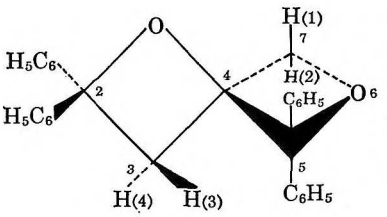
The melting point of an isolated material having the composition of a bis adduct was surprisingly low, 87–89°. After the discrepancy came to our attention we investigated the matter further and accomplished partial isolation of the ambiguities. Irradiation of benzophenone and tetramethylallene in benzene solution, as was done by Arnold and Glick, led to production of a mixture from which compounds **5** and **6** could be isolated. By thin layer chromatography, the original, low melting product was separated into three fractions. The principal component melted at 147° after recrystallization and gave no melting point depression on admixture with a sample of **5** from Arnold's laboratory. The minor components were not obtained in sufficient quantity to crystallize but infrared spectra showed that neither material was identical with **6**. It is possible that **6** was present in the low melting material but that it underwent rearrangement in the course of the chromatographic separation. Crystal seeding experiments showed that the low melting material is not merely a polymorphic form of **5**.

The nmr spectrum of **5** shows four sharp resonances in the methyl proton region. The signals are tentatively assigned as follows. When **5** was treated with



aqueous sulfuric acid under the same conditions that led to facile hydrolytic cleavage of spiro ketals, no cleavage products could be detected. The nmr spectrum of **6** shows sharp singlets at 1.29 and 1.03 ppm. Chemical evidence for the spiro ketal structure was obtained by Arnold and Glick.[2]

Compounds **13** and **14** are assigned the indicated structures mainly on the basis of the proton resonances of the methylene groups. Those in **13** should occur at lower field than those in **14** because the former are attached to a carbon atom which is also bonded to an oxygen atom. We believe that the resonance at 3.18 ppm in the spectrum of **13** should be attributed to the proton that is *cis* to the oxygen atom of the other ring. The basis for assignment is rather intuitive, and therefore far from compelling. However, one might expect the *cis* proton to be subject to a small, but significant, paramagnetic deshielding related to the paramagnetic deshielding of directly bound protons inferred to exist in water.[7] Similar reasoning leads to the following assignments of the resonances due to the methylene protons in **15**.



H(1), 4.57 ppm
H(2), 4.87 ppm
H(3), H(4), 3.40, 290 ppm

15

Two generalizations have been advanced concerning photochemical cycloaddition reactions of carbonyl compounds and alkenes.[8] First, only carbonyl compounds having the n,π* configuration in their lowest triplet states show high reactivity and, second, cycloaddition occurs only if transfer of triplet excitation from the carbonyl compound to olefinic compound is inefficient because the vertical excitation energy of the acceptor is higher than that available in the carbonyl triplet. The singlet–singlet absorption spectra of allenes have been discussed by Murrell.[9] There should be low intensity transitions having lower excitation energies than the lowest transitions of simple olefins. Such transitions may have been observed[10] in the vicinity of 2500 Å. No spectroscopic information is available concerning allenic triplets. However, one would expect the splitting between triplets and singlets to be smaller than in alkenes since the excitation effectively transfers an electron from one plane to another perpendicular to the first. In such an excited state, the electron–electron repulsion should not be decreased greatly by the singlet → triplet transition. The situation would be roughly similar to the familiar case of the n,π* states of carbonyl compounds. Consequently, the triplet states of allene might be expected to lie between those of alkenes (~82 kcal/mol) and conjugated dienes (~59 kcal/mol).[11] Acetophenone, which has an excitation energy of 74 kcal/mol,[12] adds smoothly to tetramethylallene with a quantum yield for disappearance of the ketone of 0.59. Consequently, we infer that the triplet excitation energy of the allene is significantly greater than 74 kcal/mol. Traces of materials that appear to be dimers of the allenes were noted in the vapor chromatograms in some experiments indicating that energy transfer may have occurred, but with very low efficiency.

(5) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1963, p 62.

(6) R. H. Hasek, R. D. Clark, E. U. Elam, and J. C. Martin, *J. Org. Chem.*, **27**, 60 (1962).

(7) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 180.

(8) D. A. Arnold, R. L. Hinman, and A. H. Glick, *Tetrahedron Lett.*, No. 22, 1425 (1964); N. C. Yang, *Pure Appl. Chem.*, **9**, 591 (1964); J. Saltiel, R. M. Coates, and W. G. Dauben, *J. Amer. Chem. Soc.*, **88**, 2745 (1966).

(9) J. N. Murrell, "The Theory of Electronic Spectra of Organic Molecules," John Wiley and Sons, Inc., New York, N. Y., 1963, p 79.

(10) E. P. Carr and H. Stücklen, Proceedings of the Seventh Summer Conference on Spectroscopy and its Applications, John Wiley and Sons, Inc., New York, N. Y., 1940, p 128.

(11) D. F. Evans, *J. Chem. Soc.*, 1735 (1960).

(12) W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *J. Amer. Chem. Soc.*, **86**, 4537 (1964).

TABLE I.—PHOTOADDITION OF KETONES TO ALLENES[a]

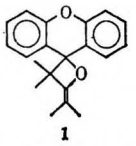
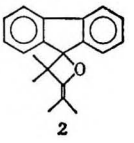
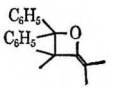
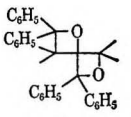
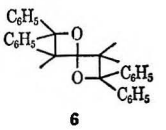
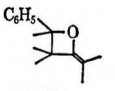
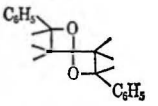
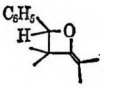
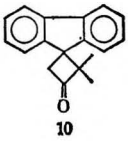
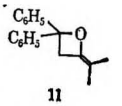
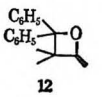
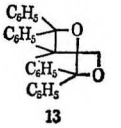
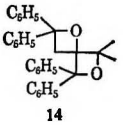
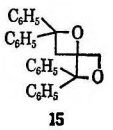
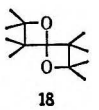
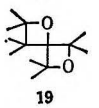
Ketone	Substrate	Products	
Xanthone	Tetramethylallene	 1	*Anal.* Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 82.23; H, 7.00 Ir, 1735 cm^{-1} Nmr, 7.38, 1.74, 1.53, 0.84 ppm Isolated yield, 60%
Fluorenone	Tetramethylallene	 2	*Anal.* Not obtained in pure form Ir, 1735 cm^{-1} Nmr, 7.2, 1.63, 1.59, 1.25 ppm
		 3	*Anal.* Calcd for $C_{20}H_{20}O$: C, 86.92; H, 7.29. Found: C, 87.04, H, 7.34 Ir, 1775 cm^{-1} Nmr, 7.2, 1.27 ppm Isolated yield, up to 73%
Benzophenone	Tetramethylallene	 4	*Anal.* Calcd for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 86.23; H, 8.14 Ir, 1735 cm^{-1} Nmr, 7.5, 1.76, 1.53, 1.15 ppm Isolated yield, 37%
		 5	*Anal.* Calcd for $C_{33}H_{32}O_2$: C, 86.05; H, 7.00. Found: C, 85.95; H, 6.87 Nmr, 7.2, 1.50, 1.43, 1.29, 0.57 ppm Isolated yield, 28%
		 6	*Anal.* See ref 2 Nmr, 7.37, 1.29, 1.03 ppm Isolated yield, 15%
Acetophenone	Tetramethylallene	 7	*Anal.* Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.44; H, 9.37 Ir, 1735 cm^{-1} Nmr, 7.39 (5), 1.66 (3), 1.63 (3), 1.53 (3), 1.42 (3), 0.82 (3) ppm Isolated yield, 25%
		 8	*Anal.* Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 82.03; H, 8.39 Nmr, 7.39 (10), 1.82 (6), 1.37 (6), 0.72 (6) ppm Isolated yield, 38%
Benzaldehyde	Tetramethylallene	 9	*Anal.* Calcd for $C_{14}H_{18}O$: C, 83.13; H, 8.97. Found: C, 83.12; H, 8.97 Ir, 1736 cm^{-1} Nmr, 7.19 (5), 5.23 (1), 1.58 (3), 1.15 (3), 1.13 (3) ppm Isolated yield, 51%
Fluorenone	1,1-Dimethylallene	 10	*Anal.* Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 86.95; H, 6.43 Ir, 1783 cm^{-1} Nmr, 7.3, 3.52, 1.10 ppm Yield (by nmr), 48%
Benzophenone	1,1-Dimethylallene	 11	*Anal.* Calcd for $C_{18}H_{18}O$: C, 86.34; H, 7.25. Found: C, 86.30; H, 7.15 Ir, 1744 cm^{-1} Nmr, 7.1, 3.49, 1.61, 1.38 ppm
		 12	Not isolated in pure form. Nmr, resonances overlapping those of **11** plus an AB pattern centered at 3.76 ppm with J = 3.6 cps
		 13	*Anal.* Calcd for $C_{31}H_{28}O_2$: C, 86.08; H, 6.53. Found: C, 85.89; H, 6.62 Nmr, 7.32, 3.26, 3.18, 0.92, 0.86 ppm Yield (by nmr), 42%
		 14	Not obtained in analytical purity Nmr, 7.3, 3.06, 2.98, 1.28; 1.19 ppm Yield (by nmr), 20%

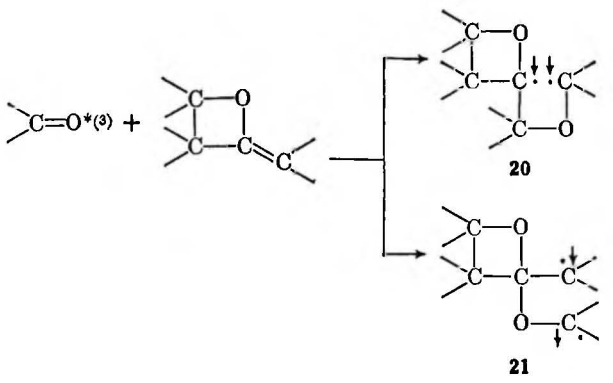
TABLE I (*Continued*)

Ketone	Substrate	Products	
Benzophenone	Allene	 15	*Anal.* Calcd for $C_{29}H_{24}O_2$: C, 86.11; H, 5.98. Found, C, 86.19; H, 6.08 Ir, none in region of interest Nmr, 7.36, AB group centered at 4.72 ppm, ($\Delta\nu$ = 18.0 cps, J_{12} = 7.2 cps) AB group centered at 3.15 ppm ($\Delta\nu$ = 22.9 cps, $J_{3,4}$ = 12.4 cps)
Acetone	Tetramethylallene	 16	*Anal.* Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.07, H, 11.88 Ir, none in region of interest Nmr, singlets at 1.59 and 1.43 ppm; ratio 1:2
		 17	*Anal.* Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.98; H, 11.94 Ir, 1732 cm^{-1} Nmr, four singlets at 1.35, 1.28, 1.19, and 1.13 ppm; ratio 1:1:2:2
		 18	*Anal.* Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.65; H, 11.34 Nmr, four singlets at 1.22, 1.10, 1.06 and 0.93 ppm; ratio 1:1:1:1
		 19	*Anal.* Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.64; H, 11.28 Nmr, three singlets at 1.38, 1.16, and 1.12 ppm (in CCl_4); ratio 1:2:1. In fluorobenzene four sharp singlets are resolved.

[a] In cases in which the relative areas are not ambiguously indicated by the structural formulas and ordinary chemical shifts, the relative areas of the nmr signals are included in parentheses after the chemical shifts.

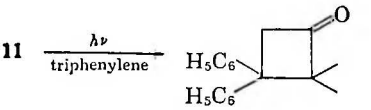
The first step of addition seems to be highly selective and is easily rationalized if an intermediate biradical having an allylic part structure is formed in preference to alternate vinylic radical structures. The only exception to the apparently preferred direction of addition was the isolation of a small amount of **16** from the reaction of acetone with tetramethylallene.

The course of the second addition step is not nearly so obvious, since two kinds of products are formed. The usual mechanism would lead to the following formulations.



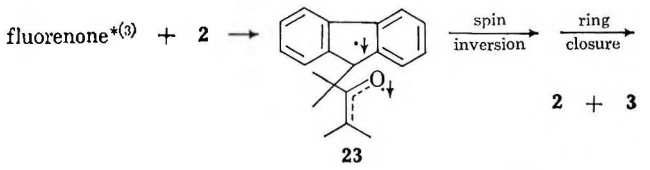
That the second step should take two courses is interesting but not astounding. One would expect that the double bonds in the enol ethers should be highly reactive because of the strain energy in the exocyclic double bonds. The high reactivity is indicated by the fact that formation of diadducts is competitive with addition to the parent allenes even though the latter are used as the reaction media. Since the reactions are very rapid one might expect that normal selectivity would not be observed. Stabilization of intermediate **20** may not be so large as would normally be expected. Three-electron bonding between the cyclic spin center and the adjacent oxygen atom may be decreased relative to that in acyclic α-oxy radicals because of decrease in the π interaction in the small-ring system. However, the factors that control competition between the two possible courses of reaction are not at all obvious. On a totally emperical basis one might expect acetophenone to show behavior intermediate between that of benzophenone and acetone. Only the spiro ketal, **8**, was isolated from acetophenone whereas with acetone both the spiro ketal, **18** and the diaoxaspiroheptane, **19**, were isolated although the former was apparently produced in the higher yield. Since the material balance was imperfect in all experiments, we now consider it unwise to attack any significance to the absence of the second bis adduct having the 2,5-dioxaspiroheptane structure from the reaction with acetophenone.

The failure of fluorenone and xanthone to form diadducts is interesting. In the former case the second addition step seems to be replaced by photoisomerization of the oxetanes to cyclobutanones, a reaction that may have some synthetic merit. The latter is almost certainly a photochemical process, although it has been studied explicitly only with **11**, one of the adducts formed from benzphenone and 1,1-dimethylallene. The rearrangement to **22** is sensitized by triphenylene.

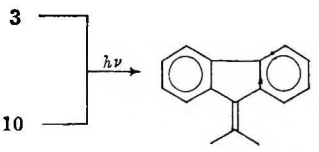


Isomerization of **2** was not studied in separate experiments because the compound could never be obtained free from the isomeric ketone, **3**. Probably cyclobutanones are formed in the course of preparative experiments by reactions in which the parent ketones serve as sensitizers. Such a mechanism deserves special comment. Consider the case of the fluorenone–tetramethylallene system. The monoadduct, **2**, would be expected to have a triplet excitation energy similar to that of fluorene (67.6 kcal/mol) whereas the excitation energy of fluorenone is only 53.3 kcal/mol.[12]

With a mismatch in excitation energies of about 14 kcal/mol, one would not normally expect energy transfer to be competitive with cycloaddition to the allene. Occurrence of the secondary reaction may indicate one of two interesting phenomena. (1) The enol ether function in 2 may interact fairly strongly with the aromatic system even they are not conjugated, or (2) bond breaking in the energy acceptor may be concerted with energy transfer.



Another product isolated from the reactions of fluorenone with tetramethylallene and 1,1-dimethylallene is isopropenylfluorene. This product could well have been formed by fragmentation of 23 with the concommitant formation of dimethylketene. We have observed that 3 and 10 the cyclobutanones formed from reaction of fluorenone with tetramethylallene and dimethylallene undergo photolysis to isopropylidenefluorene when excited by direct irradiation.



Experimental Section

Materials.—Tetramethylallene, Aldrich Chemical Co., was used directly for preparative runs. For use in quantum yield determinations the compound was purified by preparative vapor chromatography. 1,1-Dimethylallene was prepared from 3-methylbut-1-yn-3-ol by the method of Bailey and Pfeifer.[13] Allene, from Matheson Co., was used without further purification. The ketones were all reagent grade of the best purity available commercially and were further purified by distillation or recrystallization.

Procedures.—Solutions were prepared by dissolution of the appropriate ketone in the hydrocarbon, which was used in excess. Solutions were placed in constricted Pyrex ampoules (100 × 13 mm), degassed through three freeze–thaw cycles, and sealed under vacuum. The tubes were placed in the well surrounding a medium-pressure mercury lamp (Hanovia 450-W) and irradiated for periods of 5–28 days. Infrared spectra were taken with a Beckman spectrophotometer, Model IR-7, in carbon tetrachloride solutions. Microanalyses were carried out by the Spang Analytical Laboratory, Ann Arbor, Mich. Nuclear magnetic resonance spectra were determined using a Varian A-60 spectrometer. Carbon tetrachloride solutions were used except where indicated otherwise. All melting points are uncorrected.

Xanthone–Tetramethylallene.—A tube containing 900 mg of xanthone in tetramethylallene was irradiated 115 hr. The colorless crystals of xanthone slowly disappeared and a small amount of a new precipitate was formed; 71 mg of the product was collected by filtration and found to be the pinacol derived by photoreduction of xanthone, mp 160–163°. The filtrate was concentrated by evaporation and the residual oil was distilled at 0.1 torr with a bath temperature of 125–160°. The light yellow distillate (804 mg) solidified and was recrystallized from hexane, mp 114–115°. Structure 1 was assigned to the compound. A mixture of 100 mg of the product and 3 cc of 20% aqueous sulfuric acid was allowed to stand for 3 days at room temperature. The light yellow reaction mixture was extracted with 2 cc of carbon tetrachloride and the extract was dried and distilled at atmospheric pressure. The distillate had an infrared spectrum identical with that of authentic diisopropyl ketone. The residue was recrystallized from methanol and identified as xanthone by mixture melting point (173–174°).

Fluorenone–Tetramethylallene.—Two tubes, each containing 500 mg of fluorenone and 3 cc of tetramethylallene, were irradiated for 12 days. The precipitated crystals were collected by filtration and identified as 2-keto-1,1,3,3-tetramethylspiro-(cyclobutane-4,9′-fluorene), 3, colorless needles, mp 205–206° recrystsllized from ethyl acetate. The filtrate was concentrated by evaporation under vacuum at room temperature. The residual, light yellow oil was separated into three fractions by chromatography on 30 g of Florisil. The first fraction, eluted with 210 cc of pentane plus 90 cc of benzene, was identified as 9-isopropylidenefluorene:[14] mp 112–114°; yield, 82 mg, 7.4%. The second fraction (0.126 g), eluted with 150 cc of pentane and 350 cc of benzene, was a mixture of 2 and 3 and the third fraction, eluted with 280 cc of benzene and 120 cc of ether, was pure 3. The amount of 2 in the second fraction was estimated by nmr analysis; the over-all yield of 3 was 1.12 g (73%). In two other runs yields of 66 and 72% were obtained. Compound 2 was not obtained in pure form because of the ease with which it undergoes rearrangement to 3.

Benzophenone–Tetramethylallene.—A solution of benzophenone (1.0 g) and tetramethylallene (3 cc) was irradiated for 27 days in a degassed, sealed Pyrex tube. Benzopinacol, identical with an authentic sample, precipitated and was removed by filtration (0.137 g, 13.6%), mp 167–170°. The excess tetramethylallene was removed by distillation and the residual oil was distilled at 1–2 torr with a bath temperature of 130–160°. The colorless oil (0.56 g, 36.6%) was identified as 2,2-diphenyl-3,3-dimethyl-4-isopropylideneoxetane, 4. The residue from distillation (0.660 g) was chromatographed on Florisil (30 g). Elution with a mixture of pentane (400 cc) and benzene (100 cc) gave an unidentified oil (0.210 g). Further elution with a mixture of 170 cc of pentane and 170 cc of benzene gave colorless crystals (0.350 g, 27.6%), mp 87–89°, identified as 3,3,7,7-tetramethyl-1,1,6,6-tetraphenyl-2,5-dioxaspiro[3.3]heptane, 5.

A sample of the above material was separated by thin layer chromatography using benzene as a developer. Examination under ultraviolet light showed three bands. The intermediate band, which moved at the same rate as Arnold's sample of 5, was eluted with ethyl ether and recrystallized from aqueous ethanol, mp 147°. The other fractions were obtained in very samll quantities and could not be crystallized. The infrared spectra of thin films showed that neither material was identical with 6.

Compound 4 was hydrolyzed by allowing a 0.170-g sample to stand with 2 cc of 20% aqueous sulfuric acid for 2 days at room temperature. The reaction mixture was extracted with 2 cc of carbon tetrachloride, dried, and distilled at atmospheric pressure. The infrared spectrum of the distillate was identical with that of diisopropyl ketone. The residue was identified as benzophenone by its infrared spectrum.

A mixture of benzophenone (5.5 g) and tetramethylallene (3.0 g) in 300 cc of benzene was irradiated 9.5 hr in the immersion well of a high-pressure mercury lamp (Hanau Q 700). Purified nitrogen was bubbled through the solution. The solution was concentrated and distilled at 0.001 torr with a bath temperature of 120°. An oily, colorless distillate (0.61 g, 7.3%) was collected and identified as 4. The distillation residue (5.25 g of light yellow solid) was chromatographed on 400 g of neutral alumina (activity grade III). Elution with benzene gave some benzpinacol and 3.5 g of a noncrystalline product which was rechromatographed on alumina (400 g, activity grade II). Elution with a mixture of petroleum ether and benzene (9:1) gave 0.1 g of an unidentified oil and 1.02 g (15%) of a white, crystalline material which melted 150–152° after recrystallization from methanol. Comparison of the nmr spectra indicated that the material is identical with compound 6 isolated by Arnold and Glick; however, the remaining sample of the latter was insufficient to permit comparison by mixture melting point. Further elution with benzene yielded 1.90 g (27%) of 5, mp 149–151°.

Acetophenone–Tetramethylallene.—A mixture of acetophenone (4 cc) and tetramethylallene (12 cc) was irradiated for 24 days in four ampoules. Vapor chromatographic analysis indicated complete disappearance of acetophenone and the ap-

(13) W. J. Bailey and C. R. Pfeifer, *J. Org. Chem.*, **20**, 95 (1955).

(14) P. Maitland and S. H. Tucker, *J. Chem. Soc.*, 2559 (1929).

pearance of no dimers from tetramethylallene. The combined solutions were concentrated and distilled at 1 torr. The first fraction (80–110° bath temperature) was a colorless oil (2.136 g, 29%) identified as 2-phenyl-2,3,3-trimethyl-4-isopropylideneoxetane, **7**. The second fraction (140–170° bath temperature) was a colorless glass (3.867 g). Recrystallization from methanol gave 1.375 g (10%) of white crystals identified as 2,6-diphenyl-2,3,3,6,7,7-hexamethyl-1,5-dioxaspiro[3.3]heptane, **8**, mp 133–134.5°. In another run a 38% yield of **8** isolated by chromatography on silica gel using benzene as the elution solvent. An 8% yield of 2,3-diphenylbutane-2,3-diol was also isolated.

A mixture of **7** (280 mg) and 20% sulfuric acid (5 cc) was allowed to stand for 2 days at room temperature and then heated under reflux for 1 hr. The product was extracted with carbon tetrachloride and distilled at atmospheric pressure. The distillate contained diisopropyl ketone and the residue was acetophenone. Vapor chromatography showed that the two ketones were present in equimolar amounts.

Compound **8** (300 mg) was allowed to stand with 40% sulfuric acid (2.5 cc) for 24 hr at room temperature. The mixture was extracted with carbon tetrachloride and vpc analysis of the extract showed the presence of diisopropyl ketone and acetophenone in the ratio 1:2.02.

Benzaldehyde–Tetramethylallene.—A mixture of benzaldehyde (3 cc) and tetramethylallene was irradiated for 27 days in two ampoules. Vapor chromatography showed the presence of 4.4% unreacted benzaldehyde and 68% **9**. After concentration, the products were distilled at 8–10 torr (100–180° bath temperature) giving 4.24 g of light yellow oil which was purified by preparative vapor chromatography. The product was identified as 2-phenyl-3,3-dimethyl-4-isopropylideneoxetane, **9**.

A 50-mg sample of **9** was hydrolyzed by treatment with 20% sulfuric acid (1 cc) for 1 day at room temperature. The reaction mixture was extracted with carbon tetrachloride, washed, dried, and distilled at atmospheric pressure. The distillate and residue were identified respectively as diisopropyl ketone and benzaldehyde by vapor chromatography and infrared spectra.

Acetone–Tetramethylallene.—A mixture of acetone (3 cc) and tetramethylallene (6 cc) was irradiated for 20 days in two degassed, sealed Pyrex test tubes and irradiated for 20 days. Unreacted materials were removed by distillation and the residue was distilled at 17 torr. At 110–170° bath temperature a colorless oil (440 mg) was collected. Analysis by vapor chromatography of the distillate showed a major product (85%) and two unidentified minor products. The main product was separated by preparative gas chromatography and identified as 2,2,3,3-tetramethyl-4-isopropylideneoxetane, **17**.

In another experiment a solution of tetramethylallene (20 g) and acetone (400 cc) was irradiated in two portions using a 450-W mercury resonance lamp for 18 hr. During irradiation dry nitrowas bubbled through the solutions. The combined solutions were concentrated and distilled under vacuum. At 70–110° and 17 torr a liquid which deposited some crystals was obtained; at 105–115° and 1 torr 2.3 g of a yellow oil (shown by vpc to contain at least four compounds) was obtained. The crystalline material (5.60 g) was removed from the first fraction by filtration, purified by sublimation at 70° (1 torr), and identified as 1,1,3,3,-6,6,7,7-octamethyl-2,5-dioxaspiro[3.3]heptane (**19**), mp 81–82°. The filtrate was separated by preparative vapor chromatography (9-ft UCON polar, 20%, 90°) into six fractions. The first was 0.3 g of colorless oil, identified as 3-isopropylidene-2,2,4,4-tetramethyloxetane, **16**. The second fraction was 0.5 g of colorless oil identified as **17**. This material was hydrolyzed to acetone and diisopropyl ketone when treated with 20% sulfuric acid. Fractions 3 and 4 contained samll amounts of unidentified materials. Fraction 5 was 3.5 g 2,2,3,3,6,6,7,7-octamethyl-1,5-dioxaspiro[3.3]heptane, **18**. Hydrolysis with 20% sulfuric acid gave acetone and diisopropyl ketone. The sixth fraction was 2.60 g of **19**.

Fluorenone–1,1-Dimethylallene.—Three tubes, each containing fluorenone (0.5 g) and 1,1-dimethylallene (3 cc), were irradiated for 212 hr. The contents of two tubes were combined and the excess dimethylallene was removed by distillation and the residue was distilled at 1–2 torr with a bath temperature of 145–170°. The product was a yellow oil (845 mg) and was found by nmr analysis to be a mixture of **10** and 9-isopropylidenefluorene. The material was separated by chromatography on 30 g of Florisil with pentane–benzene (80:20) as the eluent. The first fraction (176 mg) was isopropylidenefluorene, mp 112–114° after recrystallization from methanol. Further elution with increasing amounts of benzene yielded colorless needles (0.572 g), mp 89–90° after recrystallization from methanol. The material was identified as **10** by elementary analysis and infrared and nmr spectroscopy (see Table I). The most significant spectral features were the strong carbonyl absorption at 1783 cm^{-1} in the infrared spectrum and the occurrence of a sharp singlet due to six methyl protons at 1.10 ppm downfield from the tetramethylsilane resonance. The yield of **10** in the distillate was measured at 48% by integration of the nmr spectrum of the crude distillate.

The contents of the thrid tube were concentrated *in vacuo* and the spectra of the residue was determined. The infrared spectrum showed no absorption in the region of the enol ether bands (~1735 cm^{-1}) and the nmr spectrum indicated the presence of only the two compounds isolated.

Benzophenone–1,1-Dimethylallene.—Six tubes, each containing benzophenone (1 g) and 1,1-dimethylallene (3 cc), were degassed, sealed under vacuum, and irradiated for 11 days. The combined contents of five tubes were concentrated and then distilled at a pressure of 2.5–4 torr with a bath temperature of 135–160°. The distillate yielded 2.56 g of brownish red oil and the residue was 3.86 g of light yellow solid. The distillate was separated into five fractions after passages through a Florisil column using pentane and 1:1 pentane–benzene as elution solvents. The first fraction was 40 mg of unidentified oil. The second was 80 mg of oil identified as a mixture of **11** and **12**. The third fraction (200 mg) was identified as 2,2-diphenyl-4-isopropylideneoxetane (**11**). The fourth fraction was 153 mg of unidentified material. The last fraction was 1.36 g of colorless oil identified as 2,2-dimethyl-3,3-diphenylcyclobutan-1-one, believed to be an artifact formed by rearrangement of **11** and **12**.

The residue was separated into two principal fractions by chromatography on Florisil using pentane containing 20% benzene as the eluent. The first fraction was recrystallized from hexane giving colorless crystals, mp 117–119°, and was identified as 7,7-dimethyl-1,1,6,6-tetraphenyl-2,5-dioxaspiro-[3.3]heptane, **13**. The second fraction contained an oil identified as 3,3-dimethyl-1,1,6,6-tetraphenyl-2,5-dioxaspiro[3.3]heptane, **14**. Integration of the nmr spectrum of the unseparated distillation residue gave the yields of **13** and **14** shown in Table I.

The vacuum distillate (0.1 g) containing **11**, **12**, and **22** was treated with 20% aqueous sulfuric acid (5 cc) at room temperature for 24 hr. The reaction mixture was extracted with carbon tetrachloride and the extract was analyzed by vapor chromatography. Equal amounts of benzophenone and methyl isopropyl ketone were found. None of the latter product was formed when the distillation residue was treated with aqueous acid under similar conditions.

The reaction mixture of the sixth irradiated tube was concentrated at room temperature under vacuum. Both the infrared and nmr spectrum of the residue showed absence of **22**. This indicates that **22** was formed during distillation by a thermal rearrangement of **11** and **12**.

Benzophenone–Allene.—Two tubes, each containing benzophenone (4 g) and liquid allene (about 10 cc) were degassed, sealed under vacuum, and irradiated for 26 days. The excess allene was removed by evaporation and the residue was crystallized from methanol. After four recrystallizations, colorless crystals, mp 127–127.5°, were isolated and identified as 1,1,6,6-tetraphenyl-2,5-dioxaspiro[3.3]heptane, **15**. Treatment of the compound with 20% aqueous sulfuric acid at room temperature for 24 hr did not lead to production of either acetone or benzophenone.

Photolysis of 3.—A solution of **3** (0.150 g) in 4 cc of benzene was irradiated for 24 hr. The resulting light yellow solution was concentrated by evaporation under vacuum. The solid residue was treated with carbon tetrachloride (1 cc) and filtered. Comparison of nmr and infrared spectra with those of authentic material showed the product to be 9-isopropylidenefluorene.

Photolysis of 10.—A solution of **10** (0.1 g) in 3 cc of benzene was irradiated for 48 hr. Examination as in the above experiment sowed that the starting material was converted quantitatively into 9-isopropylidenefluorene.

Sensitized Photolysis of 11.—A solution of **11** (0.042 g) in 5 cc of benzene saturated with triphenylene was irradiated for 24 hr. The solvent was removed by distillation under vacuum. The residue was dissolved in 2 cc of carbon tetrachloride for determination of the infrared spectrum which showed the presence of 2,2-dimethyl-3,3-diphenylcyclobutanone, **22**, in addition to residual **11**.

Quantum Yield Determination.—A solution was prepared by dissolution of 0.130 g of acetophenone and 0.062 g of chlorobenzene[15] in enough tetramethylallene to make the total volume 10 cc. Two tubes, each containing 3.4 cc of the solution, were irradiated in a merry-go-round apparatus for periods of 4 and 6 hr using solution filters containing $NiSO_4$–$CoSO_4$ and potassium acid phthalate to isolate the 3130-Å group of lines. Samples containing 3.4 cc of a mixture of 1,3-cyclohexadiene (1.312 g), benzophenone (0.916 g), and hexadecane[16] (0.1395 g) in 50.0 cc of benzene were irradiated in parallel with the reaction samples. The product mixtures were analyzed by vapor chromatography and the quantum yield for disappearance of acetophenone was calculated on the assumption that the quantum yield for dimerization of cyclohexadiene is 0.88 under the specified conditions.[16] The measured value of the quantum yield was 0.58 after 4 hr and 0.60 after 6 hr.

(15) Internal standard for vapor chromatographic analysis.
(16) G. F. Vesley, unpublished study.

Registry No.—**1**, 16717-87-6; **2**, 16717-86-5; **3**, 16717-88-7; **4**, 14315-05-0; **5**, 14315-03-8; **6**, 14315-04-9; **7**, 16717-92-3; **8**, 16717-93-4; **9**, 16717-94-5; **10**, 16717-95-6; **11**, 16717-96-7; **12**, 16717-97-8; **13**, 16717-98-9; **14**, 16718-04-0; **15**, 14315-02-7; **16**, 16718-00-6; **17**, 2570-82-3; **18**, 14315-08-3; **19**, 14315-07-2.

Acknowledgment.—This work was supported by a grant from the National Science Foundation. We are indebted to Drs. Chin-Hua Wu and Robert Ning who carried out the thin layer chromatographic separation.

Sesquiterpene Lactones of *Helenium alternifolium* (Spreng.) Cabrera. Structures of Brevilin A, Linifolin A, and Alternilin[1,2]

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Received February 12, 1968

Helenium alternifolium (Spreng.) Cabrera from near Tucuman, Argentina, furnished primarily tenulin and smaller amounts of brevilin A, previously isolated from *H. brevifolium* (Nutt.) A. Wood, linifolin A, previously isolated from *H. linifolium* Rybd., and 6,3′-dimethoxy-5,7,4′-flavone. A collection of *H. alternifolium* from near La Plata, Argentina, afforded the new sesquiterpene lactone alternilin as the sole crystallizable constituent. Structures of brevilin A, linifolin A, and alternilin have been established.

Since our last summary[4] of work on constituents of *Helenium* species, the complete stereochemistry of mexicanin A,[5] thurberilin,[6] and tetrahydrobigelovin[6] has been established and the relative configuration of bromomexicanin E[7] has been determined. A new guaianolide, virginolide, has been extracted from *H. virginicum* Blake,[1] a structure has been deduced for mexicanin H[8] and previously known lactones have been isolated from *H. plantagineum* (DC.) MacBride.[9] In the present paper we wish to report our work on the Argentinian species *H. alternifolium* (Spreng.) Cabrera which allowed us to determine the structure of two previously isolated pseudoguaianolides, brevilin A[10] and linifolin A,[11] and that of a new congener, alternilin.

Examination of *H. alternifolium* collections from near Tucuman, Argentina, furnished 6,3′-dimethoxy-5,7,4′-trihydroxyflavone[12] and tenulin[13] as the principal sesquiterpene lactone constituent. Smaller quantities of other lactones were also isolated. One of the minor lactones was identified as linifolin A, $C_{17}H_{20}O_5$, mp 201–203°,[11,14] previously isolated from *H. linifolium* Rydb., to which we had assigned[11] a gross structure stereoisomeric with that of acetylhelenalin (**2**) (Chart I),[13b,15] balduilin (**3**),[13b,16] and bigelovin (**4**).[17,18] Because hydrogenation of linifolin A afforded, in our hands,[11] a tetrahydro derivative of mp 149–150° which differed from acetyltetrahydrohelenalin (**6**), acetyldihydromexicanin C (11-epiacetyltetrahydrohelenalin), tetrahydrobalduilin (**7**), 11-epitetrahydrobalduilin, tetrahydrobigelovin (**8**), and dihydroisotenulin (**9**) and, because of a subsequent report[19] that hydrogenation of the fourth possible *trans*-fused isomer acetylmexicanin I (**5b**) afforded a substance of mp 109° which was presumably 11-epidihydroisotenulin (**10**), we were forced to conclude[11] that linifolin A differed from compounds **2**–**5** in configuration at one or more of the asymmetric centers at C-1, C-5, C-7, and C-10 and suggested[5] that, because of the inversion of the Cotton effect during hydrogenation, linifolin A might belong to the 1-*epi* series.

The physical constants of the freshly isolated linifolin A from *H. alternifolium*, however, coincided so closely with those reported for acetylmexicanin I (**5b**)[9,19] that a direct comparison was called for. Acetylation of samples of mexicanin I supplied by Dr. Romo de Vivar or isolated from *Helenium autumnale* L.[20] gave material

(1) Constituents of Helenium Species. XXI. Previous paper: W. Herz and P. S. Santhanam, *J. Org. Chem.*, **32**, 507 (1967).
(2) Supported in part by a grant from the U. S. Public Health Service (GM-05814).
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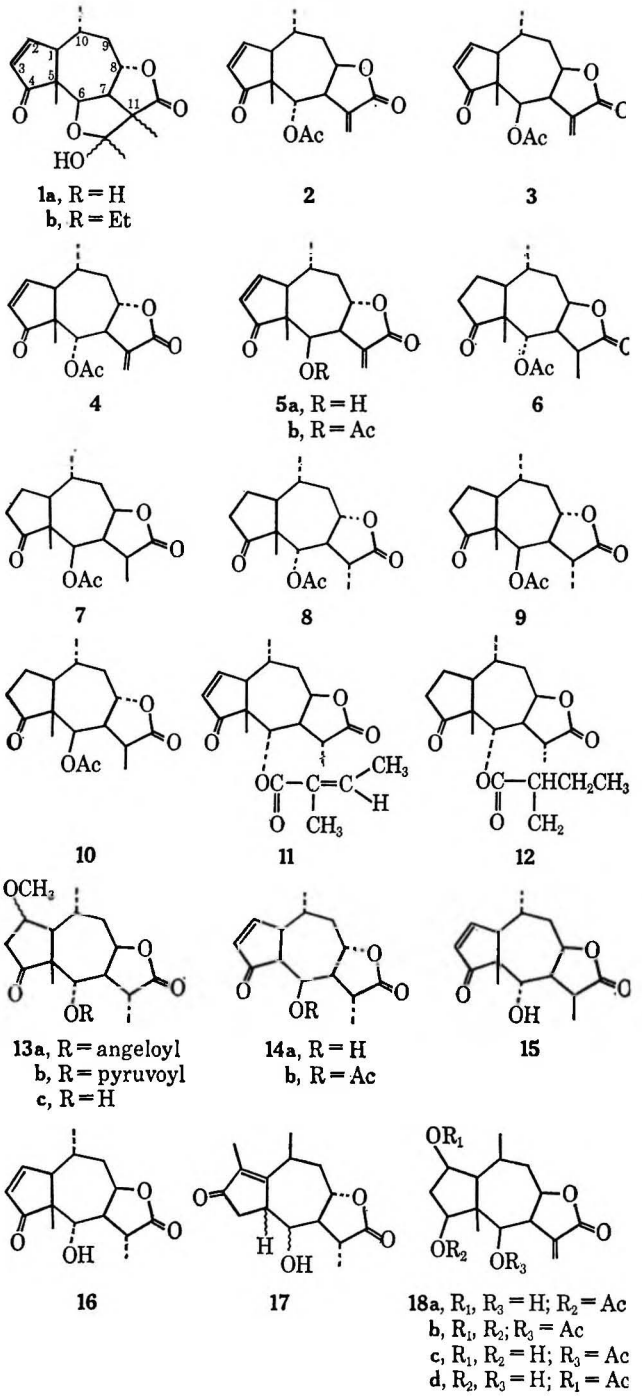
(4) W. Herz and M. V. Lakshmikantham, *Tetrahedron*, **21**, 1711 (1965).
(5) W. Herz, M. V. Lakshmikantham, and R. N. Mirrington, *ibid.*, **22**, 1709 (1966).
(6) A. Romo de Vivar, L. Rodriguez-Hahn, J. Romo, M. V. Lakshmikantham, R. N. Mirrington, J. Kagan, and W. Herz, *ibid.*, **22**, 3279 (1966).
(7) C. N. Caughlan, Mazhar-ul-Haque, and M. T. Emerson, *Chem. Commun.*, 151 (1966).
(8) J. Romo, A. Romo de Vivar, and P. Joseph-Nathan, *Tetrahedron Lett.*, 1029 (1966).
(9) M. Silva, *J. Pharm. Sci.*, **56**, 922 (1967).
(10) W. Herz, R. B. Mitra, K. Rabindran, and W. A. Rohde, *J. Amer. Chem. Soc.*, **81**, 1481 (1959).
(11) W. Herz, *J. Org. Chem.*, **27**, 4043 (1962).
(12) J. W. ApSimon, N. B. Haynes, K. Y. Sim, and W. B. Whalley, *J. Chem. Soc.*, 3788 (1963).
(13) (a) W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman, and N. Viswanathan, *J. Amer. Chem. Soc.*, **84**, 3857 (1962); (b) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *Tetrahedron*, **19**, 1359 (1963).
(14) The melting point was slightly higher than that reported earlier,[11] but the compound was identical in all respects (nmr and ir spectra, tlc) with the sample from *H. linifolium*.
(15) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *J. Amer. Chem. Soc.*, **85**, 19 (1963).
(16) W. Herz, R. B. Mitra, and P. Jayaraman, *ibid.*, **81**, 6061 (1959).
(17) B. A. Parker and T. A. Geissman, *J. Org. Chem.*, **27**, 4127 (1962).
(18) W. Herz and M. V. Lakshmikantham, *Tetrahedron*, **21**, 1711 (1965).
(19) E. Dominguez and J. Romo, *ibid.*, **19**, 1415 (1963).
(20) P. S. Subramaniam, unpublished work.

CHART I



identical in all respects with linifolin A. Since mexicanin I has been correlated[19] with tenulin, the formula of linifolin A is therefore **5b**. However, repetition of the earlier[11] hydrogenation of linifolin A again furnished a substance of mp 152–154°, $[\alpha]D$ +17.40, identical with the sample of mp 149–150° previously prepared by us[11] from linifolin A and not the material of mp 109°, $[\alpha]D$ +48°, reported by the Mexican workers. We are unable to account for this discrepancy in the physical properties of what must be 11-epidihydroisotenulin.

The second minor lactone melted sharply but variably in the range 116–127° and was identified by direct comparison as brevilin A, a substance previously[21] isolated in very low yield from *H. brevifolium* (Nutt.) A. Wood, although the empirical formula assigned earlier to brevilin A now requires correction to $C_{20}H_{26}O_5$.

The presence of an α,β-unsaturated α,β-unsubstituted cyclopentenone moiety, deduced earlier on the basis of the infrared and ultraviolet spectra, was corroborated by the nmr spectrum which exhibited the usual[13,15] doublets of doublets at 7.75 and 6.00 ppm. However, the presence of one methyl singlet at 1.01 (presumably that of C-5 methyl) and two methyl doublets at 1.50 and 1.20 ppm (C-10 and C-11 methyl) indicated that the lactone group was saturated as in tenulin[13] rather than unsaturated as in helenalin or isohelenalin.[15] The second conjugated double bond (infrared band at 1650 cm^{-1}) was therefore placed in an unsaturated side chain. The latter, already suggested by the empirical formula, was identified as an angeloyl group, because of a broad signal at 6 ppm and two characteristic vinyl methyl multiplets at 1.86 and 1.70 ppm.[4]

Catalytic hydrogenation of brevilin A (**11**) yielded a noncrystalline tetrahydro derivative (**12**) whose infrared and nmr spectra reflected changes resulting from saturation of a cyclopentenone chromophore and an angeloyl side chain. Attempts to hydrolyze **11** or **12** in an effort to confirm the direction of lactone ring closure and point of attachment of the ester function (C-6 rather than C-8)[22] were either unsuccessful or required drastic conditions leading to mixtures of desangeloyl derivatives. However, the fortuitous discovery that **13a** was formed from **11** on treatment with methanol–potassium bicarbonate appeared to afford a means of protecting the cyclopentenone function during oxidative removal of the side chain in the manner previously[4] adopted for thurberilin. Ozonolysis of **13a** furnished acetaldehyde and a pyruvate **13b** which it was expected would be cleaved under milder conditions than those required for the hydrolysis of **11**. Simultaneous elimination of the methoxy group under the influence of base was envisioned as a distinct possibility, a reaction which it was hoped would permit the direct correlation of brevilin A with one of the known epimers of desacetylisotenulin (**14a**). In fact a detailed analysis of chemical shifts and coupling constants in the nmr spectra of brevilin A derivatives indicated that brevilin belonged to either the dihydrohelenalin (**15**) or mexicanin C (**16**) series, but was not a derivative of balduilin (**3**), bigelovin (**4**), or isotenulin (**14b**).

Hydrolysis of **13b** with potassium carbonate in boiling methanol afforded as the only crystalline component of a complex mixture a new α,β-unsaturated keto lactone whose ultraviolet (λ_{max} 238 and 302 mμ, ϵ 15,700 and 110) and nmr spectra were consonant with formula **17** (exclusive of stereochemistry). This would be the result of a "neo" rearrangement of the proximate hydrolysis and elimination product.[23] Since **17** clearly differed from dihydroneohelenalin[13b] which is formed in low yield from dihydrohelenalin (**15**) on treatment with methanolic potassium carbonate and has the same gross

(21) W. Herz, R. B. Mitra, K. Rabindran, and W. A. Rohde, *J. Amer. Chem. Soc.*, **81**, 1481 (1959).

(22) Nmr signals of H-6 and H-8 were found at 5.45 br (width at half-height, $w^{1/2}$ = 3) and 4.74 tbr (5.5) ppm. Since in pseudoguaianolides containing oxygen substituents at C-6 and C-8 the signal of hydrogen under lactone oxygen generally appears at higher field than that of hydrogen under ester oxygen, this observation clearly pointed to **11** (devoid of stereochemistry) as the correct structure of brevilin A, particularly since no pseudoguaianolides with a lactone ring oriented toward C-6 have so far been found in *Helenium* and related species.

(23) The mechanism of this rearrangement in the tenulin series is discussed in reference 13a.

TABLE I

SELECTED NMR SIGNALS[a]

Compound	H-2	H-4	H-6	H-8
Flexuosin A	4.16 c	3.81 dbr (4.5)	5.98 d (4)	4.61 td (10.5, 3)
Diacetylflexuosin A	5.0 tbr (9)	4.78 dbr (4)	5.88 d (3.5)	4.68 td (11, 3)
Alternilin	4.9 c	3.78 dbr	4.88 d (3.5)	4.68 tc (11)

[a] Multiplicites are expressed by the usual symbols d doublet, t triplet, br broadened singlet, c complex signal whose center is given. Line separations are given in parentheses.

structure 17, it seemed likely that the immediate precursor of 17 was 16, *i.e.*, mexicanin C.

Hydrolysis of 13b with methanolic potassium carbonate at room temperature furnished again a complex mixture in which the presence of mexicanin C could be demonstrated by thin layer chromatography and spectrophotometrically, although the substance could not be isolated in pure form. However, since compounds of the mexicanin C series appear to possess the more stable configuration at C-11,[24] this observation does not necessarily exclude the possibility that brevilin A possesses the opposite configuration at C-11 although, for the reasons stated above, we conclude tentatively that brevilin A is angeloylmexicanin C (11).

A fourth lactone isolated in very small quantity possessed analytical values and spectroscopic properties consonant with 1b, possibly the result of a reaction between tenulin and ethanol during the isolation process rather than a naturally occurring substance. Efforts to prepare this compound from tenulin and ethanol in the presence of catalytic amounts of acid failed. However, a similar substance is formed on treatment of tenulin with ethylene glycol.[25]

Examination of a single *H. alternifolium* collection from near La Plata, Argentina, furnished no tenulin, linifolin A, or brevilin A, but gave as the sole crystallizable component a small quantity of a new sesquiterpene lactone which we have named alternilin. Alternilin, $C_{17}H_4O_{26}$, mp 193–195°, $[\alpha]^{25}D$ +11.20, exhibited infrared bands (see Experimental Section) which indicated the presence of two hydroxyl groups, an α,β-unsaturated γ-lactone, and an ester function. The empirical formula suggested that the ester function was an acetate, a hypothesis which was verified by the nmr spectrum which had a doublet at 4.88 and a methyl singlet at 1.96 ppm. The spectrum also revealed the presence of an exocyclic methylene group (doublets at 6.15 and 5.55 ppm) conjugated with a lactone (complex triplet at 4.58 ppm), two secondary hydroxyl groups (multiplet at 4.9, broadened doublet at 3.78 ppm), a methyl singlet, and a methyl doublet.

Acetylation of alternilin afforded diacetylflexuosin A (18b) of known gross structure and uncertain configuration.[26] Since flexuosin A is 18c,[26] alternilin must be 18a or 18d. A comparison of the nmr spectra of 18b, 18c, and alternilin (Table I) clearly showed that alternilin had structure 18d. Thus the broadened doublet associated with H-4 exhibits the same chemical shift in the spectra of flexuosin A and alternilin; hence C-4 of alternilin carries a free hydroxyl group as well. However, alternilin displays the sharp doublet associated with H-6 more than 1 ppm upfield from the H-6 doublets of flexuosin A and its diacetate; hence C-6 of alternilin carries a hydroxyl group. Conversely, the H-2 multiplets of alternilin and 18c are found considerably downfield from the H-2 multiplet of flexuosin A; hence C-2 of alternilin carries an acetoxyl group.

(24) Tetrahydrohelenalin is isomerized[6] to dihydromexicanin C on treatment with potassium carbonate.

(25) E. P. Clark, *J. Amer. Chem. Soc.*, **62**, 1254 (1940).

(26) W. Herz, Y. Kishida, and M. W. Lakshmikantham, *Tetrahedron*, **20**, 979 (1964).

Experimental Section[27]

Extraction of *Helenium alternifolium* (Spreng.) Cabrera. A.—Above ground plant material collected by Mr. P. R. Legname near Los Puestos, Department of Leales, Tucuman province, Argentina, on Oct 20, 1965, in the flowering stage was ground, extracted with chloroform, and worked up in the usual manner. This resulted in 66.2 g of gum which was dissolved in benzene and placed on a chromatographic column containing 1.1 kg of silicic acid (Mallinckrodt, 100 mesh). On standing, crystalline material separated from solvent at the top of the column. It was scooped out, recrystallized from benzene, and identified as tenulin, yield 6.4 g, by melting point, mixture melting point, infrared spectrum, and tlc. The remaining material was chromatographed in the usual way, 2-l. fractions being collected. Fractions 1–9 (benzene), 10–19 (benzene–chloroform 4:1), 20–29 (benzene–chloroform, 3:1), 30–39 (benzene–chloroform, 2:1), 40–49 (benzene–chloroform 1:1), 50–59 (benzene–chloroform, 1:2), and 60–69 (benzene–chloroform, 1:2) gave practically nothing or gums which were mixtures of several constituents (tlc). Fractions 70–80 (benzene–chloroform, 1:4) solidified on standing. Recrystallization from ether–hexane furnished 2.51 g of brevilin A: λ_{max} 223 and 320 mμ (ϵ 15,000); ir bands at 1775 (γ-lactone), 1710 (cyclopentenone and conjugated ester carbonyl), 1650 (double bond of side chain), and 1585 cm^{-1} (double bond of cyclopentenone); nmr signals at 7.75 dd (6, 1.5, H-2), 6.00 dd (6, 2.5, H-3), 6 c (vinyl proton of side chain), 5.45 br ($w^{1/2}$ = 3, H-6), 4.74 tbr (5.5, H-8), 1.86 dq and 1.70 m (vinyl methyls of side chain), 1.50 d (6.5, C-11 methyl), 1.20 d (6.5, C-10 methyl), and 1.01 ppm (C-5 methyl); $[\alpha]D$ −264° (c 1.00); ORD curve ϕ_{400} −1380°, ϕ_{352} −7260°, ϕ_{328} 0, ϕ_{298} −6050°, ϕ_{272} 0, ϕ_{250} −11,600° (last reading). The melting point was variable in the range 116–127°, the last being that of the analytical sample, but all samples had infrared spectra superimposable on and tlc behavior identical with that of the sample of brevilin A, mp 116–117°, previously isolated from *H. brevifolium* (Nutt.) A. Wood.

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57; O, 23.09. Found: C, 69.28; H, 7.24; O, 23.14.

Fractions 81–84 (chloroform) remained gummy, but fractions 85–87 solidified on standing. Recrystallization from methanol–water and then from acetone–isopropyl ether furnished 0.4 g of linifolin A: melting point and mixture melting point with authentic material[10] and with acetylmexicanin I[28] 201–203°; infrared spectra superimposable; nmr signals at 7.54 dd (6' 2, H-2), 6.01 dd (6, 3, H-3), 6.17 d (3) and 5.60 d (3.5, exocyclic methylene group), 5.84 d (4.5, H-6), 4.75 d (10, 3, H-8), 3.4 c (H-7), 2.02 (acetate methyl), 1.25 d (7, C-10 methyl), and 1.21 ppm (C-5 methyl). Fractions 88–91 (chloroform), 92–99 (chloroform–methanol, 99:1), 100–108 (chloroform–ether, 19:1), and 109–128 (chloroform containing increasing quantities of methanol) were mixtures (tlc). The mother liquors of fractions 85–87 were combined with fractions 88–94 and rechromato-

(27) Melting points are uncorrected. Analyses were by Dr. F. Pascher, Bonn, Germany. Ultraviolet spectra were run in 95% ethanol, infrared spectra in chloroform, rotations in chloroform, and nmr spectra in deuteriochloroform unless otherwise specified. Petroleum ether was the fraction boiling at 30–60°. ORD curves were run by Mr. Babu Rao in 95% ethanol on a JASCO Model ORD-UV 5 spectropolarimeter.

(28) We wish to thank Dr. A. Romo de Vivar for supplying an authentic sample of this compound.

graphed over silicic acid. Benzene–chloroform eluted solid material. Three recrystallizations from ethyl acetate–hexane gave 0.2 g of 6,3′-dimethoxy-5,7,4′,trihydroxyflavone: mp and mmp[29] 225–227° (lit.[12] mp 227–228°); nmr signals (DMSO-d_6) at 13.45 (5-OH), 10.33 very diffuse (7-OH and 4′-OH), 7.70 dd (9, 2) and 7.08 d (9, AB system of H-4′ and H-5′), 7.70 d (2, H-2′), 7.02 (H-8), 6.75 (H-3), 3.98, and 3.87 ppm (two methoxyls). Methylation of 40 mg of the flavone with methyl iodide and potassium carbonate in acetone followed by recrystallization from ethyl acetate–hexane furnished 28 mg of 5,6,7,3′,4′-pentamethoxyflavone, mp 169–171° (lit.[30] melting points variously reported in the range 169–179°). Comparison with an authentic specimen kindly supplied by Professor T. A. Geissman established identity.

Fractions 97–103 which contained the same constituents (tlc) were combined and rechromatographed. This resulted in the isolation of additional quantities of the above flavone and more tenulin.

B.—A second collection of *H. alternifolium* (2.7 kg) by Mr. Legname at Los Puestos on Dec 10, 1966, on extraction with chloroform and work-up in the usual manner yielded 52 g of gum which was chromatographed over 1.2 kg of silicic acid, 1-l. fractions being collected. Fractions 1–9 (benzene), 10–18 (benzene–chloroform, 4:1) and 19–25 (benzene–chloroform, 3:2) eluted practically nothing. Fractions 26–29 (benzene–chloroform, 3:2) eluted a gum which solidified on standing. Rechromatography over 120 g of silicic acid (eluents benzene–chloroform, 3:2 and 1:1) and crystallization from ether–petroleum ether afforded 2.4 g of brevilin A, mp 125–127°. Fractions 30–38 (benzene–chloroform, 3:2) eluted gums which partially solidified on standing; tlc showed this to be a mixture of two main components contaminated with several other lower R_f impurities. Rechromatography over 48 g of silicic acid followed by crystallization from acetone–isopropyl ether of the solid fractions eluted with chloroform yielded 0.65 g of linifolin A, mp and mmp 201–203°.

Fractions 39–49 (benzene–chloroform, 1:1) eluted a yellow solid. Three recrystallizations from ethyl acetate–hexane gave 0.18 g of 6,3′-dimethoxy-5,7,4′-trihydroxyflavone, mp and mmp 225–227°.

Fractions 50–58 (benzene–chloroform, 1:1) eluted semisolid material. Repeated rechromatography over three 60-g portions silicic acid gave in the benzene–chloroform (1:1) fractions 2.48 g of tenulin and 0.12 g of a new lactone: mp 185–187°; $[\alpha]^{25}D$ +22.2 (*c* 1.0); λ_{max} 228 mμ (ε 7420); infrared bands at 1775 (γ-lactone), 1709, and 1582 cm^{-1} (cyclopentenone) (the spectrum differing from that of tenulin chiefly in the absence of an –OH stretching frequency and in the fingerprint region near 1150 and 780 cm^{-1}); nmr signals at 7.70 dd (6, 2, H-2), 6.20 dd (d, 2.5, H-3), 5.24 tc (11, H-8), 4.54 d (6, H-6), 3.72 m (AB part of ABX_3 multiplet, CH_3CH_2O), 1.51, 1.30, 1.30 (C-5 methyl, C-11 methyl, and acetal methyl), 1.28 br (CH_3CH_2O), and 1.12 d (7, C-10 methyl).

Anal. Calcd for $C_{19}H_{26}O_6$: C, 68.24; H, 7.84; O, 23.92. Found: C, 68.60; H, 7.80; O, 23.64.

Fractions 59–80 (benzene–chloroform, 1:1) and 81–95 (benzene–chloroform, 2:3) were almost pure tenulin, yield 7.5 g. Fractions 96–108 (benzene–chloroform, 1:4) and 109–118 (chloroform) eluted additional quantities of impure tenulin. Further elution with ethereal and methanolic chloroform eluted polar gums which showed several spots on tlc.

C.—A collection of 0.5 kg of *H. alternifolium* collected by Dr. A. L. Cabrera in the vicinity of La Plata, Buenos Aires Province, Argentina, during the 1964–1965 growing season, was extracted and worked up in the usual way. The crude gum (25 g) was dissolved in benzene and chromatographed over 0.5 kg of silicic acid. Fractions 1–25 (400-ml portions of benzene and benzene–chloroform, 4:1) gave waxy material; fractions 26–45 (500- and 600-ml portions of benzene–chloroform, 3:1 and 2:1), fractions 46–54 (1-l. portions of benzene–chloroform, 1:1), 55–64 (1-l. portions of benzene–chloroform, 1:2), 65–74 (benzene–chloroform, 3:1), 75–84 (benzene–chloroform, 4:1), and 85–94 (benzene–chloroform, 4:1) gave small amounts of gummy mixtures (tlc) which did not yield homogeneous material when fractions containing identical spots were combined and rechromatographed. Fraction 95–105 (chloroform–methanol, 99:1) and 106–111 (chloroform–methanol, 19:1) furnished larger amounts of gum. Fraction 108 crystallized on standing. Recrystallization from chloroform afforded alternilin: mp 193–195°; $[\alpha]^{25}D$ +11.2 (*c* 1.02); infrared bands at 36,000 (sharp, double strength, two –OH), 1770 (γ-lactone), 1740 (acetate), and 1660 cm^{-1} (conjugated double bond); nmr signals (deuterioacetone and D_2O) at 6.15 d (3.5) and 5.55 d (3.5, exocyclic methylene group), 4.9 m (H-2), 4.88 d (3.5, H-6), 4.58 tc (11, H-8), 3.78 dbr (4, H-4), 3.07 c (H-7), 1.96 (acetate methyl), 1.00 d (6, C-10 methyl), and 0.90 ppm (C-5 methyl).

Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46; O, 29.59. Found: C, 62.95; H, 758; O, 29.73.

Rechromatography of fractions 107–111 which also contained alternilin (tlc) afforded in the benzene–chloroform (1:1) eluate additional quantities of alternilin, total yield 0.65 g. No other sesquiterpene lactones could be identified.

Acetylation of 0.1 g of alternilin with pyridine–acetic anhydride and work-up in the usual manner furnished a viscous gum which gradually crystallized when allowed to stand with a small amount of chloroform. Recrystallization gave diacetylflexuosin, A, mp 128–130°, identical with authentic material. The nmr spectrum exhibited signals at 6.24 d (3.5) and 5.40 d (3.5, exocyclic methylene group), 5.88 d (3.5, H-6), 5.0 tbr (9, H-2), 4.78 dbr (4, H-4), 4.58 tc (11, H-8), 3.18 c (H-7), 2.5 c (H-2), 2.13, 2.03, 2.01 (three acetate methyls), 1.07 d (6, C-10 methyl), and 0.88 ppm (C-5 methyl). The assignments were confirmed by spin decoupling experiments carried out by J. J. Schmid. Irradiation at 3.07 ppm collapsed the doublets at 6.24, 5.88, and 5.40 to singlets and affected the multiplet at 4.58. Irradiation at 4.58 ppm simplified the 3.07 multiplet to a broad triplet (J = 4). Irradiation at 4.87 and 4.50 ppm affected a complex signal near 2.5; conversely irradiation at 2.5 ppm simplified the signals at 5.0 and at 4.78 ppm.

Linifolin A. A. Preparation from Mexicanin I.—Acetylation of mexicanin I[31] from *H. mexicanum* H. B. K. or *H. autumnale* L.[20] Torr. in the usual way gave material of mp 201–203 and 202–204° indistinguishable from linifolin A.

B. Hydrogenation to Tetrahydrolinifolin A (11-Epidihydroisotenulin).—The hydrogenation of linifolin A was repeated under the conditions reported by Herz[10] and by Dominguez and Romo.[18] In both instances the product had mp 152–150° and was identical with the substance of mp 149–150° previously obtained:[10] infrared spectra superimposable; tlc behavior identical; $[\alpha]^{25}D$ +17.4° (*c* 1.01); nmr signals at 5.78 d (2.5, H-6), 4.73 m (H-8), 2.08 (acetate), 1.19 and 1.09 d (7, C-10 and C-11 methyls), and 0.88 ppm (C-5 methyl).

Reactions of Brevilin A. A. Catalytic Hydrogenation.—A solution of 0.2 g of brevilin A in ethanol was reduced with palladium–charcoal catalyst at a hydrogen pressure of 15 lb/in.^{2} Removal of ethanol *in vacuo* resulted in a gum which could not be induced to crystallize but was identified as tetrahydrobrevilin A (12) through its nmr spectrum which had signals at 5.25 br ($w^{1/2}$ = 3, H-6), 5.70 tbr (6, H-8), 1.42 d (6.5), 1.05 d (6.5), 1.04 d (6.5, three methyl doublets), and 0.80 ppm (C-5 methyl). The methyl triplet of the side chain was submerged in the methyl and methylene envelope. The substance had infrared bands (neat) at 177° and 1740 cm^{-1}, but exhibited no bands characteristic of double bonds.

B. Attempted Hydrolysis.—A solution of 0.2 g of brevilin A was refluxed for 1 hr with a methanol–water solution containing 0.2 g of potassium carbonate, cooled, salted out with sodium chloride, and extracted with ether. The ether extract was extracted with base, but only a trace of acid appeared to have been formed. The neutral fraction could not be induced to crystallize. Its nmr spectrum indicated that hydrolysis had not taken place, but that the starting material had been epimerized, presumably at C-11. Signals appeared at 7.60 dd (6, 2) and 6.07 dd (6, 3, exocyclic methylene group), 6 c (vinyl proton of side chain), 5.38 br, 4.87 c (H-8), 3 c (H-7), 1.87 dq, and 1.70 m (vinyl methyls of side chain), 1.48 d (6.5) and 1.30 d (6.5, C-11, and C-10 methyls), and 1.25 ppm (C-5 methyl).

In a modification of the above experiment, a solution of 0.15 g of brevilin A in methanol was mixed with water containing

(29) We wish to thank Professor W. B. Whalley for supplying an authentic sample.

(30) J. Gripenberg in "The Chemistry of Flavonoid Compounds," T. A. Geissman, Ed., The Macmillan Co., New York, N. Y., 1962, p 426; N. Morita, *Chem. Pharm. Bull.* (Tokyo), **8**, 59, 66 (1960); L. J. Swift, *J. Food Sci.*, **29**, 766 (1964).

(31) We wish to thank Dr. A. Romo de Vivar for supplying an authentic sample.

0.15 g of sodium bicarbonate in such a way that both substances remained in solution and was allowed to stand overnight.

This resulted in the formation of large needles of 2-methoxy-2,3-dihydrobrevilin A (**13a**) which were filtered and recrystallized from methanol–water. The product (0.08 g) had mp 203–205°; infrared bands at 1780 (γ-lactone), 1750 (cyclopentanone), 1720, and 1645 cm^{-1} (conjugated ester); nmr signals at 6.00 qbr (vinyl proton of side chain), 5.35 br ($w^{1/2}$ = 3, H-6), 4.69 tbr (6, H-8), 3.90 tbr (4, H-2), 3.20 (methoxy), 1.90 dg and 1.72 m (vinyl methyls of side chain), 1.50 d (6.5, C-11 methyl), 1.12 d (6.5, C-10 methyl), and 1.05 ppm (C-5 methyl); ORD curve ϕ_{400} 258°, ϕ_{318} 3620°, ϕ_{310} 3290 (shoulder), ϕ_{296} 0, ϕ_{278} −3100, ϕ_{250} −2010 (last reading). More material could be obtained from the mother liquor.

Anal. Calcd for $C_{21}H_{30}O_8$: C, 66.65; H, 7.99; O, 25.36. Found: C, 66.49; H, 7.69; O, 26.08.

Ozonolysis of 13a.—A solution of 0.15 g of the preceding compound in ethyl acetate was ozonized at −45° for 30 min. The reaction mixture was steam distilled into a solution of dinitrophenylhydrazine. This resulted in the precipitation of acetaldehyde 2,4-dinitrophenylhydrazone, mp and mmp 146–147°. The flask residue was extracted with ether. The ether extract was dried and evaporated and the residual gum was recrystallized from ether–hexane and ether. The product (**13b**) was formed in 60% yield and melted at 172–174°, $[\alpha]^{25}D$ 22°. It had infrared bands at 1780 (γ-lactone), 1750 (ester), and 1740 cm^{-1} (α-ketone); nmr signals at 5.30 br ($w^{1/2}$ = 3, H-6), 4.68 tbr (6, H-8), 3.90 rbr (4, H-2), 3.20 (methoxyl), 2.33 (methyl ketone), 1.40 d (7, C-11 methyl), 1.10 d (7, C-10 methyl), and 1.03 ppm (C-5 methyl).

Anal. Calcd for $C_{19}H_{28}O_7$: C, 62-28; H, 7.15, O, 30.57. Found: C, 61.90; H, 7.34; O, 30.58.

Hydrolysis of 13b. A.—A solution of 0.3 g of the preceding compound in methanol–water containing 0.3 g of potassium carbonate was allowed to stand overnight and then acidified with dilute hydrochloric acid, diluted with water, and extracted with chloroform. The extract was dried and evaporated *in vacuo*. The residue could not be induced to crystallize. Its nmr spectrum (DMSO-d_6) showed the presence of a mixture and indicated that elimination of the methoxyl group to regenerate a cyclopentenone function had taken place. This was also evident from the infrared spectrum which exhibited bands at 3580 and 3400 (bonded and nonbonded hydroxyl), 1760 (γ-lactone), 1700, and 1585 cm^{-1} (cyclopentenone) and, in the finger print region, all bands characteristic of mexicanin C (as well as others). An extra absorption at 1630 cm^{-1} was provisionally ascribed to the presence of the $\Delta^{1,2}$ isomer.

Direct comparison with the nmr spectra of mexicanin C[32] and dihydrohelenalin[33] in DMSO-d_6 demonstrated that all signals characteristic of mexicanin C were present, that dihydrohelenalin was absent, and that another α,β-unsaturated cyclopentenone, possibly the C-1 epimer of mexicanin C, was a second contaminant. Thin layer chromatography in three solvent systems confirmed the presence of mexicanin C and of two other substances. However, attempts to isolate pure mexicanin C by preparative thin layer chromatography of the mixture were not successful.

In a second experiment, 0.108 g of **13b**, 0.12 g of potassium carbonate, 5 ml of methanol, and 1.6 ml of water were stirred at room temperature for the somewhat longer period of 24 hr. The usual work-up yielded a gummy residue which showed at least four spots on tlc. Preparative tlc resolved the mixture into two main bands. The lower R_f band showed two major spots which on being recrystallized from acetone–isopropyl ether gave 2 mg of **17** (*vide infra*). The higher R_f band showed two major spots whose R_f values corresponded to those of mexicanin C and dihydrohelenalin.

B.—A mixture of 0.12 g of **13b**, 0.12 g of potassium carbonate, 2 ml of water, and 6 ml of methanol was refluxed on the steam bath for 1 hr. The solvents were evaporated *in vacuo*, the residual gum was mixed with ice water, acidified with concentrated hydrochloric acid and extracted thoroughly with chloroform. The combined extracts were washed, dried, and evaporated and the residual gum was recrystallized from acetone–isopropyl ether. There was obtained 15 mg of **17** in the form of colorless needles which sintered near 270° and melted at 282–285° with decomposition. The substance had infrared bands (Nujol) at 3380, 1770 (γ-lactone), 1680, and 1625 cm^{-1} (cyclopentenone); λ_{max} 238 and 302 mμ (ϵ_{max} 15,700 and 110); nmr signals at 5.0 m (H-8), 3.9 m (H-6), 1.65 d (J = 2, a vinyl methyl), and 1.18 d ppm (7, six protons, C-10 and C-11 methyl). It differed from dihydroneohelenalin in ir and nmr spectrum. The mixture melting point with dihydroneohelenalin was depressed.

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; O, 24.21. Found C, 67.76; 7.71; O, 24.26.

Examination of the mother liquors by tlc revealed a spot which corresponded to mexicanin C but no dihydrohelenalin.

Registry No.—Brevilin A, 16503-32-5; linifolin A, 5988-99-8; alternilin, 16434-63-2; **12**, 16434-64-3; **13a**, 16434-65-4; **13b**, 16434-66-5; **17**, 16452-39-4.

Acknowledgment.—We wish to thank Mr. P. R. Legname, Dr. A. L. Cabrera, and Dr. B. H. Braun for supplying us with plant material, Drs. P. Seeligman and V. Deulofeu for arranging the South American collections, and the Research Council of the Florida State University for a grant to help defray the cost of plant procurement.

(32) We wish to thank Dr. A. Romo de Vivar for an authentic sample of this compound.

(33) The nmr spectrum of this compound has not been recorded previously. It exhibited signals at 7.74 dd (6, 1.4, H-2), 5.96 dd (6, 3, H-3), 5.13 d (5, -OH), 4.8 tbr (6, H-8), 4.08 c ($w^{1/2}$ = 3, H-6), 1.18 d (5, C-10 and C-11 methyl), and 0.78 ppm (C-5 methyl).

The Alkaloids of *Stephania glabra*. A Direct Chemical Correlation of the Absolute Configuration of Some Benzyltetrahydroisoquinoline, Proaporphine, and Aporphine Alkaloids. A New Protoberberine Alkaloid

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Received January 10, 1968

Separation of the alkaloid bases of *Stephania glabra* yielded the proaporphines (+)-stepharine and (+)-pronuciferine, as well as the protoberberines (−)-tetrahydropalmatine, (−)-corydalmine, and (−)-stepholidine. Evidence is presented to support the structures assigned to the new alkaloids stepharine and stepholidine. The cleavage of proaporphines to benzyltetrahydroisoquinolines by sodium in ammonia is reported. The use of this cleavage reaction, considered together with the conversion of proaporphines into aporphines, makes possible a chemical correlation of the absolute configuration of several alkaloids of the benzyltetrahydroisoquinoilne, proaporphine, and aporphine groups.

In an earlier paper, we gave a preliminary account of the isolation of the dienone alkaloids stepharine (I) and pronuciferine (II) from *Stephania glabra*, as well as a simple chemical correlation of the absolute configuration of these compounds with that of related aporphines and benzyltetrahydroisoquinolines.[2] In this paper we will give additional details of this investigation, including the isolation and characterization of stepholidine (XII), a new protoberberine alkaloid.

Stephania glabra (Miers) is a large, climbing shrub belonging to the family Menispermaceae. The large tubers of this plant have been used in India for the treatment of a variety of disorders, including asthma, tuberculosis, dysentery, and fevers.[3]

The first report on the alkaloids of *S. glabra* tubers described the isolation of three alkaloids named gindarine, gindarinine, and gindaricine.[4] Subsequently, gindarine and gindarinine were shown to be identical with tetrahydropalmatine and palmatine, respectively; gindaricine was not further identified.[5,6] The work described in this paper concerns a reinvestigation of the tertiary bases of *S. glabra*;[7] a study of the quaternary alkaloids is reported elsewhere.[8,9]

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(2) M. P. Cava, K. Nomura, R. H. Schlessinger, K. T. Buck, B. Douglas, R. F. Raffauf, and J. A. Weisbach, *Chem. Ind.* (London), 282 (1964).

(3) R. N. Chopra, I. C. Chopra, K. L. Handa, and L. D. Kapur, "Chopra's Indigenous Drugs of India," 2nd ed, U. N. Chur and Sons, Ltd., Calcutta, 1958, p. 412.

(4) G. R. Chaudbry and S. Siddiqui, *J. Sci. Ind. Res.*, (India), **98**, 79 (1950).

(5) G. R. Chaudry, V. N. Sharma, and M. L. Dhar, *ibid.*, **118**, 337 (1952).

(6) The analytical values reported for gindaricine[4] suggest that it is quite possibly identical with stepharine; on the other hand, the melting point reported for gindaricine (193°) is more than 10° higher than our melting point of stepharine. It should be noted also that the rotation of gindarine (tetrahydropalmatine) is given as −261° in the discussion section of ref 4 but as +261° in the Experimental Section.

(7) Since the publication of our preliminary communication,[2] several reports have appeared concerning the alkaloids of *S. glabra*, mainly material of Caucasian origin: I. I. Shchelchokova, T. N. Il'inskaya, and A. D. Kuzovkov, *Khim. Prirodn. Soedin., Akad. Nauk SSSR, Inst. Khim. Privodn. Soedin.*, 271 (1965); K.-C. Fang, I. I. Fadeeva, and T. N. Il'inskaya, *ibid.*, 392 (1965); I. M. Rabinvich, P. N. Kibal'chick, I. I. Fadeeva, T. N. Il'inskaya, A. D. Kuzovkov, V. V. Bereshinskaya, E. A. Trutneva, and S. S. Nikitina, *Aptech. Delo*, **14**, 19 (1965). The total alkaloids reported in these papers are (−)-tetrahydropalmatine, (+)-stepharine, cycleanine, and four unidentified bases. Interestingly, (+)-stepharine was found only in Indian *S. glabra*; no product corresponding to stepholidine was encountered. In addition, (+)-stepharine has recently been isolated from *S. rotunda* [M. Tomita, M. Kozuka, and S. Uyeo, *Yakugaku Zasshi*, **86**, 460 (1966)] and *Pericampylus formosanus* [M. Tomita, M. Kozuka, and S.-T. Lu, *ibid.*, **87**, 315 (1967)].

(8) M. T. Wa, J. L. Beal, and R. W. Doskotch, *Lloydia*, in press.

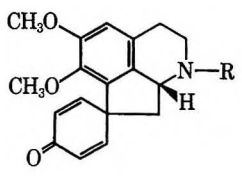
(9) R. W. Doskotch, M. Y. Malik, and J. L. Beal, *J. Org. Chem.*, **32**, 3253 (1967).

The Proaporphine Bases.—One of the major alkaloids of *S. glabra* was a previously unreported,[6] nonphenolic base $C_{18}H_{19}NO_3$, mp 179–180°, which we have named stepharine (I). Stepharine is dextrorotatory, $[\alpha]D$ +143°, and contains two methoxyl groups as shown by direct analysis. Stepharine was shown to be a secondary amine containing an NH grouping, since it was readily converted by acetic anhydride into N-acetylstepharine (III), mp 235–236°. The infrared spectrum of III, compared to that of I, showed increased absorption in the 6- to 6.2-μ region, compatible only with an amide formulation for III. Similarly, the NH group of stepharine could be methylated by formaldehyde and formic acid to give N-methylstepharine (II): mp 128–129°; $[\alpha]D$ +87°. N-methylstepharine obtained in this way was identical with a second, hitherto unreported base present in the naturally occurring alkaloid mixture from *S. glabra*. The nature of the third oxygen atom of stepharine was revealed in the course of an attempted methylation of I by formaldehyde in the presence of hydrogen and palladium. The reaction product was not N-methylstepharine, but rather N-methyltetrahydrostepharine (X). The infrared spectrum of X (but not of II) showed the presence of a strong *unconjugated* carbonyl group (5.84 μ); on the other hand, the infrared spectra of I and II (but not the spectrum of X) showed strong absorption in the 6–6.2-μ region, which could now be assigned to a highly conjugated carbonyl group. At this stage, it seemed likely that we had encountered two examples of the unknown proaporphines,[10] a new alkaloidal class originally predicted by Barton and Cohen[11] as intermediates in the biosynthetic, oxidative transformation of benzylisoquinolines to aporphines. Our supposition was confirmed when stepharine underwent smoothly the dienone–phenol rearrangement on heating with aqueous hydrochloric acid to give the known aporphine alkaloid (−)-tuduranine (VII). It is of interest to note that none of the isomeric rearrangement product VIII could be detected. Finally, excellent additional support for the proaporphine structure was found in the sodium and liquid ammonia cleavage of N-acetylstepharine (III)

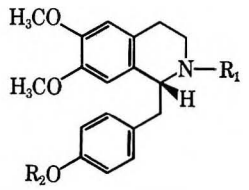
(10) The generic name proaporphine was independently proposed both by us[2] and by M. Shamma and W. A. Slusarchyk [*Chem. Rev.*, **64**, 59 (1964)]. The name appears to have received general acceptance by other workers in the field.

(11) D. H. R. Barton and T. Cohen, "Festschrift Arthur Stoll," Birkhauser A. G., Basel, 1957, p 117.

and N-methylstepharine (II) which gave (−)-N-acetylnorarmepavine (IV)[12] and (−)-armepavine (VI), respectively. At this time, Bernauer described the isolation and complete structure of pronuciferine (II), the first identified proaporphine alkaloid;[13] the same alkaloid, together with a closely related base, was reported simultaneously from a different plant source.[14] Since it was quickly determined by direct comparison that pronuciferine and N-methylstepharine (II) were identical, no further structural studies with the proaporphines I and II were carried out in our laboratories.[15]

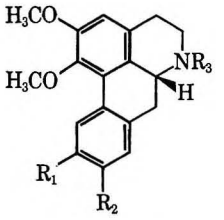


I, R = H
II, R = CH_3
III, R = $COCH_3$

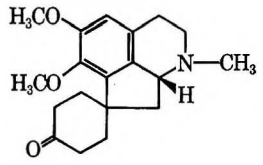


IV, R_1 = $COCH_3$; R_2 = H
V, R_1 = $COCH_3$; R_2 = CH_3
VI, R_1 = CH_3; R_2 = H

Other workers have determined the absolute configuration of armepavine.[16] We have found that the reductive cleavage product of pronuciferine (II) is (−)-armepavine, which has the D (or *R*) configuration at C-1, as indicated in structure VI. It follows, therefore, that both pronuciferine (II) and stepharine (I) must also have the D (or *R*) configuration at the corresponding asymmetric carbon atom. Furthermore, since we found that stepharine is rearranged by acid to (−)-tuduranine (VII),[17] and Bernauer reported that borohydride reduction of pronuciferine (N-methylstepharine) followed by acid treatment yields (−)-nuciferine (IX), it follows that both of the aporphine alkaloids (−)-tuduranine and (−)-nuciferine must belong stereochemically to the D (or *R*) series, as shown in structures VII and IX. The demonstration of the



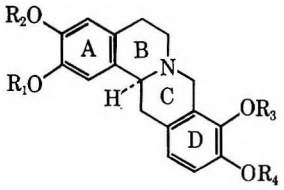
VII, R_1 = OH; R_2 = H; R_3 = H
VIII, R_1 = H; R_2 = OH; R_3 = H
IX, R_1 = R_2 = H; R_3 = CH_3

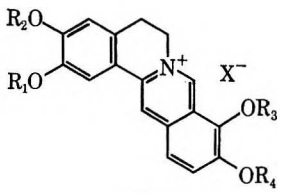


X

stereochemistry of nuciferine (IX) is particularly significant, since it has not been possible previously to prove chemically the absolute configuration of an aporphine alkaloid which lacks oxygen-containing functional groups on the benzyl-derived aromatic ring.[18,19]

The Protoberberine Bases.—As has been reported,[4-6] (−)-tetrahydropalmatine (XI) was present in a large quantity in *S. glabra* tubers. In addition, two phenolic bases were isolated, both of which yielded (−)-tetrahydropalmatine on treatment with diazomethane. The first phenolic base, mp 174–175°, had the composition $C_{20}H_{23}O_4N$, $[\alpha]D$ −310°. On the basis of its composition and methylation to (−)-tetrahydropalmatine (XI), this alkaloid could be only one of the following four compounds: (−)-corydalmine (XV), (−)-tetrahydrocolumbamine (XVI), (−)-tetrahydrojatrorrhizine (XVII), or (−)-tetrahydropalmatrubine (XVIII). Direct comparison of its solution infrared spectrum with that of synthetic (±)-corydalmine[20] showed that it was (−)-corydalmine (XV). Only the enantiomeric (+)-corydalmine had been isolated previously from natural sources.[21,22]

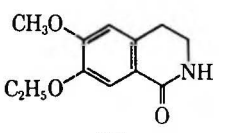




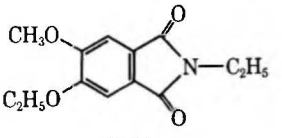
XI, R_1 = R_2 = R_3 = R_4 = CH_3
XII, R_1 = R_4 = H; R_2 = R_3 = CH_3
XIII, R_1 = R_3 = H; R_2 = R_4 = CH_3
XIV, R_1 = R_4 = C_2H_5; R_2 = R_3 = CH_3
XV, R_1 = R_2 = R_3 = CH_3; R_4 = H
XVI, R_1 = H; R_2 = R_3 = R_4 = CH_3
XVII, R_1 = R_3 = R_4 = CH_3; R_2 = H
XVIII, R_1 = R_2 = R_4 = CH_3; R_3 = H

XIX, R_1 = R_4 = H; R_2 = R_3 = CH_3; X = Cl

The second phenolic base was a new alkaloid which we have named stepholidine. Stepholidine crystallizes as a hydrate ($C_{19}H_{21}NO_4 \cdot H_2O$): mp 158–160°; $[\alpha]D$ −311°. Its molecular weight (327) was confirmed by mass spectrometry. The composition of stepholidine and its methylation to give (−)-tetrahydropalmatine (XI) indicate that it has a structure corresponding to XI in which two of the methoxyls are replaced by hydroxyl groups. In order to determine the position of the hydroxyls, stepholidine was treated with excess diazoethane and the resulting O,O-diethylstepholidine (XIV) was oxidized with permanganate. The neutral fraction yielded 6-methoxy-7-ethoxy-1-keto-1,2,3,4-tetrahydroisoquinoline (XX). The isolation of XX served to fix the position of one methoxyl and one ethoxyl group in ring A of diethylstepholidine (XIV). The acidic fraction from the oxidation was converted into a



XX



XXI

(12) The synthesis of IV is included in the Experimental Section.

(13) K. Bernauer, *Helv. Chim. Acta*, **46**, 1783 (1963).

(14) L. J. Haynes, K. L. Stuart, D. H. R. Barton, and G. W. Kirby, *Proc. Chem. Soc.* (London), 280 (1963); see also footnote 5a in ref 13.

(15) Since 1963, seven proaporphines and eight reduced proaporphines have been isolated in the course of various phytochemical investigations. Some of this work has been summarized briefly in a recent review on the aporphine alkaloids: M. Shamma, in "The Alkaloids," Vol. IX, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1967, p 1. A more complete review of the proaporphine alkaloids will appear shortly: K. L. Stuart and M. P. Cava, *Chem. Rev.*, in preparation.

(16) M. Tomita and J. Kunitomo, *Yakugaku Zasshi*, **82**, 734 (1962).

(17) An independent report of the acid-catalyzed rearrangement of I to VII appeared recently: M. Tomita and M. Kozuka, *ibid.*, **86**, 871 (1966).

(18) The structure of a new type of dienone alkaloid, androcymbine, was determined making use of our general dienone cleavage method: A. R. Battersby, R. B. Herbert, L. Pijewska, and F. Santavy, *Chem. Commun.*, 228 (1965). The cleavage of a different type of dienone base, (+)-O-methylsalutaridine, to (−)-laudanosine, has also been reported very recently by this method: D. H. R. Barton, D. S. Bhakuni, R. James, and G. W. Kirby, *J. Chem. Soc., Sect. C*, 128 (1967).

(19) The absolute configuration of a number of aporphines have been deduced on the basis of optical rotatory data: C. Djerassi, K. Mislow, and M. Shamma, *Experientia*, **18**, 53 (1962); M. Shamma, *ibid.*, **18**, 64 (1962).

(20) S. A. Telang and C. K. Bradsher, *J. Org. Chem.*, **30**, 752 (1965).

(21) I. Imaseki and H. Taguchi, *Yakugaku Zasshi*, **82**, 1214 (1962).

(22) The melting point of our (−)-corydalmine is 174–175°, in reasonable accord with the recorded value[20] of 187.5–188.5° for synthetic (±)-corydalmine. On the other hand, natural (+)-corydalmine and (±)-corydalmine derived from it are said to melt at 238–239° and 213–215°, respectively.[21] We are unable to offer an explanation for these discrepancies.

mixture of ethylimides from which only 4-ethoxy-5-methoxy-N-ethylphthalimide (XXI), also derived from ring A of XIV, was isolated.

On the basis of the above results, stepholidine could have only structure XII or structure XIII. Since XIII represents the known alkaloid scoulerine, a direct infrared comparison of scoulerine and stepholidine was made; it showed the two bases to be distinctly different. (−)-Stepholidine is thus securely represented by structure XII. Finally, stepholidine was dehydrogenated with iodine to the corresponding dehydro derivative, isolated as the yellow chloride (XIX), mp 270–273°. This compound was identical with stepharanine chloride, a minor constituent of the quaternary alkaloid mixture of *S. glabra*,[8] the structure of which was determined in quite an independent manner.[9]

Experimental Section[23]

Preliminary Fractionation of the Alkaloids.—Commercial (Indian) *Stephania glabra* root tubers (25 kg) were ground well and extracted exhaustively with ethanol, and the concentrated ethanol extract was digested with 0.2 *M* aqueous phosphoric acid. The pH of the aqueous acid extract was increased in three stages (pH 2, 7, and 10) by addition of alkali. At each stage the alkaloids were extracted with ether and any insoluble material was then removed by filtration. Each of the six fractions thus obtained (F_a–F_f) was put individually through the entire separation procedure in an attempted further separation. The final fractions obtained are described in Table I.

TABLE I

Stephania glabra FRACTIONS

Fraction	Wt, g	Description
F_a	43.5	Ether extractable at pH 2
F_b	12.0	Ether insoluble at pH 2
F_c	117.5	Ether extractable at pH 7
F_d	234.0	Ether insoluble at pH 7
F_e	14.0	Ether extractable at pH 10
F_f	100.0	Chloroform extractable at pH 10
Total	421.0	

Unfortunately, tlc patterns indicated that each of the above fractions was still a complex mixture with considerably carryover from one fraction to the next. Since all of the compounds isolated in this investigation were found in the major fractions (F_c and F_d), further details of isolation are recorded only for these fractions.

In addition to the weights recorded in Table I, crude crystalline (−)-tetrahydropalmatine (28.5 g) was isolated during the processing of fraction F_c, and crude crystalline stepharine (59.6 g) was isolated during the processing of fraction F_c.

Examination of Fraction F_c. A. Isolation of (−)-Tetrahydropalmatine (XI).—A solution of fraction F_c (94 g) in chloroform was extracted with dilute aqueous sodium hydroxide solution to remove phenolic constituents; the remaining solution of nonphenolic base in chloroform was extracted with 5% hydrochloric acid to remove stepharine (see below). The chloroform solution was evaporated to dryness *in vacuo* to give, after crystallization, 31 g of (−)-tetrahydropalmatine hydrochloride, mp 201–203°, identical with an authentic sample. The free base (XI) was crystallized from methanol: mp 140.5–142°; $[\alpha]^{25}D$ −299° (*c* 1.0, ethanol) (lit.[24] 142°, $[\alpha]D$ −292°).

B. Isolation of Stepharine (I).—The hydrochloric acid extract (section A, above) was made basic with ammonia and was extracted with chloroform. The chloroform layer was extracted in turn with McIlvaine buffer solutions of pH 5.2, 3.0, and 2.0, in that order. Each of the buffer extracts was worked up in the usual way with ammonia and chloroform.

The extract of pH 5.2 yielded 14.7 g of crude material which was recrystallized from acetone to give stepharine, colorless crystals: mp 179–180° dec; $[\alpha]^{27}D$ +144° (*c* 1.88, chloroform); λ_{max}^{KBr} 3.10 μ (NH), 3.28, 3.44, and 3.58 (CH), and 6.01 and 6.17 (cross-conjugated dienone). Stepharine is sensitive to air and light, even in the solid state, and gradually turns brown on standing. The analytical sample was recrystallized from 2-butanone.

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71; CH_3O, 27.49. Found: C, 72.84; H, 6.56; N, 4.69; CH_3O, 27.49.

C. Isolation of Pronuciferine (II).—The extract of pH 3.0 (section B, above) gave crude material, which was purified by chromatography on grade II neutral alumina (eluents, benzene and chloroform) and recrystallized from ether to give approximately 5 g of pure pronuciferine: mp 127–129° dec; $[\alpha]^{25}D$ +86.4° (*c* 1.94, chloroform) [lit.[25] mp 127–129°; $[\alpha]^{25}D$ +99.0 ± 1.0° (*c* 0.205 chloroform)]. This material was identical with an authentic specimen of pronuciferine.

The extract of pH 2.0 was worked up similarly but failed to give crystalline material.

Transformation Products of Stepharine (I) and Pronuciferine (II). A. Pronuciferine (II).—A mixture of stepharine (2.5 g), formic acid (5.5 ml), and formaldehyde (5.5 ml of a 35% aqueous solution) was heated on a steam bath for 4 hr. The reaction mixture was diluted with water and was washed with ether; it was then made basic with ammonia and was extracted with chloroform. The chloroform extract afforded a residue which was chromatographed with benzene on grade II neutral alumina to give 1.7 g (67%) of pronuciferine [mp 128–129°, $[\alpha]^{25}D$ +87° (*c* 1.71, chloroform)] identical with naturally occurring material (section C, above).

B. (−)-Armepavine (VI).—Small portions of sodium metal and a solution of pronuciferine in toluene were added alternately and with stirring to 500 ml of liquid ammonia at −50°. Addition of each successive portion of sodium was delayed until the color of dissolved sodium from the previous addition had been discharged. In this way, 0.9 g of sodium and 1.0 g of pronuciferine (in 100 ml of toluene) were added to the reaction mixture during 3 hr. The reaction product was worked up in the usual way to give 0.75 g of crude phenolic base, which was recrystallized several times from acetone to yield 0.13 g of pure (−)-armepavine (VI), mp 138–139°. Crystallization of a mixture of equal parts of (−)- and (+)-armepavine gave (±)-armepavine, mp 158–161°, which was identical with an authentic synthetic sample.

C. Tuduranine (VII).—A solution of stepharine (0.250 g) in 6 *N* hydrochloric acid was heated under nitrogen on a steam bath, for 15 hr. The reaction mixture was cooled and filtered to give tuduranine hydrochloride: mp 280° dec; $[\alpha]^{25}D$ −125° (*c* 1.45, aqueous methanol), which was obtained in good yield and was identical with an authentic sample.

Attempts to detect the presence of the other possible product of the reaction, VIII, which is an isomer of tuduranine, were unsuccessful.

D. N-Acetylstepharine (III).—A solution of stepharine (7.3 g) and acetic anhydride (4 ml) in 100 ml of ether was stirred at 0° for 1 hr. The resulting preciptate was collected by filtration and was recrystallized from methanol to give 6.3 g (76%) of N-acetylstepharine as glistening needles: mp 235–236° dec; $[\alpha]^{24}D$ −80° (*c* 1.57, chlorom); λ_{max}^{KBr} 3.42 (CH), 6.04 and 6.07–6.2 μ (cross-conjugated dienone and N-acetyl).

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13; CH_3O, 18.33. Found: C, 70.60; H, 6.34; N, 4.10; CH_3O, 17.92.

E. N-Methyltetrahydrostepharine (X).—A solution of 0.58 g of stepharine and 0.074 g of formaldehyde in methanol was stirred at room temperature for 1.5 hr. (The formaldehyde–methanol solution was prepared by diluting 1 g of a 37% aqueous formaldehyde solution to 10 g with methanol and taking a 2-g aliquot of the dilute solution.) The reaction mixture was then hydrogenated at room temperature under atmospheric pressure in the presence of 200 mg of 10% palladium-on-charcoal catalyst. The usual work-up gave a residue which was subjected to chromatography on neutral grade I alumina with benzene. N-Methyltetrahydrostepharine (X) was obtained as colorless needles: mp 114–115°; λ_{max}^{KBr} 3.43 and 3.6 (CH), 5.84 μ (unconjugated six-membered-ring ketone).

(23) Analyses were performed by Midwest Microlab, Inc., Indianapolis Ind. Melting points are uncorrected.

(24) H. G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, 1961, p 340.

(25) K. Bernauer, *Helv. Chim. Acta.*, **47**, 2119 (1964).

Anal. Calcd for $C_{19}H_{23}NO_5$: C, 72.35; H, 7.99; N, 4.44; CH_3O, 19.68; CH_3N, 4.76. Found: C, 72.35; H, 8.17; N, 4.91; CH_3O, 19.28; CH_3N, 3.50.

Transformation Products of N-Acetylstepharine (III). A. 1-(*p*-Hydroxybenzyl)-6,7-dimethoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline (IV).—N-Acetylstepharine (1.0 g) and sodium metal (0.92 g) were added alternately in small portions to 500 ml of liquid ammonia at −50° during 1.25 hr (see section B). The reaction mixture was treated with ammonium chloride and was worked up in the usual way to give 0.95 g of crude phenolic base. Recrystallization of the latter from methanol gave 0.55 g (55%) of 1-(*p*-hydroxybenzyl)-6,7-dimethoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline (IV), mp 234–235°, $[\alpha]^{25}D$ −90° (*c* 0.485, chloroform), which was identical with authentic material (see below).

B. **1-(*p*-Methoxybenzyl)-6,7-dimethoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline (V).**—A solution of 0.19 g of IV and excess diazomethane–ether azeotrope in methanol was kept at 0° for 1 week. The reaction mixture was worked up in the usual way and the resulting crude nonphenolic base was chromatographed on grade I neutral alumina with benzene to give 1-(*p*-methoxybenzyl)-6,7-dimethoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline (V), mp 111–112° (from cyclohexane–ether).

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94; CH_3O, 26.19. Found: C, 71.16; H, 7.37; N, 3.96; CH_3O, 25.97.

Synthesis of 1-(*p*-Hydroxylbenzyl)-6,7-dimethoxy-2-acetyl-1,-2,3,4-tetrahydroisoquinoline (IV). A. 1-(*p*-Benzyloxybenzyl)-6,7-dimethoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline.—A solution of 1-(*p*-benzyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride[26] (5.0 g) in methanol (50 ml) was treated with sodium borohydride (1.2 g), added in small portions. After 30 min the reaction mixture was poured into water and extracted with ether and the ether extracts were dried over magnesium sulfate and evaporated to an oil [1-(*p*-benzyloxybenzyl)-6,7-dimethyl-1,2,3,4-tetrahydroisoquinoline].

The oil was dissolved in pyridine (10 ml), acetic anhydride (10 ml) was added, and the resulting reaction mixture was warmed on the steam bath for 15 min. After the usual work-up with water, ether, aqueous base, and aqueous acid solutions, 1-(*p*-benzyloxybenzyl)-6,7-dimethoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline was obtained as colorless microcrystals, mp 119–122° (from aqueous methanol), 4.0 g (79%). The analytical sample, mp 136–138°, was obtained by two additional recrystallizations.

Anal. Calcd for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Found: C, 74.84; H, 6.50; N, 3.06.

B. **1-(*p*-Hydroxybenzyl-6,7-dimethoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline.**—A solution of 1-(*p*-benzyloxybenzyl)-6,7-dimethoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline (3.0 g) in 170 ml of methanol was hydrogenated for 16 hr in the presence of 0.78 g of 5% palladium on charcoal under 40-psi initial hydrogen pressure. A colorless oil was obtained which crystallized from ethanol as colorless plates (1.7 g, 72%), mp 215–216°.

Anal. Calcd for $C_{20}H_{23}NO_4$: C, 59.59; H, 5.28; N, 7.72. Found: C, 59.60; H, 5.35; N, 7.66.

Examination of Fraction F_d. A. Isolation of (−)-Corydalmine (XV).—Fraction F_d (210 g) was extracted with chloroform in a Soxhlet apparatus. The chloroform-insoluble material (120 g) was discarded. The chloroform-soluble material (90 g) was separated into a phenolic fraction and a nonphenolic fraction and the latter was worked up with hydrochloric acid to give an additional 80 g of tetrahydropalmatine hydrochloride and small amounts of stepharine and N-methylstepharine.

The phenolic fraction (an aqueous alkaline solution) was adjusted to pH 7 with ammonium chloride and was extracted with chloroform to give a mixture of crude phenolic bases (19.7 g) which was reextracted with 1:2 acetone–chloroform. The material soluble in acetone–chloroform (11.2 g) was chromatographed on grade III neutral alumina with the same solvent mixture to give 0.5 g of (−)-corydalmine (XV): mp 173–174° dec from methanol; $[\alpha]^{30}D$ −310° (*c* 1.385, ethanol); λ_{max}^{EtOH} (neutral) 214 μ (log ε 4.43), 276 (3.78); λ_{max}^{EtOH} (acid) 212 mμ (log ε 4.40), 231 (4.20), 274 (3.82); λ_{max}^{EtOH} (base) 217 mμ (log ε 4.47), 278–284 (3.85). The infrared spectrum of (−)-corydalmine ($\lambda_{max}^{CHCl_3}$ 2.79, 3.31, 3.39, 3.52, 6.21 μ) was identical with that of an authentic sample of synthetic (±)-corydalmine. Treatment of (−)-corydalmine with diazomethane gave (−)-tetrahydropalmatine: mp 141°; $[\alpha]^{28}D$ −271° (*c* 1.63, ethanol).

B. **Isolation of Stepholidine (XI).**—The material not soluble in 1:2 acetone–chloroform (8.5 g) (see section A) yielded a substance crystallizing directly from acetone in fine needles, mp 126–138° (*in vacuo*), which was designated stepholidine: $[\alpha]^{18}D$ −311° (*c* 0.523, ethanol); λ_{max}^{EtOH} (neutral) 214 mμ (log ε 4.40), 287 (3.79); λ_{max}^{EtOH} (base) 219 mμ (log ε 4.46), 243–248 (4.09), 297–298 (3.82) (no ultraviolet absorption shift in acidic medium); λ_{max}^{KBr} 2.80 (OH), 3.08 (OH), 3.44 and 3.60 (CH), 6.18, and 6.28 μ.

The infrared spectrum of stepholidine differs in many respects from that of l-scoulerine, mp 193–195° (lit.[27] mp 195° or 204°).

The analytical sample was prepared by thin layer chromatography on silica gel with 1:3 methanol–chloroform (to remove traces of corydalmine), mp 158–160° dec.

Anal. Calcd for $C_{19}H_{21}NO_4 \cdot H_2O$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.08; H, 6.81; N, 4.06. Calcd for $C_{19}H_{21}NO_4$: mol wt, 327.4. Found: mol wt, 327 (mass spectrum).

Transformation Products of Stepholidine (XII). A. 2,10-Dihydroxy-3,9-dimethoxy-5,6-dihydrobenz[*a*]acridinium Chloride (XIX).—A solution of stepholidine (0.33 g, 1 mmol) and iodine (0.76 g, 3 mmol) in 50 ml of ethanol was refluxed on a steam bath for 1 hr. On treatment with a dilute aqueous solution of sodium bisulfite, the reaction mixture deposited 0.2 g of a yellow precipitate of the dihydrobenz[*a*]acridinium iodide. The precipitate was dissolved in the minimum volume of 1:1 acetone–water and the resulting solution was passed through a column of IRA-410 ion exchange resin (chloride form). The product was recrystallized from 0.1% hydrochloric acid to give 2,10-dihydroxy-3,9-dimethoxy-5,6-dihydrobenz[*a*]acridinium chloride (XIX) as yellow needles, mp 270–273° dec, identical in all respects with a sample of natural stepharanine chloride.[5]

B. **(−)-Tetrahydropalmatine (XI).**—A solution of (−)-stepholidine (XII) and excess diazomethane–ether azeotrope in methanol was kept at 0° for several days to give (−)-tetrahydropalmatine (XI): mp 141°, $[\alpha]^{25}D$ −258° (*c* 1.6, ethanol).

C. **(±)-Stepholidine.**—An aqueous solution of 0.08 g of XIX (section A) was treated with sodium borohydride (0.05 g) at room tempeature. The resulting precipitate was recrystallized from methanol to give colorless needles of (±)-stepholidine, mp 126–130° dec, the infrared spectrum of which was superimposable on that of (−)-stepholidine (XII) (chloroform solution spectra).

D. **O,O-Diethylstepholidine (XIV).**—A solution of (−)-stepholidine (XII) (0.950 g) and excess diazoethane ether azeotrope in methanol (25 ml) was kept at 0° for several days to give O,O-diethylstepholidine (XIV). The crude product was oxidized directly without further purification or characterization (see below).

Degradation Products from O,O-Diethylstepholidine (XIV). A. 6-Methoxy-7-ethoxy-1-keto-1,2,3,4-tetrahydroisoquinoline (XX).—A solution of 0.58 g of O,O-diethylstepholidine (XIV) in 1.5% sulfuric acid was adjusted to pH 7 with an aqueous sodium carbonate solution and was treated dropwise at room temperature with a solution of 1.04 g of potassium permanganate in 45 ml of water. The reaction mixture was heated at 60–70° for 10 min. It was cooled, made basic with potassium hydroxide, and extracted with chloroform. The chloroform extract was worked up in the usual way to give approximately 0.1 g of O,O-diethylstepholidine and a brown oil which was chromatographed with benzene on neutral grade IV alumina to give 0.02 g of 6-methoxy-7-ethoxy-1-keto-1,2,3,4-tetrahydroisoquinoline (XX), mp 189–190°, identical in all respects with authentic material.

B. **4-Ethoxy-5-methoxy-N-ethylphthalimide (XXI).**—The basic aqueous layer from the degradation of O,O-diethylstepholidine (see section A, above) was worked up in the usual way to give an acidic residue (0.08 g), which was then treated with acetyl chloride (0.3 ml) in benzene (3 ml). After removal of excess acetyl chloride and solvent, the presumed diacid anhydride was converted into the corresponding half amide by treatment with ethylamine in benzene–ether. The crude half amide was heated with acetic anhydride (1 ml) and sodium acetate (0.1 g) on a steam bath for 0.5 hr to give the crude imide XXI, obtained in the form of a brown gummy residue. The residue was chromatographed with 1:1 benzene–petroleum ether (bp 30–60°) on grade III neutral alumina to give two 3-ml eluate fractions containing only noncrystalline material, followed by two 3-ml fractions containing 4 mg of 4-ethoxy-5-methoxy-N-ethylphthalimide (XXI), mp 190–194°, identical with authentic material.

(26) M. Tomita and H. Yamaguchi, *Pharm. Bull.* (Tokyo), 1, 10 (1953).

(27) See ref 24, p 334.

Registry No.—I, 2810-21-1; 1-(*p*-hydroxybenzyl)-6,7-dimethoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline, 16562-16-6; III, 4880-87-9; IV, 16562-06-4; V, 16562-07-5; VI; 524-20-9; VII, 517-97-5; X, 16562-08-6; XV, 16562-09-7; XIX, 13509-87-0; XX, 16562-11-1; (−) XXI, 16562-12-2; (−) XII, 16562-13-3; (±) XII, 16562-14-4; 1-(*p*-benzyloxybenzyl)-6,7-dimethoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline, 14347-98-9.

Acknowledgments.—We are grateful to the National Institutes of Health for grants (GM 05640 and NB 04529) in partial support of this work. We also thank the following of our colleagues for generous gifts of comparison samples: Dr. K. L. Stuart, (+)-pronuciferine and (−)-tuduranine hydrochloride; Professor C. K. Bradsher, (±)-corydalmine; Dr. R. H. F. Manske, (−)-scoulerine; Professor M. Tomita, isoquinolone XIX; and Dr. Y. Watanabe, imide XX.

Steroids. LXXIX. Synthesis and Reactions of Oxiranes Obtained from 3- and 17-Keto Steroids[1]

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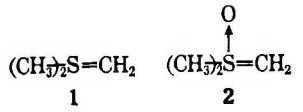
Received January 19, 1968

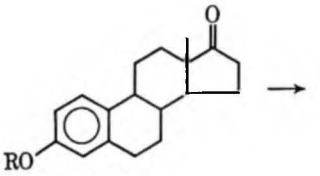
The synthesis of oxiranes from 3- and 17-keto steroids is described. Dimethylsulfonium methylide (1) reacted with estrone in a highly stereoselective manner by α-side addition of CH_2. α-Side addition also predominated in the reaction of 1 with 3-keto-5α steroids (although an earlier claim of stereospecificity has to be modified to stereoselectivity), whereas dimethyloxosulfonium methylide (2) gave products resulting from β-side attack on the 3-keto group. Stereochemistry of the products was demonstrated by chemical conversions. The oxiranes reacted with amines to yield amino alcohols. Spiro-17β-oxiranylestra-1,3,5(10)-trien-3-ol (4a) reacted with sodium cyanide at steam-bath temperature to yield 17α-cyanomethyl-3,17β-estradiol (5e), but under more strenuous conditions the product of this reaction was estrone.

The report by Corey and Chaykovsky[2] that dimethylsulfonium methylide (1) and dimethyloxosulfonium methylide (2) react with ketones and aldehydes to yield oxiranes opened a convenient route to a number of new steroid derivatives by reaction with readily available steroidal ketones. We report here on the preparation and properties of some new steroid oxiranes formed in this manner.[3]

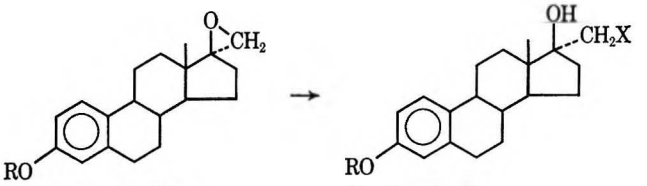


1 2

Estrone (**3a**) reacted smoothly with the sulfonium ylide **1** to yield a single oxirane (**4a**), identified as such by an infrared band at 3040 cm^{-1} and an AB quartet in the nmr spectrum.[4] The stereochemistry at C-17 was demonstrated by reduction with lithium aluminum hydride to the known 17α-methyl-3,17β-estradiol (**5a**).[5] The melting point of the crude diol was not depressed by admixture with authentic **5a** prepared from estrone and methyllithium.



3a, R = H
b, R = CH_3



4a, R = H
b, R = CH_3

5a, R = X = H
b, R = CH_3; X = H
c, R = H; X = $-NC_5H_{10}$
d, R = H; X = $-NHCH_2C_6H_5$
e, R = H; X = −CN

The nmr peak for the 18-CH_3 of oxirane **4a** was at 56 cps while that of the diol **5a** was at 54 cps. The observation that the 18-CH_3 is only slightly less shielded in the oxirane **4a** than in the alcohol **5a** is consistent with the results of Bertin and Nedelec in the androstane series. They reported the 18-CH_3 to shift upfield by δ 0.03 (*ca.* 2 cps) in going from 17β-oxirane to 17α-methyl-17β-ol. On the other hand, there was an upfield shift of δ 0.12 (7 cps) on going from a 17α-oxirane to a 17β-methyl-17α-ol.[3b]

While the conversion in high yield into essentially pure 17α-methyl-3,17β-estradiol was good evidence for stereospecific formation of the 17β-oxirane, the melting range of **4a** was wide enough to suggest a possibility of the presence of the C-17 epimer. When the reaction was repeated using the 3-methyl ether of estrone (**3b**) as substrate, oxirane **4b** (18-methyl resonance at 55.5 cps) and alcohol **5b** (18-methyl resonance at 54 cps) were obtained in high yield by the same sequence

(1) (a) For part LXXVIII, see D. Rosenthal, C. F. Lefler, and M. E. Wall, *Tetrahedron*, **23**, 3583 (1967). (b) This research was carried out under Contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health. (c) Abstracted in part from work done by R. C. Corley in partial fulfillment of the requirements for the Ph.D. degree at North Carolina State University at Raleigh. (d) Portions of this work were presented at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, Abstracts 92P. See also C. E. Cook, R. C. Corley, and M. E. Wall, *Tetrahedron Lett.*, 861 (1965).

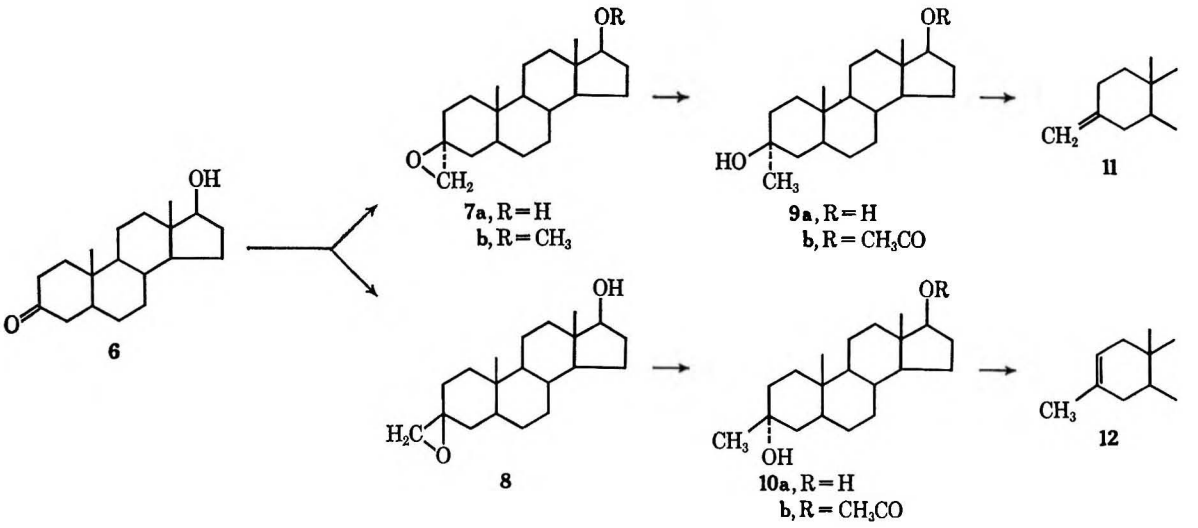
(2) (a) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 3782 (1962); (b) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1353 (1965).

(3) For results of other workers in this area, see, *inter alia*, (a) G. Drefahl, K. Ponsold, and H. Schick, *Ber.*, **97**, 3529 (1964); (b) D. Bertin and L. Nedelec, *Bull. Soc. Chim. Fr.*, 2140 (1964); (c) H. G. Lehmann, O. Engelfried, and R. Wiechert, *J. Med. Chem.*, **8**, 383 (1965).

(4) Unless otherwise noted, all nmr spectra were obtained at 60 Mc in deuteriochloroform with tetramethylsilane as internal standard.

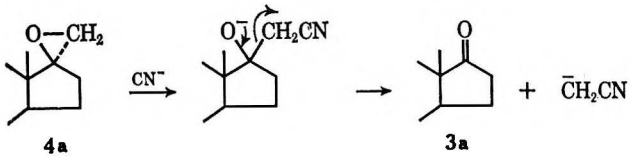
(5) (a) E. Haack, G. Stoek, and H. Voigt, *Naturwissenschaften*, **41**, 429 (1954); (b) L. F. Fieser, *Experientia*, **6**, 312 (1950).

SCHEME I



of steps. Nmr spectra showed trace peaks at 50.5 and 43 cps in the oxirane and alcohol, respectively, which could be due to 18-methyl resonances of not more than 5% of the 17 epimers.[6] Thin layer chromatography also showed only traces of the epimers. Thus with 17-ketones the reaction of sulfonium ylide **1** is highly stereoselective, in contrast to that of oxosulfonium ylide **2**, which yields mixtures of C-17 epimers.[3a,b]

The spirooxirane **4a** reacted smoothly with piperidine and benzylamine in the presence of phenol[7] to yield the substituted amino alcohols **5c** and **5d**. However, prolonged heating of **4a** with sodium cyanide in N,N-dimethylformamide at 110° gave neither the expected β-hydroxynitrile (**5e**) nor its dehydration product. Instead a high yield of estrone was obtained. Acetonitrile was identified in the solution by its retention time on gas chromatography, and the reaction appears to be simply a reverse aldol-type reaction of the anion of the hydroxynitrile **5e**. Reaction in ethylene



4a **3a**

glycol for 24 hr at 120–130° also gave a 40% yield of estrone, but milder conditions (ethylene glycol on a steam bath for 2 hr) gave the desired nitrile **5e**.

When the 3 ketone, dihydrotestosterone (**6**), was treated with ylide **1**, the major product was the β-spirooxirane **7a**, readily obtained in high purity by chromatography on alumina, which separated a small amount of by-product, believed to be the methyl ether of **7a** (**7b**) on the basis of analysis, nmr peaks at 46 (18-CH_3), 53 (19-CH_3), 154 (epoxide CH_2), and 202 cps (OCH_3), and absence of OH bands in the infrared spectrum (Scheme I). Our earlier report of stereospecificity in this reaction[1d] should now be modified to stereoselectivity, since the α isomer (**8**) is also obtained (see below). The α isomer **8** is obtained exclusively when ketone **6** is treated with oxosulfonium ylide **2**.

The stereochemistry of epoxides **7a** and **8** was demonstrated by reduction with lithium aluminum hydride to the epimeric 3-methyl-3,17β-androstanediols **9a** and **10a**. These compounds have been reported by Pelc, who obtained them by reaction of methyl Grignard reagent with dihydrotestosterone and assigned stereochemistry by analogy with known examples.[8] Although Pelc's assignment of configuration appeared reasonable, we felt that an unequivocal demonstration was desirable. Therefore monoacetates **9b** and **10b** were subjected to the dehydrating conditions used by Barton in a study of epimeric 3-methylcholestanols.[9] Nmr spectroscopy clearly demonstrated *exo*-methylene structure **11** for the product from **9b** and endocyclic structure **12** for the product from **10b**. Nmr showed that prolonged treatment of *exo*-methylene **11** with trifluoroacetic acid isomerized it to the endocyclic compound **12**. Reasoning analogous to that of Barton[9] confirms Pelc's assignments of structures **9** and **10**[8] and leads to the structures shown for **7a** and **8**.[1d] Wolff, *et al.*,[10] and Lehmann, *et al.*,[3c] have also reported the oxirane isomer of mp 173–175°. Whereas the former assumed structure **7a**, the latter adduced evidence for structure **8** and prepared **7a** by an independent route. Their results are in accord with those presented here.

The epoxides **7a** and **8** were not separable by tlc under the conditions used, but the corresponding diols **9a** and **10a** and monoacetates **9b** and **10b** were. When the crude product from reaction of ketone **6** and sulfonium ylide **1** was reduced with lithium aluminum hydride and the product acetylated, tlc showed the presence of epimeric acetates **9b** and **10b**, which were separated by preparative tlc. The acetates were also separable by gas chromatography. Complete peak separation was not achieved, making quantitative analysis difficult, but comparison with known mixtures showed **9b** and thus β-oxide **7a** to predominate by a 2:1 ratio.

Analogous results were obtained in the reaction of cholestanone (**13**) with sulfonium ylide **1**. The crude mixture of epoxides (shown to be a mixture by tlc) was reduced with lithium aluminum hydride to the methylcholestanols. Separation by preparative tlc gave the epimeric 3-methylcholestanols **16**. Again, gas chromatography on the crude reduction product indicated

(6) Methyl resonances for the other likely impurities, the methyl ethers of estrone and estradiol, occur at 53 and 47 cps.

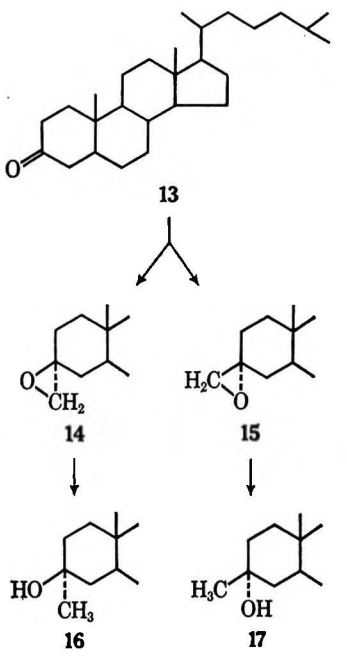
(7) R. Gedeon and V. Gyar, French Patent 1,333,946 (Aug 2, 1963).

(8) B. Pelc, *Collect. Czech. Chem. Commun.*, **25**, 1924 (1960).

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

(10) M. E. Wolff, W. Ho, and R. Kwok, *J. Med. Chem.*, **7**, 577 (1964).

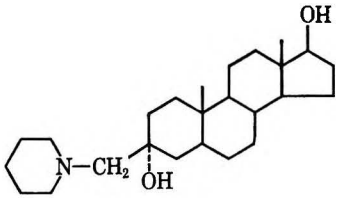
SCHEME II



16 (and thus epoxide 14) to predominate by a 2:1 ratio (Scheme II).

In contrast, cholestanone reacted with the oxosulfonium ylide 2 to give a single epoxide shown to be 15 by direct reduction with lithium aluminum hydride to 3β-methylcholestan-3α-ol (17). None of epimer 16 was observed on thin layer chromatography. These stereochemical results are consistent with those reported by Corey and Chaykovsky.[2b]

Epoxide 8 upon treatment with piperidine and phenol smoothly reacted to form the β-amino alcohol 18. In



all of the ring-opening reactions of the epoxides described, we expected attack of the nucleophile on the least hindered carbon of the oxirane ring to yield a tertiary alcohol. That this was the case was readily demonstrated by the nmr technique of Chapman and King.[11] The amino alcohol 18 in dimethyl sulfoxide-d_6 exhibited a doublet (J = 5 cps) centered at 260 cps for the 17-OH and a singlet at 214 cps for the tertiary 3-OH. Also there was a singlet (2 H) at 127.5 cps for the NCH_2CO protons. The stereochemistry of 18 follows from that of 8 and the mode of attack. Similarly, the hydroxynitrile 5e gave a singlet in dimethyl sulfoxide-d_6 at 293 cps (exchangeable with D_2O) for the tertiary 17-OH and a singlet at 158 cps for the $OCCH_2$-CN group. There were no peaks in the OCH_2 region. Structures of the amino alcohols 5c and 5d were assigned by analogy.

Experimental Section[4]

All reactions involving ylides were carried out under nitrogen in oven-dried apparatus. Tetrahydrofuran was distilled from lithium aluminum hydride just before use. Dimethyl sulfoxide was distilled from calcium hydride at reduced pressure and stored over molecular sieve. Melting points were taken on a Kofler apparatus. Unless otherwise noted optical rotations were obtained in chloroform solution (c approximately 1–2). Analyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

Spiro-17β-oxiranylestra-1,3,5(10)-trien-3-ol (4a).—A 50.2% suspension of sodium hydride in oil (19.2 g, 0.40 mol) was washed with tetrahydrofuran by decantation. Dry dimethyl sulfoxide (300 ml) was added and the sodium salt prepared by stirring and heating for *ca.* 0.75 hr at 70–75° under nitrogen.[2] Tetrahydrofuran (300 ml) was added and the mixture cooled to −5°. Then a solution of 82 g (0.40 mol) of trimethylsulfonium iodide in 700 ml of dimethyl sulfoxide was added rapidly with stirring. During this addition the reaction mixture solidified, and another 400 ml of tetrahydrofuran was added. Next, a solution of 27.0 g (0.1 mol) of estrone in 800 ml of tetrahydrofuran was added. After 2 hr at 0 to −5°, the mixture was allowed to warm to room temperature, poured into 2000 ml of water, and extracted with three 1000-ml portions of chloroform. The combined chloroform layers were dried over sodium sulfate overnight and evaporated. The product was sometimes contaminated with 5–10% of estrone, and the melting point was 170–177° after one recrystallization from methylcyclohexane. The estrone could be removed by crystallization from benzene to yield oxirane 4a: mp 181–183°; $[\alpha]D$ +61°; nmr peaks at 56 (singlet, 18-CH_3) and 172 cps (quartet, J = 5 cps, oxirane CH_2).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.04; H, 8.59.

17α-Methyl-3,17β-estradiol (5a). A.—Epoxide 4a (0.5 g) was refluxed for 5 hr with excess $LiAlH_4$ in 50 ml of tetrahydrofuran. Ethyl acetate (50 ml) was slowly added to the reaction mixture and then it was poured into 200 ml of 5% HCl. After two extractions with 100-ml portions of benzene, the organic layers were combined, washed with water, dried over Na_2SO_4, and evaporated. The white residue weighed 0.51 g: mp 187–190°; nmr peaks at 54 and 77 cps (singlets, 18- and 17-CH_3).

B.[5a]—In a dry flask under nitrogen, 0.5 g of estrone in 50 ml of tetrahydrofuran was slowly added to excess methyllithium in tetrahydrofuran–ether solution (55 ml). The solution was stirred 1.5 hr at room temperature and refluxed for 5 hr. Excess reagent was decomposed by addition of 10 ml of methanol followed by 10 ml of water. The mixture was poured into 200 ml of 5% HCl and extracted with benzene. From the benzene, after washing with water, drying over Na_2SO_4, and evaporation, there was obtained 0.56 g of off-white solid, mp 174–183°. Purification of 0.25 g by preparative thin layer chromatography (silica gel HF_{254}, 20% ethyl acetate in benzene) gave 45 mg of estrone (mp and mmp 254–258°) and 144 mg of diol 5a, mp 188–190°, undepressed in a mixture with the substance prepared by method A.

Spiro-17β-oxiranyl-3-methoxyestra-1,3,5(10)-triene (4b).—The 3-methyl ether of estrone (5.0 g, 17.6 mmol) was allowed to react with dimethylsulfonium methylide (63 mmol) in the manner described for estrone. After 1.5 hr the mixture was poured into water and the product obtained by extraction with chloroform. The product was crystallized from aqueous methanol: mp 97–107°. Chromatography on alumina (50 g, activity III) and elution with benzene yielded 4.7 g (90%) of white solid which showed no carbonyl absorption in the infrared, but contained trace impurities (tlc). These were removed from a 300-mg sample by preparative tlc and recrystallization from ethyl acetate to yield the analytical sample: mp 103–105°; nmr peaks at 55.5 (singlet, 18-CH_3) and 167 cps (quartet, J = 5 cps, oxirane CH_2); $[\alpha]D$ +56°.

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.46; H, 8.95.

When the reaction was repeated on a 100-mg scale (using NaH washed free of oil), and the total product (94 mg) examined by nmr spectroscopy, the 18-CH_3 peak at 55.5 cps was accompanied by a trace peak at 50.5 cps. Separate integration was not possible, but the small peak was 3.5% of the height of the main peak.

Reduction of a homogeneous aliquot of the crude epoxide (70 mg) with $LiAlH_4$ gave 60 mg of crude 3-methoxy-17α-methylestra-1,3,5(10)-trien-17β-ol. The nmr peak at 54 cps (singlet, 18-CH_3) was accompanied by a trace peak at 43 cps about 3% as intense as the major peak, and tlc showed a trace of impurity slightly faster moving than the main spot.

(11) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).

17α-N-Piperidinomethyl-3,17β-estradiol (5c).—Oxirane **4a** (10 g, 35.2 mmol) containing a small percentage of estrone was dissolved in 100 ml of piperidine, and 3 g of phenol[7] was added. After a 24-hr reflux period, tlc showed the reaction to be complete. The mixture was poured into 500 ml of water and extracted with two 200-ml portions of ether. The combined ether layers were washed with two 100-ml portions of water and 100 ml of saturated sodium chloride solution. Evaporation left a yellow gum. Crystallization from methanol yielded 7.5 g of pale yellow crystals, mp 191–195°. Recrystallization from benzene gave 5.7 g (44%) of **5c**, mp 196.5–198°. One more recrystallization gave the analytical sample: mp 197–198°; $[\alpha]_D$ +41°.

Anal. Calcd for $C_{24}H_{35}NO_2$: C, 78.00; H, 9.55; N, 3.79. Found: C, 78.05; H, 9.51; N, 4.07.

17α-N-Benzylaminomethyl-3,17β-estradiol (5d).—Oxirane **4a** (14 g, 49 mmol) was refluxed with 50 ml of benzylamine and 3 g of phenol.[7] The reaction was followed by gas chromatography (on SE-30) until starting material had almost completely disappeared (29 hr). The cooled solution was poured into 300 ml of water and extracted with ether. The ether was washed with water, dried (sodium sulfate), and evaporated, leaving an oily residue. After several triturations with water to remove benzylamine, the residue was a sticky gum. Trituration of this with methanol yielded 4 g of crystals, mp 189–196°. The filtrate was evaporated and the residue triturated with benzene to yield 4.5 g, mp 192–197°. Chromatography of the filtrate from this crop on 150 g of alumina (Woelm, activity III) gave more product. Recrystallization of the various crops from methanol–methylene chloride gave a total of 11.2 g (58%) of **5d**, mp 193–196°. Three more recrystallizations gave the analytical sample: mp 199–201°; $[\alpha]_D$ +30° (in methanol); nmr peak at 50 cps (singlet, 18-CH_3) in dimethyl sulfoxide-d_6.

Anal. Calcd for $C_{26}H_{33}NO_2$: C, 79.75; H, 8.50; N, 3.58. Found: C, 80.01; H, 8.60; N, 3.51.

Estrone.—A mixture of 0.5 g (1.75 mmol) of oxirane **4a**, 0.45 g (9 mmol) of sodium cyanide, and 2.5 ml of N,N-dimethylformamide (DMF) was heated for 22 hr at 110° under a reflux condenser. The liquid which had condensed on the inside of the condenser was rinsed into a flask with more DMF and examined by gas chromatography (12-ft SE-30 column at 50°, flame ionization detector). A small peak of retention time 1.3 min was observed before the large DMF peak at 2.4 min. This result was identical with that given by a solution of acetonitrile in DMF (2.9 mg/ml). Varying the concentration of acetonitrile caused the size of this peak to change. The dark reaction mixture was poured into water (300 ml) and extracted with benzene (three 100-ml portions). The combined benzene extracts were washed thoroughly with water, dried (sodium sulfate), and evaporated. The crude residue (0.53 g) melted at 245–251°. Recrystallization from benzene gave 0.32 g of estrone, mp 249–254°, and a third recrystallization raised the melting point to 252–255°. The product was identified as estrone by melting point, mixture melting point, and comparison of infrared spectra.

When 100 mg of oxirane **4a** was heated at 120–130° for 24 hr with 4 ml of ethylene glycol and 200 mg of sodium cyanide, and the reaction worked up by pouring into water and extracting with ether, the product consisted mainly of estrone (*ca.* 40% by gas chromatography) and an unidentified product more polar than either estrone or the β-hydroxynitrile **5e**.

17α-Cyanomethyl-3,17β-estradiol (5e).—Oxirane **4a** (0.5 g, 1.75 mmol) was dissolved in 20 ml of ethylene glycol and 1 g of sodium cyanide added. After 2 hr on a steam bath, all the starting material had reacted. The mixture was poured into water and the solid which formed (203 mg) was filtered off. Extraction of the filtrate with ether gave another 276 mg of product. Thin layer chromatography indicated one major product plus a small amount of estrone. The product **5e** (69% yield) was isolated by preparative tlc on silica gel HF_{254} (30% ethyl acetate in benzene). A second chromatography followed by crystallization from benzene gave the analytical sample: mp 227–228°; $[\alpha]_D$ +32° (in methanol); nmr peaks (DMSO-d_6) at 49 (singlet, 18-CH_3), 158 (broad singlet, $-CH_2CN$), 293 (singlet, exchanges with D_2O, 17-OH), and 535 cps (singlet, exchanges with D_2O, ArOH).

Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50. Found: C, 76.77; H, 8.14; N, 4.43.

Spiro-3β-oxiranyl-5α-androstan-17β-ol (7a) and 17β-Methoxyspiro-3β-oxiranyl-5α-androstane (7b).—A solution of dimethylsulfonium methylide (prepared as described for **4a**) was treated with 29 g (0.10 mol) of dihydrotestosterone (**6**) in 500 ml of tetrahydrofuran. Tlc showed that the reaction required 2.5 hr at 0–5° for completion. The mixture was then allowed to warm to room temperature and poured into water (1500 ml) containing 25 ml of acetic acid. Extraction with chloroform yielded a white solid which was recrystallized from benzene. Four crops weighing 5.2, 7.0, 5.6, and 12.5 g were obtained. The third crop was used for further reactions. A portion of the remainder (20 g) was chromatographed on 400 g of alumina (activity III). Elution with benzene gave three fractions. The first (1.4 g, mp 160–161°, $[\alpha]_D$ +8°) was assigned the ether structure **7b** on the basis of analysis, infrared spectrum (oxirane CH_2 at 3035 cm^{-1}, no OH), and nmr peaks at 46 (18-CH_3), 53 (19-CH_3) 154 (oxirane CH_2), and 202 cps (singlet, OCH_3).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.35; H, 10.89.

The second fraction, a mixture, upon rechromatography yielded 0.1 g of the ether and 4.0 g of **7a**, and the third fraction (14.4 g) upon recrystallization from benzene yielded 11.4 g of **7a**: mp 193–196°; $[\alpha]_D$ +6° (*cf.* ref 3c); nmr peaks at 154 (singlet, CH_2 of oxirane), 53 (19-CH_3), and 45 cps (18-CH_3).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.86; H, 10.58.

3α-Methyl-5α-androstane-3β-diol (9a) and 3α-Methyl-17β-acetoxy-5α-androstan-3β-ol (9b).—**7a** (1.00 g) was treated with 0.40 g of lithium aluminum hydride in 200 ml of tetrahydrofuran. The mixture, which contained much solid, was refluxed for 5 hr. Excess hydride was decomposed with ethyl acetate. The reaction mixture was added to 5% HCl and extracted with ether. The ether was washed with $NaHCO_3$ solution and saturated NaCl solution and dried (Na_2SO_4). Evaporation left 0.88 g of solid, which was recrystallized from methanol to yield four crops: 150 mg, mp 193–195°; 360 mg, mp 193–195°; 220 mg, mp 192–195°; and 125 mg, mp 190–195°. There were nmr peaks at 74 (3-CH_3), 49 (19-CH_3), and 44 cps (18-CH_3), and $[\alpha]_D$ was +19° (lit.[8] mp 186–188°; $[\alpha]_D$ +12°). Acetylation of diol **9a** (pyridine–acetic anhydride at room temperature) yielded monoacetate **9b**: mp 207.5–208° (from ether); $[\alpha]_D$ +10° (lit.[8] mp 194–195°; $[\alpha]_D$ +12°); nmr peaks at 122 (CH_3COO), 75 (3α-CH_3), 49 (19-CH_3), and 47.5 cps (18-CH_3).

Dehydration of 3α-Methyl-17β-acetoxy-5α-androstan-3β-ol.—The tertiary alcohol **9b** (70 mg) was dissolved in 10 ml of dry pyridine and cooled to 0°. Then 0.2 ml of phosphorus oxychloride was added and the solution allowed to warm slowly to room temperature.[9] It was then poured into 250 ml of water and extracted with ethyl acetate (three 100-ml portions). The combined ethyl acetate solution was washed thoroughly with water, dried, and evaporated, leaving 54 mg of pale yellow gum (crude **11**) which exhibited infrared bands at 3070, 1645, and 890 cm^{-1} (*exo*-methylene) and nmr peaks at 276 (=CH_2), 122 (CH_3COO), 53 (19-CH_3), and 48 cps (18-CH_3).

To the nmr sample was added 5 drops of trifluoroacetic acid, and the solution was heated in a sealed vial on a steam bath for 24 hr. The solvents were evaporated and the nmr spectrum was rerun. The olefinic proton peak had shifted to 219 cps and the 19-CH_3 to 44 cps. The 3-CH_3 protons of **12** appeared at 98 cps and the acetate and 18-CH_3 protons were unchanged.[12]

Spiro-3α-oxiranyl-5α-androstan-17β-ol (8).[10]—A mixture of 8.24 g (0.192 mol) of 50.2% sodium hydride in oil, 42.6 g of trimethyloxosulfonium iodide (0.194 mol), and 888 ml of dry dimethyl sulfoxide was stirred under nitrogen at room temperature until gas evolution ceased. Solid dihydrotestosterone (27.53 g, 0.095 mol) was added and the solution stirred for 16 hr at room temperature and then for 2 hr at 50°. The solution was poured into 2 l. of water, and the solid which precipitated was filtered off and recrystallized from acetonitrile. Four crops were obtained: 6.5 g, mp 172–175°; 10.0 g, mp 172–175°; 4.7 g, mp 172–175°; and 1.8 g, mp 170–174°. Total yield was 79%. The filtrate from the last crop showed only traces of epoxide on tlc, the bulk of the material consisting of more polar substances. Recrystallization of part of the first crop from acetonitrile gave prisms which changed to needles at *ca.* 160° and melted at 173–174°. Recrystallization of another portion from methanol gave plates which changed to needles at *ca.* 168° and melted at 174–176°: mmp 141–160° with isomer **7a**; $[\alpha]_D$ +7° (lit.[10] mp 173–175°; $[\alpha]_D$ +3°); nmr peaks at 157 (singlet, oxirane CH_2), 52 (19-CH_3), and 45 cps (18-CH_3).

(12) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press Inc., New York, N. Y., 1959, p 61. Compare, *e.g.*, α-pinene (340 cps) and β-pinene (294 cps).

3β-Methyl-5α-androstane-3α,17β-diol (10a) and 3β-Methyl-17β-acetoxy-5α-androstan-3α-ol (10b).—The oxirane **8** (3.00 g) was reduced with lithium aluminum hydride as described for **7a**. The reaction was worked up by addition of excess ethyl acetate, followed by slow addition of water until all gray material became white. Filtration and evaporation left 2.59 g (86%) of white solid, mp 167–170°. Recrystallization from methanol gave white needles of diol **10a**: mp 169–171° after drying *in vacuo* over refluxing toluene; $[\alpha]_D$ +8°; nmr peaks at 82 (3-CH_3) and 44 cps (19-CH_3) (lit.[8] mp 168–170°; $[\alpha]_D$ +8°).

The monoacetate **10b** was prepared (acetic anhydride in pyridine) and recrystallized from aqueous acetone. White needles were obtained: mp 207–209° (214–215° after drying *in vacuo* over refluxing toluene); $[\alpha]_D$ +6° (lit.[8] mp 205–207°; $[\alpha]_D$ +5°); nmr peaks at 122 (CH_3COO), 72 (3β-CH_3), 46 (19-CH_3) and 47.5 cps (18-CH_3).

Dehydration of 10b.—By the procedure used for dehydration of **9b**, 300 mg of acetate **10b** yielded 258 mg of a pale yellow solid (crude **12**): nmr peaks at 122 (CH_3COO), 98 (CH_3C=), 48 (18-CH_3), and 44 cps (19-CH_3).[12]

Reaction of Dimethylsulfonium Methylide with Cholestan-3-one and Reduction of Crude Product.—The sodium salt of dimethyl sulfoxide was prepared from 208 mg (4.3 mmol) of 50% sodium hydride in oil and 12 ml of dimethyl sulfoxide. Tetrahydrofuran (5 ml) was added and the mixture cooled to −5°. A solution of 880 mg of trimethylsulfonium iodide in 7 ml of dimethyl sulfoxide was added rapidly with stirring, followed by 500 mg (1.3 mmol) of cholestan-3-one in 7 ml of tetrahydrofuran. The mixture was stirred for 0.5 hr at −5°, allowed to warm to room temperature, and poured into water. Extraction with hexane yielded 424 mg (82%) of crude epoxide mixture (infrared band at 3040 cm^{-1}, no carbonyl band). On tlc using 10% acetone–hexane, it showed a single spot different from starting material. On continuous tlc using benzene as eluent, two spots were observed, the less polar of which corresponded in R_f to the epoxide obtained from cholestan-3-one and dimethyloxosulfonium ylide.

The crude epoxide was dissolved in 50 ml of tetrahydrofuran. Half of the solution was transferred to a flask and stirred for 1 hr with 300 mg of lithium aluminum hydride. After addition of a few drops of ethyl acetate, the mixture was poured into 100 ml of 1 *N* HCl, and the mixture was extracted with ether. The ether was washed with water, sodium bicarbonate solution, and saturated sodium chloride, and dried over Drierite. Evaporation left 226 mg of a gum. The total sample was dissolved in benzene and an aliquot submitted to preparative tlc (10% acetone–hexane on silica gel H, visualized with Morin dye). The two major bands were removed and eluted with ethyl acetate. After two crystallizations from methanol, the more polar product, 3α-methylcholestan-3β-ol (**16**), melted at 147–149° (lit.[9] mp 147–149°). The less polar 3β-methylcholestan-3α-ol (**17**) melted at 126–127° (lit.[9] mp 126–127°).

An aliquot of the benzene solution of the crude reduction product was analyzed by gas chromatography on a 12-ft column of 1% SE-30 at 240°. The two cholestanols were not completely separated under these conditions, but by comparison with standard mixtures, the 3α-methylcholestan-3β-ol was shown to predominate by a ratio of 2:1. When ether solutions of the pure isomers were stirred for 20 min with 1 *N* HCl, gas chromatography showed that no isomerization occurred.

Reaction of Dimethyloxosulfonium Methylide with Cholestan-3-one and Reduction of the Crude Product.—The reaction was carried out using 208 mg of 50% NaH in oil, 950 mg of trimethyloxosulfonium iodide, and 500 mg of cholestan-3-one in 15 ml of dimethyl sulfoxide and 7.5 ml of tetrahydrofuran. After being stirred for 16 hr at room temperature, the solution was heated at 50° for 2 hr and poured into 50 ml of distilled water. The mixture was extracted with hexane (yield 253 mg) and then with ethyl acetate (yield 163 mg). Both crops were shown by tlc (benzene on silica gel H, continuous flow) to consist of a single product with an R_f equal to that of the less polar epoxide from the preceding reaction.

Reduction of the crude epoxide was carried out as in the preceding case. The product, 3β-methylcholestan-3α-ol (**17**), melted at 126–127° (lit.[9] mp 126–127°) after crystallization from methanol.

Reaction of Dihydrotestosterone with Dimethylsulfonium Methylide and Reduction of the Crude Product.—Sodium hydride (575 mg of 56% suspension in oil, 13.4 mmol) was washed with two 5-ml portions of tetrahydrofuran (by stirring, allowing to settle, and pipetting off the supernatant liquid) and dried in the reaction flask in a stream of nitrogen. Dimethyl sulfoxide (15 ml) was added and the sodium salt formed by stirring at 60–70° for 0.75 hr. After addition of 25 ml of tetrahydrofuran the mixture was cooled below −5° and trimethylsulfonium iodide (2.80 g, 13.7 mmol) in 10 ml of dimethyl sulfoxide was added. After 5 min of stirring, the mixture (*ca.* −10°) was treated with 30 ml of tetrahydrofuran containing 1.00 g (3.45 mmol) of dihydrotestosterone (**6**). A flocculent white precipitate formed immediately. The mixture was allowed to warm to −5° and maintained at −6 to −4°. The reaction was monitored by tlc and was complete in 3 hr. The mixture was then allowed to warm to 15°, poured into 500 ml of water, allowed to stand overnight, and filtered to yield 967 mg of white solid.

The crude product was dissolved in 50 ml of tetrahydrofuran. Half of the solution was treated with 25 ml of tetrahydrofuran and 600 mg of lithium aluminum hydride. The mixture was refluxed for 3 hr, ethyl acetate and water were added, and the mixtue was poured into 200 ml of 1 *N* HCl. Extraction with three 50-ml portions of ethyl acetate, followed by washing of the combined organic layers with water, 5% $NaHCO_3$, and saturated NaCl, drying over Drierite, and evaporation, left a foam. Acetylation (acetic anhydride–pyridine) yielded 521 mg of a mixture. Of several tlc solvents tried, 40% ethyl acetate–hexane gave the best separation. The mixture was dissolved in benzene and an 80-mg aliquot chromatographed on silica gel H using the above solvent system. The purified substances obtained were recrystallized from hexane to yield 3α-methyl-17β-acetoxyandrostan-3β-ol (**9b**), mp 206.5–207.5°, and 3β-methyl-17β-acetoxyandrostan-3α-ol (**10b**), mp 213.5–215° (see above).

A sample of the crude acetate mixture was analyzed by gas chromatography on a 6-ft column of 1% QF-1 at 190°. Comparison with a standard mixture showed that **9b** predominated by a ratio of 2:1.

3β-(N-Piperidinomethyl)androstane-3α,17β-diol (18).—Oxirane **8** (4.5 g, 14.8 mmol) in 50 ml of piperidine was treated with 3 g of phenol and refluxed for 48 hr. The solution was poured into water, and an amorphous solid which formed was filtered off and recrystallized from aqueous methanol to yield a white solid, mp 168–172° (4.7 g, 81%). Further recrystallization from aqueous methanol, benzene, and aqueous methanol again gave prisms which changed to needles at *ca.* 160° and melted at 178–179°. The compound showed singlet nmr peaks in dimethyl sulfoxide-d_6 at 49 (18-CH_3), 54 (19-CH_3), and 127.5 cps (N-CH_2) (ratio 3:3:2), a doublet centered at 260 cps (J = 5 cps), and a singlet at 214 cps, both exchangeable with D_2O.

Anal. Calcd for $C_{28}H_{43}O_2N$: C, 77.07; H, 11.13; N, 3.60. Found: C, 76.71; H, 11.33; N, 3.48.

Registry No.—**4a**, 16669-01-5; **4b**, 16669-02-6; **5a**, 302-76-1; **5c**, 16669-04-8; **5d**, 16669-05-9; **5e**, 16669-06-0; **7a**, 2066-43-5; **7b**, 16669-08-2; **8**, 2384-24-9; **9a**, 2066-31-1; **9b**, 2066-32-2; **10a**, 2233-69-4; **10b**, 2611-37-2; **11**, 16669-14-0; **18**, 16669-15-1.

Acknowledgment.—We thank Mrs. Beverly Turner and Mrs. Ingeborg Harper for experimental assistance with the preparation of nitrile **7** and the experiments on stereoselectivity of reactions of **1** with the steroidal 3-ketones.

Steroids of Unnatural Configuration. Synthesis and Properties of Ring B Modified 17α-20-Ketopregnanes

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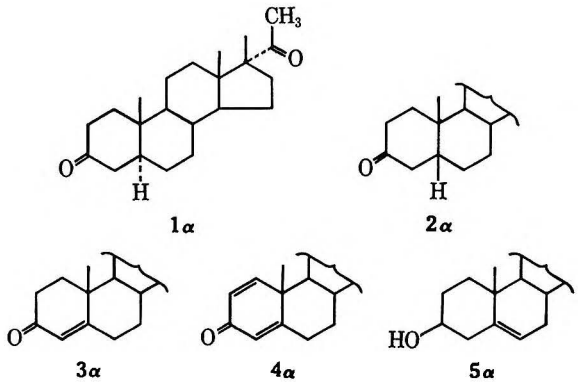
Received January 17, 1968

17α-Pregnenolone acetate served as starting material for synthesis of a series of 17α-6,20- and 17α-7,20-diketopregnanes. The corresponding 17β compounds were also prepared. The effect of C-17 configuration on optical rotation and nmr and mass spectra has been investigated.

The synthesis and properties of the following 17α-20-ketopregnanes,[2] 5α,17α-pregnane-3,20-dione (**1α**), 5β,17α-pregnane-3,20-dione (**2α**), 17α-Δ⁴-pregnene-3,-20-dione (17α-progesterone, **3α**), 17α-Δ¹,⁴-pregnadiene-3,20-dione (**4α**), and 17α-Δ⁴-pregnene-3β-ol-20-one (17α-pregnenolone, **5α**), have previously been reported.[3] Base-catalyzed reaction of such compounds leads, through a common enol or enolate ion, to an equilibrium mixture of both C-17 epimers; in the case of the above compounds mixtures containing 73 ± 2% of 17β resulted, irrespective of the variation in functionality of ring A. Compounds **1–5** exhibited another constant property, namely a 17.5-Hz downfield shift of the resonance of the C-18 methyl protons in the 17α isomer compared with the 17β although the absolute value of the chemical shifts varied from compound to compound. These results led to the conclusion that no significant conformational transmission or other long-range effect is operative from ring A to ring D. The synthesis of the ring B modified steroids described in the present work was undertaken to examine the possibility that structural changes closer to ring D might lead to observable long-range effects.



The starting material for synthesis of compounds in the 17α series was 17α-pregnenolone acetate (**6α**) which could be prepared[4] in 58–66% over-all yield from commercially available 16α,17α-oxidopregnenolone acetate *via* lithium aluminum hydride reduction, acetylation, and Serini–Logemann reaction. Syntheses starting from pregnenolone acetate (**6β**) provided the corresponding 17β isomers and also served to elaborate some of the appropriate experimental conditions for work in the 17α series. (See Scheme I.)

Oxidation of **6β** with *t*-butyl chromate solution[5] afforded 7-ketopregnenolone acetate (**7β**) in 50–60% yield and this, in turn, was converted in 53% yield into Δ³,⁵-pregnadiene-7,20-dione (**8β**) by treatment with mineral acid.[6] Hydrogenation of **8β** over palladium on charcoal was allowed to proceed until 1 equiv of hydrogen was absorbed. The resulting mixture of starting material and di- and tetrahydro products afforded 61% of the dihydro product, Δ⁵-pregnene-7,20-dione (**9β**), upon chromatography. The tetrahydro product, 5α-pregnane-7,20-dione (**10β**), could be obtained by hydrogenation of either **8β** or **9β**. The stereochemistry of **10β** at C-5 was assigned on the basis of analogy with results observed in the cholestane series[7] and the ORD results presented below.

When the *t*-butyl chromate oxidation procedure was applied in the less readily available 17α series, the yield of 17α-7-ketopregnenolone acetate (**7α**) from **6α** was a disappointing 40%. A second product not observed in the 17β series, 17α,5β,6β-oxidopregnan-3β-ol-20-one acetate (**11α**, 15%) could be isolated by chromatography of the mother liquors on silica gel. Assignment of the structure of **11α** is based on its independent synthesis from **6α** with *m*-chloroperbenzoic acid (*vide infra*). In the hope of improving the yield of **7α**, reaction time, temperature, and concentration of reactants were varied without success. However, when a more concentrated *t*-butyl chromate solution was used, a third product,[8] 17α-pregnane-3β,5α-diol-6,20-dione 3-acetate (**12α**), was isolated in 14% yield in addition to 40% **7α** and 14% **11α**. Epimerization of **12α** in alkaline solution followed by reacetylation of the 3-hydroxyl group afforded the known[9] 17β isomer, pregnane-3β,5α-diol-6,20-dione 3-acetate (**12β**). The structure of **12α** was further established by independent synthesis (*vide infra*).

The acid-catalyzed conversion employed in the 17β series could not be used for synthesis of 17α-Δ³,⁵-pregnadiene-7,20-dione (**8α**) from **7α** since appreciable epimerization at C-17 would be anticipated.[10] Attempted elimination of acetic acid from **7α** by heating in aqueous acetic acid alone or in the presence of *p*-toluenesulfonic acid did not yield appreciable quantities of **8α**. The elimination could be effected in 37%

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(2) For convenience and in order to emphasize their structural relationship, each pair of C-17 isomers has been designated by a numeral followed by α or β to indicate the stereochemistry at C-17.

(3) M. B. Rubin and E. C. Blossey, *J. Org. Chem.*, **29**, 1932 (1964).

(4) M. B. Rubin and E. C. Blossey, *Steroids*, **1**, 453 (1963).

(5) W. Logemann and P. Giraldi, *Gazz. Chim. Ital.*, **81**, 548 (1951).

(6) (a) C. W. Marshall, R. C. Ray, J. Laos, and B. Riegel, *J. Amer. Chem. Soc.*, **79**, 6308 (1957); (b) A. Nickon and J. F. Bagli, *ibid.*, **83**, 1498 (1961).

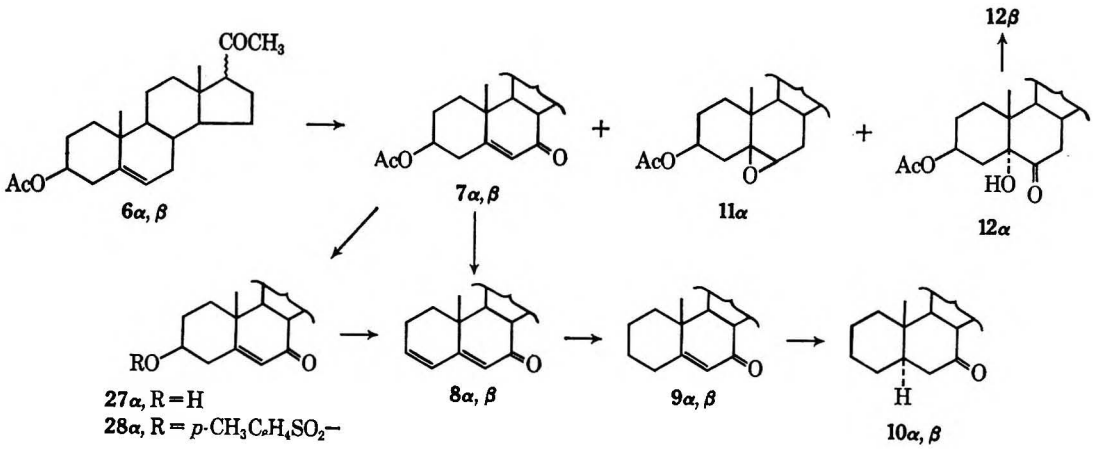
(7) I. M. Heilbron, W. Shaw, and F. S. Spring, *Rec. Trav. Chim. Pays-Bas*, **57**, 529 (1938).

(8) Reaction of the 5α,6α-oxide **19α** with *t*-butyl chromate under similar conditions resulted in conversion into **12α** while **11α** was recovered largely unchanged suggesting that epoxidation by *t*-butyl chromate proceeds to the extent of at least 28%. Failure to isolate epoxides from the reaction of **6β** may have been due to solubility factors.

(9) L. Knof, *Ann. Chem.*, **657**, 171 (1962).

(10) M. B. Rubin, *Steroids*, **2**, 561 (1963), and references contained therein.

SCHEME I



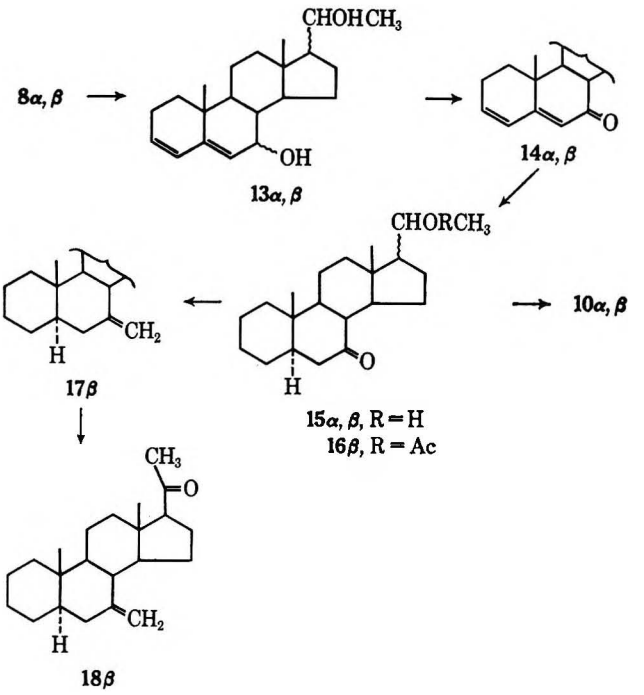
yield by allowing 7α to stand for several hours on a column of neutral alumina.[11] Alternatively, 7α could be converted quantitatively into the free alcohol (27α) with sodium carbonate in aqueous alcohol. Attempted dehydration of the alcohol was not successful. However, tosylation of 27α, followed by heating with dimethyl sulfoxide in the presence of excess lithium carbonate, afforded 8α in 52% over-all yield from 7α.

Hydrogenation of 8α was allowed to proceed until 1.15 equiv of hydrogen were absorbed[12] and afforded 39% 17α-Δ^5-pregnene-7,20-dione (9α). Complete hydrogenation of either 8α or 9α yielded 68 or 81%, respectively, 5α,17α-pregnane-7,20-dione (10α).

Each Δ^5-7-ketone (9α, 9β) afforded a single product (10α, 10β) upon catalytic hydrogenation. As noted above, it has been shown in the cholestane series that such reductions afforded products having the 5α configuration. To establish the stereochemistry of 10α and 10β unequivocally, their ORD curves were examined. These showed the strong positive (10β) and negative (10α) Cotton effects characteristic of 20-keto steroids[10] but allowed no conclusions concerning C-5 stereochemistry. The 20-ketone function was, therefore, removed in the following way. Reduction of 8α or 8β with lithium aluminum hydride afforded mixtures of $\Delta^{3,5}$-diene-7,20-diol ($13\alpha,\beta$) which were oxidized to the corresponding $\Delta^{3,5}$-dien-20-ol-7-ones ($14\alpha,\beta$) with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone or activated manganese dioxide. Hydrogenation of these afforded the corresponding 5α-20-ol-7-ones ($15\alpha,\beta$) which could be oxidized to 10α or 10β. The structure of 15β was further confirmed by acetylation to give known[13] 5α-pregnane-20β-ol-7-one acetate (16β) (Scheme II). The ORD curves of 15α and 15β were almost superposable and exhibited low-intensity, negative Cotton effect curves characteristic[14] of 5α-7-keto steroids.

The availability of 15β allowed synthesis of 7-methylene-5α-pregnan-20-one (18β). Reaction of 15β with

SCHEME II



methyl triphenylphosphorane according to the procedure of Sondheimer and Mechoulam[15] afforded 7-methylene-5α-pregnan-20β-ol (17β) in 32% yield. This was oxidized with chromium trioxide–pyridine to 18β.[16] Attempted preparation of 7-methylene-$\Delta^{3,5}$-pregnadien-20-one from 14β by the same sequence was unsuccessful.

Pregnenolone acetate (6β) and 17α-pregnenolone acetate (6α) also served as starting materials for synthesis of a series of 6,20-diketones. The known 5α,6α-oxidopregnan-3β-ol-20-one acetate (19β) was conveniently prepared from 6β using *m*-chloroperbenzoic acid[17] and was converted with chromic acid[9] into 12β, identical with the material obtained by base-catalyzed isomerization of 12α. Similar epoxidation of 6α furnished a mixture of oxides from which were isolated the 5β,6β-oxide (11α), previously obtained from the *t*-butyl chromate oxidation of 6α, in 30% yield, and the

(11) Alkaline alumina, which might be more effective in promoting the conversion of 7α into 8α has been found to cause appreciable isomerization of 17α to 17β epimers. No such isomerization was observed in this work with neutral alumina.

(12) The use of an excess over 1 equiv of hydrogen was necessary because the separation of 9α from 8α proved difficult. The low yield of 9α is partly due to this overreduction.

(13) J. Romo, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **17**, 1413 (1952).

(14) C. Djerassi and R. Ehrlich, *J. Amer. Chem. Soc.*, **78**, 440 (1956); C. Djerassi, W. Closson, and A. E. Lippman, *ibid.*, **78**, 3163 (1956); C. Djerassi and W. Closson, *ibid.*, **78**, 3761 (1956).

(15) F. Sondheimer and R. Mechoulam, *ibid.*, **79**, 5029 (1957).

(16) This scheme was not applied in the 17α series because of the small amount of 15α available.

(17) This reaction afforded a mixture of oxides from which the pure isomers could be isolated.

TABLE I
NMR AND MOLECULAR ROTATION DATA

20-Ketopregnane	Chemical shifts[a] of methyl protons, Hz: C_{18} 17β	C_{18} 17α	ΔC-18[b]	C_{19} 17β	C_{19} 17α	C_{21} 17β	C_{21} 17α	Molecular rotation,[c] deg: 17β	17α	ΔMD[d]
1. 3β-Acetoxy, 5α,6α-oxide (**19**)	34.5	52.0	17.5	64.8	64.6	127.2	126.9	+54	−483	+537
2. 3β-Acetoxy, 5β,6β-oxide (**11**)	36.0	53.6	17.6	61.0	60.5	127.2	127.5	+209	−318	+527
3. Δ⁴-6-Keto (**24**)	39.5	57.0	17.5	58.0	57.0	127.5	127.0	+320	−154	+474
4. Δ²,⁴-6-Keto (**25**)	39.0	56.6	17.6	60.0	59.5	127.0	128.6	+303	−203	+506
5. 5α-Hydroxy-6-keto (**23**)	35.5	45.5	10.0	46.5	53.2	126.5	128.0		−508	
6. 3β-Acetoxy-5α-hydroxy-6-keto (**12**)	36.5	48.2	11.7	48.8	54.0	127.7	129.2	−58	−505	+447
7. Δ³,⁵-7-Keto (**8**)	41.6	56.8	15.2	68.0	66.4	127.0	127.0	−837	−1410	+573
8. 3β-Acetoxy-Δ⁵-7-keto (**7**)	40.2	54.7	14.5	73.4	71.6	128.4	127.7	−253	−709	+456
9. Δ⁵-7-Keto (**9**)	39.7	54.5	14.8	71.3	69.7	127.0	126.0	−377	−801	+424
10. 5α-7-Keto (**10**)	37.6	53.4	15.8	63.0	62.2	126.0	126.0	−16	−417	+401

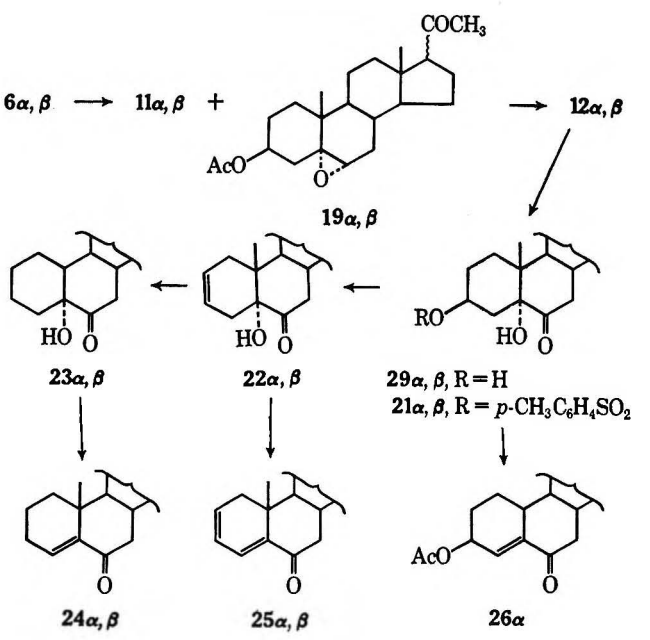
[a] In hertz from tetramethylsilane. Spectra were determined on 0.3 *M* solutions in deuteriochloroform containing tetramethylsilane using a Varian Associates A-60 spectrometer. [b] Chemical shift (hertz) of 17α isomer minus shift of 17β. [c] Rotations were measured using 1% solutions in chloroform at the sodium D line. [d] MD of 17β minus 17α.

5α,6α-oxide, **19**α, in 50% yield. Chromic acid oxidation of **19**α afforded 89% **12**α identical with the material obtained previously. The configurations assigned to **11**α and **19**α are consistent with the nmr spectra of these compounds. It has been shown[18] with a variety of steroid 5,6-epoxides that the magnitude of the coupling constant between C-6 and C-7 protons depends on configuration. For α-epoxides, the 6β-proton resonance appears as a doublet with J = 3.3–4.1 Hz whereas the 6α proton of β-epoxides also appears as a doublet but with J = 2.1–2.7 Hz. The spectrum of **19**α exhibited a doublet at τ 7.06 with J = 3.8 while **11**α exhibited a doublet at τ 6.95 with J = 2.5.

Hydrolysis of the ester group of the hydroxy ketones **12**α and **12**β afforded the corresponding free alcohols **29**α and **29**β which were converted into the tosylates **21**α and **21**β. Heating each tosylates in dimethyl sulfoxide yielded 17α- or 17β-Δ²-pregnen-5α-ol-6,20-dione (**22**α and **22**β). The position of the double bond in these compounds was assigned by analogy with the reaction of cholestane-3β,5α-diol 3-tosylate.[19] Catalytic hydrogenation of each isomer to the saturated 5α-hydroxy-6,20-dione (**23**α and **23**β) and then dehydration with thionyl chloride pyridine gave 17α-Δ⁴-pregnene-6,20-dione (**24**α) and its 17β isomer (**24**β). Similarly, dehydration of **22**α and **22**β afforded 17α- and 17β-Δ²,⁴-pregnadiene-6,20-dione (**25**α and **25**β) and dehydration of **20**α afforded 17α-Δ⁴-pregnene-3β-ol-6,20-dione 3-acetate (**26**α) (Scheme III). The yields obtained in both the 17α and 17β series were comparable.

No attempt was made to prepare 6,20-diketones unsubstituted at C-5 since epimerization could then occur[20] at both C-5 and C-17 in the projected equilibration studies. The results of these studies will be published in the future together with the results obtained with various ring C and ring D modified 20-ketopregnanes. It is noteworthy that no gross differences were observed in the reactivity of compounds in the 17α or 17β series. However, optical rotations and nmr and mass spectra of isomeric 20-ketones merit discussion.[21]

SCHEME III



Examination of the optical rotation data summarized in Table I shows that in every case the 17α isomer is the more levorotatory of the two, the molecular rotation differences ($M^{17\beta}D - M^{17\alpha}D$) ranging from 401 to 573°. This is in accord with previous observations and provides a confirmation of the assigned stereochemistry. However, as noted in our previous work,[4] the constant value of ΔMD = 550 ± 20 assigned by earlier workers[22] applies only to a limited number of cases involving changes in functionality of ring A.

The distinguishing features of the nmr spectra of ring A modified 20-ketones were (1) a nearly constant value (127.8 ± 0.5 Hz) for the chemical shift of the C-21 protons, (2) a slight (0.5–1.0 Hz) upfield shift of the C-19 protons in 17α isomers relative to 17β, and (3) a pronounced, constant downfield shift of C-18 protons in 17α isomers (ΔC-18 = 17.5 ± 0.2 Hz). The nmr results obtained in the present work are summarized in Table I. The C-21 protons fall in the range 126–129 Hz for the 20 compounds examined in good agreement with the earlier results. The C-19 protons of 17α isomers were shifted to higher field by 0.2–1.6 Hz with the exception of no.

(18) A. D. Cross, *J. Amer. Chem. Soc.*, **84**, 3206 (1962).
(19) H. Reich, F. E. Walker, and R. W. Collins, *J. Org. Chem.*, **16**, 1753 (1951).
(20) In the case of 6-ketocholestanone, it has been shown that 12% of the 5β isomer is present at equilibrium: N. L. Allinger, M. A. Darooge, and R. B. Hermann, *ibid.*, **26**, 3626 (1961).
(21) Results of an investigation of the gas chromatographic behavior of a large number of 20-keto steroids including the compounds obtained in this work are being published separately: M. B. Rubin and A. P. Brown, *J. Gas Chromat.*, in press.
(22) (a) C. W. Marshall and T. F. Gallagher, *J. Biol. Chem.*, **179**, 1265 (1949); (b) C. W. Shoppee, *J. Chem. Soc.*, 1671 (1949).

5 and 6, the 5α-hydroxy 6-ketones **23** and **22** where the C-19 protons of the 17β isomer appear at 6.7 and 5.2 Hz higher field, respectively, than those of the 17α isomers. The 5α-hydroxy 6-ketones also show unusually small values for ΔC-18 of 10.0 and 11.7 Hz, respectively.[23] Examination of ΔC-18 for the remaining compounds shows that the constants downfield shift of 17.5 Hz for the C-18 protons of 17α isomers is also observed with the 5,6-oxides (**19**, **11**) and the unsaturated 6-ketones (**24**, **25**). However, all of the 7-ketones (**7**–**10**) exhibit lower values of ΔC-18 ranging from 14.5–15.8 Hz. These results might suggest a change of the spatial relationship between C-17 substituent and the neighboring angular methyl group in 7-ketones. Such a change is not apparent from examination of models nor is it supported by the results of equilibration studies with these compounds. In fact, equilibrated mixtures[24] of **8**, **9**, and **10** contained 18–20% 17α isomer in reasonably close agreement with the value of 23 ± 2% observed previously[4] with compounds **1**–**5**.

It has recently been reported[25] that significant differences are observed at *m/e* 71, 124, 229, 244, and 272 in the mass spectra of the epimeric progesterones **3**α and **3**β. These differences were attributed in part (*m/e* 71 and 244 peaks) to intensive rupture of the 15–16 and 13–17 bonds caused by the presence of the 17α-acetyl group. It seemed of interest to examine the generality of this behavior and, accordingly, mass spectra of the Δ⁴-pregnene-6,20-diones (**24**α and **24**β) and 5α-pregnane-7,20-diones (**10**α and **10**β) were determined. The intensities of those peaks where significant differences between the two isomers were observed are presented in Table II. It is immediately apparent that

TABLE II

INTENSITIES[a] OF CHARACTERISTIC PEAKS IN MASS SPECTRA[b]

		m/e						
Compound	M⁺	71	79	85	136	229	233	234
24α (Δ⁴-6-one)	9.6 (314)	1.6	0.7	1.3	0.7	5.9	2.1	3.3
24β	7.3	0.7	3.3	3.5	2.3	1.2	0.2	
		178	202	231	246	298		
10α (5α-7-one)	3.5 (316)	...	2.4	1.5	15.3	0.9		
10β	4.4	3.7	0.3	2.6	2.1	2.3		

[a] $\%\Sigma_{40}$. [b] Mass spectra were determined on an Atlas CH-4 instrument: ionizing voltage 70 eV; ion source temperature 150°.

there are considerable differences between the two isomers in both cases. The very pronounced difference at *m/e* 244 (9.4% in **3**α, 1.2% in **3**β) observed with the progesterones is also evident with the 5α-7-ones **10**α and **10**β, shifted to *m/e* 246 as expected. However, no such difference is observed with the Δ⁴-6-ones **24**α and **24**β. Instead, a pronounced difference is observed 15 mass units lower at *m/e* 229. The variations in the peak at *m/e* 71, assigned to the fragment formed by rupture of the 13–17 and 15–16 bonds accompanied by hydrogen migration in the case of **3** (3.4% in **3**α, 1.0% in **3**β), were also observed in the spectra of **24**α and **24**β but not at *m/e* 71 or 73 in the case of **10**α and **10**β. These results support the conclusion that the configuration of the acetyl group at C-17 plays a role in determining the relative importance of various fragmentations, but further investigation is required to provide a rational interpretation of the results.

Experimental Section[26]

Δ⁵-Pregnene-7,20-dione (9β).—A solution of 5.0 g (16.0 mmol) of Δ³,⁵-pregnadiene-7,20-dione[6a,b] (**8**β) in 250 ml of ethyl acetate with 0.50 g of 10% palladium on charcoal was hydrogenated at 27° and atmospheric pressure (738 mm). After 33 min, 407 cc (16.0 mmol) of hydrogen were absorbed, and the reaction was terminated. The catalyst was removed by filtration through a Celite filter cake and washed with ethyl acetate. Evaporation of the combined solvents gave 5 g of solid: λ_{max} (EtOH) 238 mμ (ε 10,000) (74% **9**β) and 279 (750) (3% **8**β). Thin layer chromatography of the crude product on silica gel with 1:4 diethyl ether–benzene as the eluent and iodine as the indicator indicated the presence of a third component, presumably 5α-pregnane-7,20-dione (**10**β). Chromatography of the product on 250 g of Florisil with benzene–ethyl acetate (99:1–95:5; 17 1-l. portions) afforded 3.7 g of impure **9**β. Crystallization alternately from benzene–hexane and ethanol–water gave 3.0 g (60%) of Δ⁵-pregnene-7,20-dione (**9**β), mp 160–161°.

Crystallization from ethanol afforded the analytical sample: mp 163–164°; $\alpha^{30}D$ −120°; λ_{max} 237 mμ (ε 13,500); 5.87, 6.04, 6.13 (sh) μ; nmr τ 4.40 (1 H), 7.91 (3 H), 8.81 (3 H), 9.33 (3 H) ppm.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.11; H, 9.90.

5α-Pregnane-7,20-dione (10β). A. From Δ³,⁵-Pregnadiene-7,20-dione (8β).—A 5.0-g (16.0 mmol) sample of **8**β in 250 ml of ethyl acetate with 0.50 g of 10% palladium on charcoal was hydrogenated at 26° and atmospheric pressure (736 mm). After 70 min, uptake of hydrogen ceased with the absorption of 826 ml of hydrogen (32.7 mmol). The catalyst was removed by filtration and washed with ethyl acetate. The combined solvents were evaporated to give 5.1 g of white solid which was chromatographed on 250 g of Florisil. Elution with pure benzene and benzene–ethyl acetate (99:1; 14 × 1 l.) gave 3.8 g of material. One crystallization from ethanol afforded 3.0 g of 5α-pregnane-7,20-dione (**10**β), mp 148–149°. An additional 0.37 g (total yield 67%) of **10**β was obtained from the mother liquor.

Crystallization from ethanol–water gave the analytical sample: mp 148–149°; $\alpha^{30}D$ −4.8°; λ_{max} 5.89 μ; nmr τ 7.91 (3 H), 8.95 (3 H), 9.38 (3 H) ppm.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.60; H, 10.30.

B. From Δ⁵-Pregnene-7,20-dione (9β).—A 180-mg (0.57 mmol) sample of **9**β in 15 ml of ethyl acetate with 18 mg of 10% palladium on charcoal was hydrogenated at 28° and atmospheric pressure (741 mm). A total of 10.1 cc of hydrogen (0.4 mmol) was absorbed after 15 min. Filtration and removal of the solvent gave a white solid. One crystallization from methanol gave 126 mg (70%) of **10**β, mp 147°, identical with the **10**β described above.

C. From 5α-Pregnan-20β-ol-7-one (15β).—Nitrogen was bubbled through a solution of 100 mg of **15**β in 13 ml of acetone distilled from potassium permanganate for 30 min. The stirred solution was cooled to 10°, and 0.20 ml of Jones reagent,[27] similarly flushed with nitrogen, was rapidly added. After 6–7 min at 10° the reaction mixture was diluted with 100 ml of water. Filtration of the crystalline precipitate afforded 86 mg (86%) of **10**β, mp 147–149°, identical in all respects with the material described above.

***t*-Butyl Chromate Oxidation of 17α-Pregnenolone Acetate.**—A 1.10-g sample of **6**α in 5 ml of dry carbon tetrachloride was oxidized with 30 ml of *t*-butyl chromate solution prepared by the procedure of Logemann and Giraldi.[5] The reaction mixture was maintained at 50–60°. After 2 hr, 4 ml of acetic anhydride

(23) It has been suggested [A. I. Cohen, B. T. Keller, E. J. Becker, and P. A. Diassi, *J. Org. Chem.*, **30**, 2175 (1965)] that certain steroidal α-hydroxy ketones exist in solution in the form of hydrogen-bonded dimers. The possibility that the anomalous results observed in the nmr spectra (deuteriochloroform) of **23** and **12** might be due to such a phenomenon is supported by infrared studies. Both **12**α and **12**β exhibit free hydroxyl absorption at 3580 cm^{-1} and bonded, concentration-dependent absorption at 3460 cm^{-1} in chloroform solution.

(24) A. P. Brown, unpublished results.

(25) V. I. Zaretskii, N. S. Wulfson, and V. G. Zaikin, *Tetrahedron*, **23**, 3683 (1967).

(26) Melting points are corrected. Ultraviolet spectra were determined in ethanol solution, infrared spectra in potassium bromide pellets except where noted otherwise, optical rotations in 1% chloroform solutions, and nmr spectra in deuteriochloroform solution containing tetramethylsilane. Hexane refers to a commercial petroleum fraction of bp 60–67°.

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

were added, and after an additional 2 hr, 6 ml of acetic acid were added over a 90-min period. The reaction was maintained at 50–60° for 6 hr after the addition of the acetic acid, and then allowed to stand at room temperature overnight. The excess chromate was reduced by the portionwise addition of 100 ml of 10% aqueous oxalic acid solution. The carbon tetrachloride solution was washed with 10% sodium carbonate solution which was back-washed with fresh carbon tetrachloride. The combined organic phases were washed with water and dried. Evaporation of the solvent afforded 1.18 g of a yellow solid: λ_{max} 236 mμ (ε 4900, 37% 7α).

Two crystallizations of the crude product from ethyl acetate–hexane afforded 284 mg of 17α-Δ⁵-pregnene-3β-ol-7,20-dione acetate (7α), mp 214–216°. The mother liquors were chromatographed on 35 g of silica gel with 5% diethyl ether in benzene as the eluent; 35-ml fractions were collected. Fractions 3–5 afforded 353 mg of impure starting material which was crystallized from acetone–water to give 290 mg of 6α, mp 170°. Fractions 17–19 afforded 151 mg of 7α which were crystallized from ethyl acetate–hexane to give an additional 55 mg (40% total yield) of 7α.

Crystallization from methanol afforded a sample of 7α for analysis: mp 217–218°; $\alpha^{25}D$ −190°; λ_{max} 236 mμ (ε 13,200); ($CHCl_3$) 5.78, 5.88, 5.99, 6.12, 8.10 μ.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.94; H, 8.57.

Fractions 6–14 (9 × 35 ml) afforded 129 mg (15%) of 17α-5β,6β-oxidopregnan-3β-ol-20-one acetate (11α).

Crystallization from methanol–water afforded an analytical sample: mp 126–126.5°; $\alpha^{27}D$ −85°; λ_{max} ($CHCl_3$) 5.78, 5.88, 8.15 μ; nmr τ 5.07–5.50 (1 H, complex), 6.95 (1 H, d, J = 2.5 Hz), 7.90 (3 H), 7.99 (3 H), 9.00 (3 H), 9.10 (3 H) ppm.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.75; H, 9.17. Found: C, 73.87; H, 9.06.

m-Chloroperbenzoic Acid Oxidation of 17α-Pregnenolone Acetate.—To a 5.0-g sample of 6α in 20 ml of chloroform at 25° was added a solution of 3.5 g of *m*-chloroperbenzoic acid (technical) in 30 ml of chloroform. The addition was carried out over a 10-min period. After an additional 25 min the excess peracid was reduced by the slow addition of a 10% sodium sulfite solution. The organic layer was separated, washed with sodium bicarbonate solution and water, and then dried. Evaporation of the solvent gave 5.43 g of the mixed α- and β-oxides which were chromatographed on silica gel with 6–8% ether in benzene. Fractions 5–8 (four-250 ml portions) contained 2.3 g (44%) of 17α-5β,6β-oxidopregnan-3β-ol-20-one acetate (11α) identical with the material obtained in the *t*-butyl chromate oxidation of 6α.

Continued chromatography of the above sample (nine 250-ml fractions) gave a total of 2.6 g of 17α-5α,6α-oxidopregnan-3β-ol-20-one acetate (19α), mp 216–219°. This material was used without further purification.

Crystallization of a sample from methylene chloride–isopropyl ether furnished the analytical sample: mp 221.5–223°; $\alpha^{27}D$ −129°; λ_{max} (CH_2Cl_2) 5.78, 5.87, 8.12 μ; nmr τ 4.75–5.25 (1 H, complex), 7.06 (1 H, d, J = 3.8 cps), 7.86 (3 H), 7.98 (3 H), 8.91 (3 H), 9.12 (3 H) ppm.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.75; H, 9.17. Found: C, 73.93; H, 9.26.

17α-Pregnane-3β,5α-diol-6,20-dione 3-Acetate (12α). A. From 17α-Pregnenolone Acetate (6α).—A portion of the *t*-butyl chromate solution prepared according to the procedure of Logemann and Giraldi[5] was concentrated below 40° under reduced pressure to half of its original volume. A 30-ml portion of this concentrated chromate solution was used for the oxidation of 2.2 g of 17α-pregnenolone acetate (6α). The reaction procedure was identical with that described above. The crude product, λ_{max} 234 mμ (ε 5900, 45% 7α), was crystallized from ethyl acetate–hexane to give 1.07 g of solid, mp 197–205°. Chromatography of this mixture with 5% ether in benzene, followed by crystallization from chloroform–hexane gave 282 mg (15%) of 17α-pregnane-3β,5α-diol-6,20-dione 3-acetate (12α) identical with the material described below.

B. From 17α-5α,6α-Oxidopregnan-3β-ol-20-one Acetate (19α).—To a 2.6-g sample of 19α in 20 ml of acetone at 10° was added 0.7 ml of 75% chromic acid solution.[9] After 1 min an additional 0.7 ml of the chromic acid solution was added, followed after 30 min by the addition of another 0.35 ml. After a total reaction time of 1 hr the reaction mixture was diluted with water, and the precipitated product was taken up in ethyl acetate. The ethyl acetate was washed with water, dried, and evaporated to give 2.7 g of impure product, mp 255–259°. Crystallization from chloroform–hexane gave 2.4 g (89%) of 17α-pregnane-3β,5α-diol-6,20-dione 3-acetate (12α), mp 258–260°.

An analytical sample was prepared by crystallization from chloroform–hexane: mp 259–261°; $\alpha^{27}D$ −129°; λ_{max} (CH_2Cl_2) 2.83; 5.81 (sh), 5.85, 8.08 μ; nmr τ 4.75–5.10 (1 H, complex), 6.07 (1 H), 7.89 (3 H), 8.04 (3 H), 9.11 (3 H), 9.21 (3 H) ppm.

Anal. Calcd for $C_{23}H_{34}O_6$: C, 70.74; H, 8.76. Found: C, 70.83; H, 8.80.

17α-Δ⁵-Pregnene-3β-7,20-dione (27α).—To an ice-cold solution of 4.2 g of 7α in 380 ml of methanol were added 190 ml of water containing 17.5 g of potassium carbonate. After stirring at room temperature for 2 hr, the solution was neutralized with concentrated hydrochloric acid. The methanol was removed under reduced pressure on the steam bath, and the resulting aqueous suspension was extracted three times with ethyl acetate which was washed with water and dried. Removal of the solvent afforded 3.8 g (98%) of 17α-Δ⁵-pregnen-3β-ol-7,20-dione (27α), mp 177–179°.

Crystallization from methanol afforded an analytical sample: mp 182–183°; $\alpha^{25}D$ −191°; λ_{max} 237 mμ (ε 13,200); ($CHCl_3$) 2.67, 2.80 (br), 5.87, 5.98, 6.11 μ.

Anal. Calcd for $C_{21}H_{30}O_3 \cdot H_2O$: C, 72.38; H, 9.26. Found: C, 72.46; H, 9.26.

17α-Δ⁵-Pregnen-3β-ol-7,20-dione Tosylate (28α).—A mixture of 3.59 g of crude 27α and 3.6 g of *p*-toluenesulfonyl chloride in 11 ml of pyridine was kept at room temperature for 2 hr and then at 0° overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate solution was washed with 5% sulfuric acid, 10% sodium bicarbonate, and water and dried. Removal of the solvent *in vacuo* at room temperature gave 5.3 g (100%) of 17α-Δ⁵-pregnen-3β-ol-7,20-dione tosylate (28α) as an oil which gradually solidified. The crude tosylate was used without further purification for the preparation of the 17α-dienone 8β. Both the crude and purified tosylates were unstable and had to be used shortly after their preparation.

Crystallization of the tosylate from methylene chloride–isopropyl ether afforded an analytical sample: mp 129.5°; $\alpha^{30}D$ −131°; λ_{max} 224 mμ (ε 23,700); ($CHCl_3$) 5.99, 6.10, 6.25, 6.37, 8.63, 10.33, 10.60, 11.20, 11.51, 11.94 μ.

Anal. Calcd for $C_{28}H_{36}O_5S$: C, 69.38; H, 7.49; S, 6.62. Found: C, 69.18; H, 7.51; S, 6.42.

17α-Δ³,⁵-Pregnadiene-7,20-dione (8α). A. From 17α-Δ⁵-Pregnen-3β-ol-7,20-dione Tosylate (28α).—A solution of 5.2 g of 28α in 300 ml of anhydrous dimethyl sulfoxide (DMSO) containing 20 g of lithium carbonate was heated at 100° under nitrogen for 3.5 hr. Approximately 80% of the DMSO was removed by vacuum distillation at 100°. The residue was taken up in ethyl acetate and the lithium carbonate removed by filtration. The ethyl acetate was washed with water and dried. Evaporation of the solvent left 3.1 g of a reddish brown oil: λ_{max} 278 mμ (ε 16,000, 76% 8α). Chromatography of the oil on 155 g of silica gel with 5% diethyl ether in benzene (eight 125-ml portions) afforded 2.1 g of solid from which 1.77 g (52%) of 17α-Δ³,⁵-pregnadiene-7,20-dione (8α), mp 126–127°, were obtained in two crops from isopropyl ether–hexane.

Crystallization of 8α from ethanol–water provided the analytical sample: mp 130–131.5°; $\alpha^{30}D$ −452°; λ_{max} 278 mμ (ε 23,400); 5.90, 6.01, 6.14, 6.26 μ; nmr τ 3.95 (2 H), 4.45 (1 H), 7.91 (3 H), 8.90 (3 H), 9.07 (3 H) ppm.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.82; H, 8.82.

B. From 17α-Δ⁵-Pregnen-3β-ol-7,20-dione Acetate (7α).—A 2.46-g sample of 7α was placed on a column of 70 g of neutral alumina using 5% diethyl ether in benzene as the solvent. After 2.5 hr the column was washed with 2 l. of ethyl acetate. Evaporation of the ethyl acetate afforded 1.67 g of solid: λ_{max} 278 mμ. Chromatography of the crude product on 85 g of silica gel with 4% diethyl ether in benzene gave 990 mg of impure 8α and 386 mg of starting material. The 17α-dienone was treated with activated charcoal and crystallized from acetone–hexane to give 645 mg (37%) of 8α, mp 130–131°, which was identical with that obtained from 28α.

17α-Δ⁵-Pregnene-7,20-dione (9α).—A solution of 824 mg (2.63 mmol) of 8α in 60 ml of ethyl acetate with 80 mg of 10% palladium on charcoal was hydrogenated at 30° and atmospheric

pressure (744 mm). After the uptake of 77.5 ml (3.08 mmol) of hydrogen, the reaction was terminated. The catalyst was removed by filtration and washed, and the solvent was evaporated to give 799 mg of white solid: λ_{max} 237 mμ (ε 9400, 71% 9α). Chromatography of the sample on 40 g of silica gel with 1–1.5% diethyl ether in benzene (19 × 40 ml) afforded 481 mg of impure 9α. Crystallization from methylene chloride–hexane afforded 323 mg (39%) of 17α-Δ⁵-pregnene-7,20-dione (9α), mp 133–134.5°.

An analytical sample was obtained by crystallization from methylene chloride–hexane: mp 134–134.5°; $\alpha^{30}D$ −255°; λ_{max} 236 mμ (ε 12,600); 5.88, 6.00, 6.14 μ; nmr τ 4.40 (1 H), 7.91 (3 H), 8.85 (3 H), 9.11 (3 H) ppm.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.92; H, 9.86.

17α-5α-Pregnane-7,20-dione (10α). A. From 17α-Δ⁸,⁵-Pregnadiene-7,20-dione (8α).—A 251-mg sample of 8α in 25 ml of ethyl acetate with 25 mg of 10% palladium on charcoal was hydrogenated at atmospheric pressure. After the absorption of hydrogen ceased, the catalyst was removed by filtration and evaporation of the solvent gave a white solid which was chromatographed on 20 g of silica gel. Elution with 5% diethyl ether in benzene (four 100-ml portions) gave 171 mg (68%) of 17α-5α-pregnane-7,20-dione (10α), mp 127–130°.

Crystallization of 10α from ethanol–water afforded the analytical sample: mp 130.5–131.5°; $\alpha^{30}D$ −132°; λ_{max} 5.88 μ; nmr τ 7.90 (3 H), 8.98 (3 H), 9.11 (3 H) ppm.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.86; H, 9.79.

B. From 17α-Δ⁵-Pregnene-7,20-dione (9α).—A 100-mg sample of 9α in 15 ml of ethyl acetate with 11 mg of 10% palladium on charcoal was hydrogenated at room temperature and atmospheric pressure. After the absorption of hydrogen ceased, the reaction was worked up as described above to give 99 mg of white solid. One crystallization from methanol–water gave 81 mg (81%) of 10α, mp 129–130.5°, identical with a sample prepared from 8α.

C. From 17α-5α-Pregnan-20ε-ol-7-one (15α).—A solution of 39 mg of the mixed C-20 alcohols 15α in 5 ml of acetone was flushed with nitrogen and oxidized as described above for 15β. Thin-layer and gas chromatography of the crude product showed it to be a single compound with an R_f value and retention time identical with those of an authentic sample of 10α. Crystallization from methanol–water afforded, in two crops, 20 mg (50%) of 10α, mp 130–131°, identical with an authentic sample.

Δ⁸,⁵-Pregnadiene-7ε,20ε-diol (13β).—To an ice-cold solution of 5.5 g of 8β in 200 ml of tetrahydrofuran (THF), 2 g of lithium-aluminum hydride was slowly added. The stirred reaction mixture was heated to reflux for 1 hr and then cooled in an ice bath. The excess $LiAlH_4$ was destroyed by the slow addition of aqueous THF. The precipitated aluminum hydroxide was removed by filtration through a Celite filter cake and washed with ethyl acetate. The combined solvents were evaporated to give 5.9 g (107%) of the mixed alcohols of Δ⁸,⁵-pregnadiene-7ε,20ε-diol (13β) as a white foam which was used without further purification: λ_{max} 235 mμ (ε 17,500); (CH_2Cl_2) 2.69, 2.82 μ.

Δ⁸,⁵-Pregnadien-20β-ol-7-one (14β).—A 5.5-g sample of crude 13β in 460 ml of dry chloroform was treated with 39 g of activated manganese dioxide (Beacon Chemical Co.) under nitrogen. The stirred solution was kept at room temperature for 36 hr. The manganese dioxide was removed by filtration through a Celite filter cake and washed with chloroform. Evaporation of the solvent left 5.3 g of a yellow glass: λ_{max} 278 mμ (ε 16,700, 78% 14β). Chromatography of the glass on 170 g of neutral alumina gave 1.7 g (31%) of Δ⁸,⁵-pregnadien-20β-ol-7-one (14β) used without further purification in the next step: mp 151.5–154.5°; λ_{max} 273 mμ (ε 20,600); (CH_2Cl_2) 2.72, 6.03, 6.15, 6.28 μ.

The remainder of the material contained 14β mixed with starting material which could be recycled.

5α-Pregnan-20β-ol-7-one (15β).—A 1.55-g (4.86 mmol) sample of 14β in 75 ml of ethyl acetate with 0.16 g of 10% palladium on charcoal was hydrogenated at room temperature and atmospheric pressure. The uptake of hydrogen ceased with the absorption of 254 ml (theoretical: 248 ml) of hydrogen. Removal of the catalyst by filtration and evaporation of the solvent gave 1.6 g of white solid which was crystallized alternately from benzene–hexane and methanol to give 700 mg of 5α-pregnan-20β-ol-7-one (15β): mp 155–156°; λ_{max} (CH_2Cl_2) 2.66, 5.90 μ; ORD (dioxane, c 0.1), $[\alpha]_{400}$ −220°, $[\alpha]_{350}$ −350°, $[\alpha]_{318}$ −760°, $[\alpha]_{285}$ 0°, $[\alpha]_{257}$ +150°. By concentration of the mother liquor an additional 530 mg (79% total yield) of 15β were obtained mp 150–152°. The acetate, prepared in the usual way, had mp 198–199° and $\alpha^{30}D$ −45° (lit.[13] mp 202–203°, $\alpha^{30}D$ −33°).

17α-Δ⁸,⁵-Pregnadiene-7ε,20ε-diol (13α).—A 421-mg sample of 8α in 50 ml of ice-cold tetrahydrofuran was treated with 0.40 g of lithium aluminum hydride. The reaction mixture was heated to reflux for 1 hr and cooled, and the excess $LiAlH_4$ was destroyed. After filtration through a Celite filter cake, the solvent was removed to give 406 mg (96%) of the mixed alcohols of 17α-Δ⁸,⁵-pregnadiene-7ε,20ε-diol (13α) as a colorless oil. The crude diol was used directly without further purification.

17α-Δ⁸,⁵-Pregnadien-20ε-ol-7-one (14α).—To a solution of 406 mg of 13α in 5 ml of dioxane were added 355 mg of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). After standing at room temperature for 28 hr the reaction mixture was filtered to remove the precipitated hydroquinone. The hydroquinone was washed with 20 ml of methylene chloride, and the combined filtrate and washings were evaporated. The residue was taken up in methylene chloride which was washed with a total of 90 ml of 10% sodium hydroxide and 70 ml of water and dried. Removal of the solvent left 301 mg of a red oil: λ_{max} 278 mμ (ε 18,400, 87% 14α). Chromatography of the oil on 9 g of neutral alumina with 8% diethyl ether in benzene (139-ml portions) gave a total of 195 mg (55%) of the mixed C-20 alcohols of 17α-Δ⁸,⁵-pregnadien-20ε-ol-7-one (14α) as an oil: λ_{max} ($CHCl_3$) 2.68, 6.06, 7.16, 6.28 μ. A second chromatography of the mixed alcohols failed to bring about their separation.

17α-5α-Pregnan-20ε-ol-7-one (15α).—An 84-mg (0.27 mmol) sample of 14α in 10 ml of ethyl acetate with 20 mg of 10% palladium on charcoal was hydrogenated at room temperature and atmospheric pressure. Hydrogen uptake ceased with the absorption of 7.5 ml of hydrogen. Removal of the catalyst by filtration and evaporation of the solvent left an oil which was chromatographed on 3 g of silica gel with 10% diethyl ether in benzene; 3-ml fractions were collected. A total of 43 mg of the mixed alcohols of 17α-5α-pregnan-20ε-ol-7-one (15α) were obtained as an oil: λ_{max} ($CHCl_3$) 2.69, 5.89 μ; ORD (dioxane, c 0.1), $[\alpha]_{400}$ −180°, $[\alpha]_{350}$ −285°, $[\alpha]_{318}$ −640°, $[\alpha]_{275}$ +260°.

7-Methylene-5α-pregnan-20-one (18β).—A five-necked round-bottomed flask was fitted with a nitrogen inlet, a thermometer well, an addition funnel, a rubber septum, and a partial take-off head. To 1.9 g (5.4 mmol) of methyltriphenylphosphonium bromide suspended in 30 ml of anhydrous ether, under nitrogen, was added 3.3 ml (5.4 mmol) of 1.6 *N* *n*-butyl lithium in *n*-hexane (Foote Mineral Co.). After the mixture was stirred for 2 hr, a solution of 343 mg (1.08 mmol) of 5α-pregnan-20β-ol-7-one (15β) in 70 ml of ether was added. The mixture was stirred at room temperature an additional 4 hr and allowed to stand overnight.

The ether was removed by distillation while being replaced with anhydrous tetrahydrofuran until the temperature of the reaction mixture reached 60–65°. The mixture was heated to reflux for 7.5 hr, cooled, and diluted with water. The crude product was extracted into ether which was washed with water and saturated sodium chloride and dried. Evaporation of the solvent yielded 1.13 g of a red solid which was chromatographed on silica gel with benzene. A total of 210 mg of material was obtained which was crystallized from methylene chloride–hexane to give 110 mg (32%) of 7-methylene-5α-pregnan-20β-ol (17β): mp 132–133°; λ_{max} 2.84, 6.10, 11.39 μ.

A 200-mg sample of crude 7-methylen-20β-ol was added to the reagent prepared from 2.5 ml of pyridine and 190 mg of chromic acid.[28] The reaction mixture was stirred for 30 min and allowed to stand at room temperature overnight. It was then poured into water and the crude product was collected by filtration. The filtrate was extracted with ether and the residue was taken up in the same solvent. The combined ether fractions were washed with water and saturated sodium chloride and dried to give 120 mg of crude product which was treated with Norit A and crystallized from aqueous methanol to yield 93 mg (47%) of 7-methylene-5α-pregnan-20-one (18β), mp 109–112°.

Crystallization from methylene chloride–hexane afforded the analytical sample: mp 111–111.5°; $\alpha^{27}D$ −1°; λ_{max} (CH_2Cl_2) 5.88, 6.09, 11.30 μ.

Anal. Calcd for $C_{22}H_{34}O$: C, 84.02; H, 10.90. Found: C, 83.95; H, 10.42.

(28) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 722 (1953).

Pregnane-3β,5α-diol-6,20-dione 3-Acetate (12β).—A 177-mg sample of **12α** in 18 ml of 1:1 dioxane–2 *N* methanolic potassium hydroxide was allowed to stand under nitrogen for 48 hr. The potassium hydroxide was neutralized with acetic acid, and the solvent was removed under reduced pressure at room temperature. The residue was taken up in ethyl acetate which was washed with water and dried. Removal of the solvent afforded a white solid which was acetylated overnight with a few drops of acetic anhydride in pyridine. The excess reagents were removed *in vacuo* at room temperature, and the residue chromatographed on silica gel with 20% ether in benzene. The appropriately combined fractions (determined by tlc) were crystallized alternately from methanol and chloroform–hexane to give 37 mg (21%) of pregnane-3β,5α-diol-6,20-dione 3-acetate (**12β**), mp 223–224.5°, identical with an authentic sample.[5]

Pregnane-3β,5α-diol-6,20-dione 3-Tosylate (21β).—To a 4.5-g sample of pregnane-3β,5α-diol-6,20-dione 3-acetate (**12β**) in 480 ml of ice-cooled methanol was added a solution of 22 g of potassium carbonate in 242 ml of water. The reaction mixture was stirred for 2 hr at room temperature. The potassium carbonate was neutralized with concentrated hydrochloric acid and the methanol removed under reduced pressure on the steam bath. The product was recovered by extraction into ethyl acetate which was evaporated to give 4.4 g (110%) of crude pregnane-3β,5α-diol-6,20-dione (**29β**) used without further purification.

The crude diol (4.4 g) was treated with 4.4 g of *p*-toluenesulfonyl chloride in 35 ml of pyridine. After standing at room temperature for 1 hr, the reaction mixture was kept at 0° overnight. The mixture was poured into water, and the crude product was taken up in ethyl acetate which was washed with dilute acid and water and dried. Removal of the solvent gave a solid which was crystallized from methylene chloride–isopropyl ether to give a total of 5.8 g (100%) of pregnane-3β,5α-diol-6,20-dione 3-tosylate (**21β**), mp 166–167°.

Crystallization from isopropyl ether afforded the analytical sample: mp 166–166.5° dec; $\alpha^{30}D$ −22°; λ_{max} ($CHCl_3$) 2.85, 5.85, 6.26, 8.55, 10.66, 11.61 μ.

Anal. Calcd for $C_{28}H_{38}O_6S$: C, 66.90; H, 7.62; S, 6.38. Found: C, 67.21; H, 7.77; S, 6.15.

Δ²-Pregnen-5α-ol-6,20-dione (22β).—A 4.0-g sample of the tosylate **21β** together with 10 g of Li_2CO_3 was heated for 2 hr under nitrogen in 200 ml of dimethyl sulfoxide. The dimethyl sulfoxide was removed by vacuum distillation, and the residue was taken up in ethyl acetate. The ethyl acetate was washed with water, dried, and evaporated to give 2.42 g of solid. This crude product was chromatographed on silica gel with 10% ether in benzene. A total of 1.29 g (49%) of Δ²-pregnen-5α-ol-6,20-dione (**22β**), mp 180–190° dec, was obtained which was used without further purification: λ_{max} (KBr), 2.86, 5.85, 5.92 μ.

Pregnan-5α-ol-6,20-dione (23β).—A solution of 454 mg (1.34 mmol) of **22β** in 65 ml of ethyl acetate with 45 mg of 10% palladium on charcoal was hydrogenated at 27° and atmospheric pressure (734 mm). After 1 hr 35.1 ml (theoretical, 34.3 ml) of hydrogen were absorbed. Filtration of the reaction mixture to remove the catalyst, and evaporation of the solvent gave 424 mg of solid. Crystallization from methanol yielded 344 mg (76%) of pregnan-5α-ol-6,20-dione (**23β**) used without further purification: mp 215–223° dec; λ_{max} 2.86, 5.86 (sh), 5.91 μ.

Δ²,⁴-Pregnadiene-6,20-dione (25β).—To a solution of 690 mg of **22β** in 4.5 ml of pyridine at 0° was added 0.25 ml of thionyl chloride. After 20 min the reaction mixture was diluted with water. The product was taken up in ethyl acetate which was washed with dilute acid and water and dried. Evaporation of the solvent gave 561 mg of a sticky, yellow solid: λ_{max} 315 mμ (ε 3260, 39% **25β**). Chromatography on silica gel with 4% ether in benzene afforded 227 mg of material. Treatment with decolorizing charcoal and crystallization from methylene chloride–hexane yielded 118 mg (18%) of Δ²,⁴-pregnadiene-6,20-dione (**25β**), mp 137.5–141°.

Crystallization from isopropyl ether gave the analytical sample: mp 142.5–144°; $\alpha^{27}D$ +97°; λ_{max} 313 mμ (ε 8400); 5.89, 6.01, 6.19, 6.52 μ.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.34; H, 8.87.

Δ⁴-Pregnene-6,20-dione (24β).—A 275-mg sample of **23β** in 5 ml of pyridine at 0° was treated with 0.5 ml of thionyl chloride. After 25 min the reaction mixture was treated as described in the preparation of **25β** above. Evaporation of the solvent gave 222 mg of a sticky, yellow solid: λ_{max} 241 mμ (ε 5600); 82% (**24β**). Chromatography on silica gel with 3% ether, followed by treatment with decolorizing charcoal and crystallization from methanol–water furnished 129 mg (50%) of Δ⁴-pregnene-6,20-dione (**24β**), mp 112.5–114°.

An analytical sample was obtained by crystallization from methanol–water: mp 116–117°; $\alpha^{27}D$ +102°; λ_{max} 239 mμ (ε 6800); 5.87, 5.92, 6.19 μ.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80,20; H, 9.67.

17α-Pregnane-3β,5α-diol-6,20-dione (29α).—To a solution of 2.5 g of **20α** in 220 ml of ice-cold methanol was added a solution of 1.9 g of potassium carbonate in 110 ml of water. After standing at room temperature for 2 hr, the reaction mixture was made neutral to litmus with concentrated hydrochloric acid and the methanol was removed under reduced pressure on the steam bath. The precipitated diol was taken up in ethyl acetate which was washed with water, dried, and evaporated to give 2.15 g (97%) of 17α-pregnane-3β,5α-diol-6,20-dione (**29α**), mp 262–272°. This impure diol was used without additional purification.

The analytical sample was prepared by crystallization from methanol and drying at the reflux temperature of toluene: mp 288–289.5°; $\alpha^{27}D$ −121°; λ_{max} 2.82, 2.94, 5.87 μ.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.62; H, 9.15.

17α-Pregnane-3β,5α-diol-6,20-dione 3-Tosylate (21α).—A mixture of 1.22 g of **29α** and 1.22 g of *p*-toluenesulfonyl chloride in 4.5 ml of pyridine was kept at room temperature for 2 hr and then at 0° overnight. Dilution of the reaction mixture with water followed by extraction with ethyl acetate which was washed with dilute acid, water, dried, and evaporated afforded 1.73 g (98%) of 17α-pregnane-3β,5α-diol-6,20-dione 3-tosylate (**21α**) as a tacky solid. The tosylate was used directly without purification.

Crystallization from isopropyl ether furnished an analytical sample: mp 169° dec; $\alpha^{27}D$ −112°; λ_{max} ($CHCl_3$) 2.84, 5.85, 6.25, 8.56, 10.67, 11.59 μ.

Anal. Calcd for $C_{28}H_{38}O_6S$: C, 66.90; H, 7.62; S, 6.38. Found: C, 66.59; H, 7.11; S, 6.07.

17α-Δ²-Pregnen-5α-ol-6,20-dione (22α).—A 1.63-g sample of the crude tosylate (**21α**) in 80 ml of DMSO containing lithium carbonate was heated under nitrogen at 100° for 5 hr. The DMSO was removed by vacuum distillation and the residue was taken up in ethyl acetate. The lithium carbonate was removed by filtration. The ethyl acetate was washed with water and dried. Evaporation of the solvent gave 1.14 g of a yellow solid. Chromatography on silica gel with 5% ether in benzene gave a total of 433 mg (40%) of 17α-Δ²-pregnen-5α-ol-6,20-dione (**22α**), mp 225–230°, used without further purification.

Crystallization from methylene chloride–isopropyl ether afforded an analytical sample: mp 231–233°; $\alpha^{30}D$ −117°; λ_{max} ($CHCl_3$) 2.70, 5.85, 6.03 μ; nmr τ 4.38 (2 H, br), 7.89 (3 H), 9.10 (3 H) 9.30 (3 H) ppm.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.21; H, 9.13.

17α-Pregnen-5α-ol-6,20-dione (23α).—A solution of 361 mg of **22α** in 50 ml of ethyl acetate with 40 mg of palladium on charcoal was hydrogenated at 22° and atmospheric pressure (744 mm). After 35 min, 33.9 ml of hydrogen were absorbed. The catalyst was removed by filtration through a Celite filter cake and washed with ethyl acetate. Evaporation of the combined filtrate and washings gave 371 mg (103%) of 17α-pregnan-5α-ol-6,20-dione (**23α**), mp 193–198°.

Crystallization from methylene chloride–isopropyl ether afforded the analytical sample: mp 208–209.5°; $\alpha^{27}D$ −153°; λ_{max} ($CHCl_3$) 2.84, 5.86 μ.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.83; H, 9.57.

17α-Δ²,⁴-Pregnadiene-6,20-dione (25α).—Thionyl chloride (0.35 ml) was added to a solution of 303 mg of 17α-Δ²-pregnen-5α-ol-6,20-dione (**22α**) in 4 ml of pyridine at 0°. After 20 min the reaction mixture was diluted with water. The product was taken up in ethyl acetate which was washed with dilute acid, dilute bicarbonate solution, water, and saturated sodium chloride solution and dried. Evaporation of the solvent yielded 274 mg of solid: λ_{max} 314 mμ (ε 3700), 48% **25α**. Chromatography on silica gel with 4% ether in benzene gave a total of 120 mg of material which was treated with Norit A and crystallized from methanol–water to give 75 mg (26%) of 17α-Δ²,⁴-pregnadiene-6,20-dione (**25α**), mp 144–147°.

The analytical sample was prepared by crystallization from methanol–water: mp 144.5–147.5°; $\alpha^{27}D$ −65°; λ_{max} 315 mμ (ε 7700); 5.89, 5.95, 6.15, 6.40 μ.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.45; H, 9.08.

17α-Δ⁴-Pregnene-6,20-dione (24α).—To a 366-mg sample of 17α-pregnan-5α-ol-6,20-dione (**23α**) in 3.3 ml of pyridine at 0° was added 0.5 ml of thionyl chloride. After 20 min the reaction mixture was diluted and treated as described above for the preparation of **25α** to give 266 mg of a yellow solid: λ_{max} 241 mμ (ε 5400, 80% **24α**). Chromatography on silica gel with 4% ether gave 193 mg of material which was crystallized from isopropyl ether–hexane to give 134 mg (42%) of 17α-Δ⁴-pregnene-6,20-dione (**24α**), mp 134–136°.

Crystallization from methylene chloride–hexane furnished the analytical sample: mp 134.5–136°; $\alpha^{30}D$ −49°; λ_{max} 240 mμ (ε 6800); 5.87, 5.96, 6.18 μ.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.10; H, 9.62.

17α-Δ⁴-Pregnen-3β-ol-6,20-dione Acetate (26α).—A 117-mg sample of 17α-pregnane-3β,5α-diol-6,20-dione 3-acetate (**20α**) in 0.5 ml of pyridine at 0° was treated with 0.02 ml of thionyl chloride as described above. Work-up gave 109 mg of a white solid: λ_{max} 234 mμ (ε 4200, 60% **26α**). Chromatography on neutral alumina with 10% ether in benzene followed by crystallization gave 48 mg (43%) of 17α-Δ⁴-pregnen-3β-ol-6,20-dione acetate (**26α**), mp 198–202°.

Crystallization from isopropyl ether afforded the analytical sample: mp 207–208°; λ_{max} 233 mμ (ε 7000); ($CHCl_3$) 5.76, 5.88, 6.10 μ.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.34; H, 8.74.

Registry Nos.—**7α**, 16649-44-8; **8α**, 16649-22-2; **9α**, 16703-88-1; **9β**, 16649-23-3; **10α**, 16649-24-4; **10β**, 16703-89-2; **11α**, 16649-45-9; **12α**, 16649-25-5; **12β**, 2723-04-8; **13β**, 16649-46-0; **14α**, 16649-27-7; **14β**, 16649-28-8; **15α**, 16649-29-9; **15β**, 16649-30-2; **17β**, 16649-31-3; **18β**, 16649-32-4; **19α**, 16720-14-2; **21α**, 16649-33-5; **21β**, 16703-90-5; **22α**, 16649-47-1; **22β**, 16649-34-6; **23α**, 16649-35-7; **23β**, 16649-36-8; **24α**, 16649-37-9; **24β**, 16703-91-6; **25α**, 16649-38-0; **25β**, 16649-39-1; **26α**, 16649-40-4; **27α**, 16649-41-5; **28α**, 16649-42-6; **29α**, 16649-43-7.

Acknowledgment—Financial assistance from the National Institutes of Health (Grant A-3943) and the Squibb Institute of Medical Research is gratefully acknowledged. A. P. B. also wishes to acknowledge receipt of a NASA Predoctoral Fellowship. The ORD curves were obtained through the courtesy of M. Marsh of Eli Lilly and Co. A stimulating discussion with Dr. P. Diassi is also acknowledged.

C-18-Functional Steroids. V.[1a] Synthesis of Androstane Derivatives[1b]

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Received March 12, 1968

Methods for the preparation of C-18 functional androstane and androstene derivatives from pregnane compounds are described. C-20-hydroxy steroidal 18-nitriles are dehydrated to give the $\Delta^{17,20}$-olefins. Hydroxylation with osmic acid followed by periodate cleavage gives the corresponding 17β-alcohols. Less successful is the Beckmann rearrangement of 20-oximes derived from 18-nitriles which gives rise to 17β-amines. Degradation of these amines gives rise to mixtures of alcohols and olefins.

In continuing our study of C-18-substituted steroids, the preparation of C-18-substituted androstane derivatives was required. Some of these compounds have been obtained by total synthesis,[2,3] by microbiological conversions,[4] from conessine,[5–7] from iodine–lead tetraacetate treatment of C-20 carboxamides followed by removal of C-20,[8] and from C-18-functional pregn-20-ones *via* a Baeyer–Villiger degradation.[9] The present compounds were made by application of the Barton reaction to pregnane derivatives. A few of the substances obtained recently have been prepared from conessine.[10]

The synthetic problem involved was that a side chain is needed for the functionalization step[11] but its removal is necessary to obtain the final product. Since a method applicable to 3-keto-Δ⁴ analogs was sought, the use of ozonolysis, etc., for side-chain oxidation was contraindicated. A mild method, involving elimination, osmylation, and periodate cleavage was therefore employed. Although the 3-keto-Δ⁴ system is capable of reacting with OsO_4,[12] the side chain was attacked selectively under the conditions we employed.

Treatment of 20α-hydroxy-5α-pregnane with nitrosyl chloride in pyridine solution gave the corresponding nitrite ester which on photolysis furnished the 18-oxime **1**.[10a] Dehydration with acetic anhydride afforded the nitrile **2**[10a] (Scheme I). Saponification of the ester followed by treatment with *p*-toluenesulfonyl chloride produced the tosylate **4**. Elimination formed the *trans*-olefin **5**, the stereochemistry of which was assigned on the basis of the nmr spectrum as in our previous work.[1a] Hydroxylation with OsO_4 furnished one predominant diol, presumably the 20β-hydroxy compound

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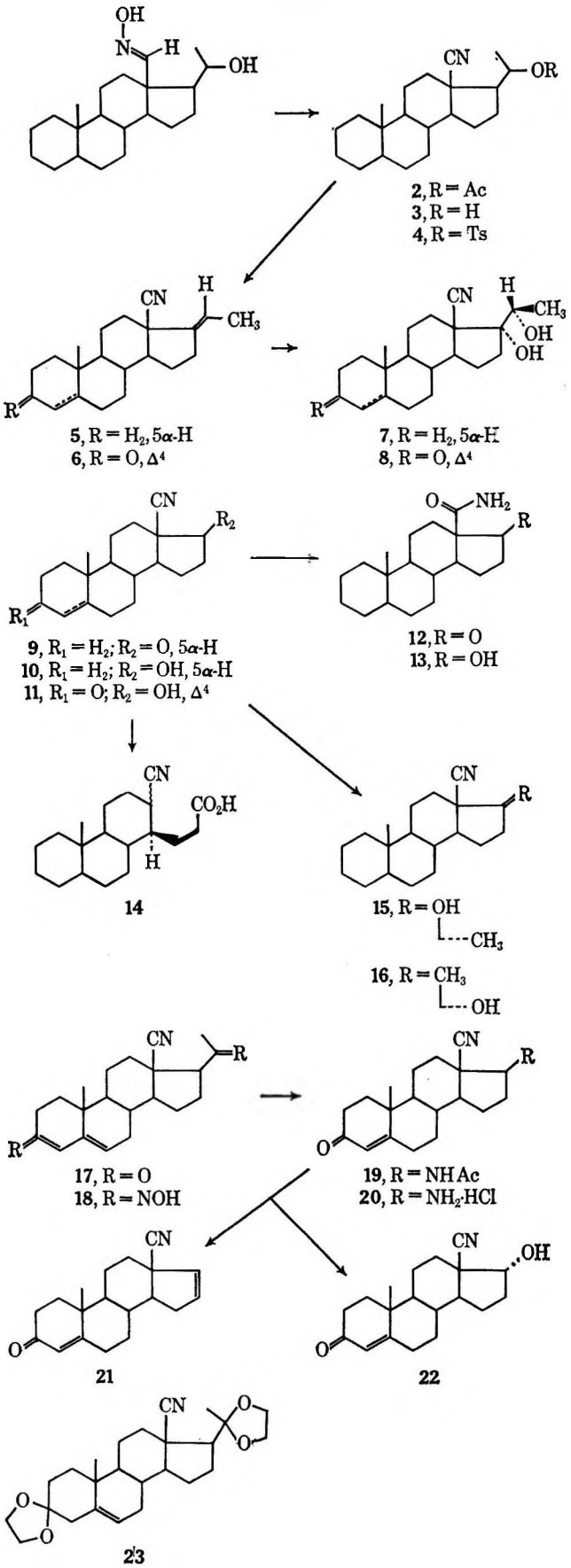
SCHEME I



7. Cleavage with periodic acid[13] gave the 17-ketone **9**, which on reduction with LiAl(*t*-BuO)$_3$H afforded the 17β-ol **10**. The 17β configuration of the hydroxyl group was expected from the steric course of reduction and was further substantiated by the broad triplet[14] at 231 Hz due to the 17α proton in the nmr spectrum. The 17-methyl derivatives **15** and **16** were obtained by treatment of **9** with CH_3MgBr. The 17β-methyl configuration was assigned to **16**, in which deshielding of the methyl group by the nitrile function was evident in the nmr spectrum. Attempted hydrolysis of **9** with sodium hydroxide gave, *via* a reverse enolate condensation, a mixture of seco steroid C-13 epimers **14**, as shown by two angular methyl resonances and a D_2O exchangable proton resonance centered at 457 Hz in the nmr spectrum. A proton at 178 Hz, due to the 13-H which is geminal to the nitrile group, was also present. Successful hydrolysis of **9** to the 18-carboxamide **12** was achieved with sulfuric acid and reduction at C-17 gave **13**. The 3-keto-Δ^4 compounds **8** and **11** were obtained from **6**[1a] in analogous fashion.

A less fruitful removal of the side chain in the 3-keto-Δ^4 series involved the Beckmann rearrangement of C-20 oximes.[15]

Conversion of progesterone-18-nitrile[16] into the 3,20-bisethylenedioxy compound **23** was not a useful approach since the C-20 protecting group could not be hydrolyzed selectively. Enol ether formation at C-3 gave **17** which afforded the 20-oxime **18**. Beckmann rearrangement with $POCl_3$ gave in low yield the amide **19**, which on hydrolysis with concentrated HCl gave the amine **20**. Treatment of **20** with nitrous acid gave two products—one was the olefin **21** as shown by the nmr spectrum. The second compound, **22**, was shown to be a 17α-alcohol by nmr spectroscopy. The signal due to the 17β proton[14] was a broad doublet rather than a triplet as expected for a 17α proton. Moreover, the signal appeared 30 Hz downfield from the expected value for the 17β-hydroxy compound due to shielding by the nitrile group (*cf.* **11**). The course of the deamination differs in 18-nonfunctional steroids[17] but is similar in simple cyclopentylamines.[18]

Experimental Section[19]

18-Oximino-5α-pregnan-20α-ol (1).—Nitrosyl chloride was bubbled into a stirred, ice-cold solution of 8.5 g of 20α-hydroxy-5α-pregnane in pyridine, until a greenish brown color persisted. The resulting suspension was stirred for 5 min and poured into ice–water. The resulting precipitate was collected giving 9.0 g of 20α-hydroxy-5α-pregnane nitrite: ν_{max}^{KBr} 1645, 1605 cm^{-1}; nmr 44 (18-H$_3$), 48 (19-H$_3$), 84 (21-H$_3$, J = 6.5 Hz), 328 Hz (20-H, broad). The nitrite ester was air dried, dissolved in 200 ml of toluene, and subjected to photolysis for 6 hr with a 200-W

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(19) Melting points were determined with a Thomas–Hoover apparatus equipped with a corrected thermometer. Infrared spectra were obtained with a Beckman IR-8 or Perkin-Elmer 337 instrument. Microanalyses were performed by the Microanalytical Department, University of California at Berkeley. Optical rotations were obtained in a 0.5-dm tube with a Rudolph photoelectric polarimeter. Nmr spectra were obtained at a field strength of 60 MHz on samples in deuteriochloroform solution on a Varian A-60 or A-60A instrument, using tetramethylsilane as internal standard. When only small amounts of sample were available, a Varian C-1024 computer was used for time averaging.

medium-pressure mercury lamp equipped with a Pyrex filter. The solid which precipitated during the photolysis was separated to give 1 g of product. A second crop, mp 187–191°, obtained by concentration and washing with hexane, weighed 3 g. Recrystallization from benzene–hexane gave pure material: mp 198–200° (lit.[10a] mp 197–198° when prepared in another way); ν_{max}^{KBr} 3320, 3175, 3080 cm^{-1}; nmr 45.5 (19-H$_3$), 71 (21-H$_3$, J = 6.0 Hz), 238 (20-H, broad), 446 Hz (18-H).

20α-Hydroxy-5α-pregnane-18-nitrile Tosylate (4).—The product was obtained by treatment of 20α-hydroxy-5α-pregnane-18-nitrile[10] with p-toluenesulfonyl chloride in pyridine. Recrystallization from hexane–benzene gave the analytical sample: mp 133–136°; $[\alpha]^{20}D$ −67° (c 0.006, $CHCl_3$); nmr 48 (19-H$_3$), 83 (21-H$_3$) (J = 6.0 Hz), 287 (20-H, broad), 146 Hz (CH$_3$ of p-tosyl group).

Anal. Calcd for $C_{28}H_{39}NO_3S$: C, 71.60; H, 8.37; N, 2.98; S, 6.82. Found: C, 71.47; H, 8.11; N, 2.99; S, 6.74.

5α-Pregn-17-ene-18-nitrile (5).—A solution of 1.7 g of **4** in 50 ml of pyridine was heated under reflux for 3 days, poured into ice–water, and filtered. The precipitate (0.5 g) was purified by preparative tlc on silica gel to give 0.2 g of **5**, and 0.25 g of recovered **4**. The filtrate was evaporated to recover an additional 1.1 g of **4**. Compound **5** was recrystallized from methylene chloride to give the analytical sample: mp 90–91°; $[\alpha]^{20}D$ −38° (c 0.34, $CHCl_3$); nmr 50 (19-H$_3$), 96 Hz (21-H$_3$, J = 6.5 Hz).

Anal. Calcd for $C_{21}H_{31}NO$: C, 84.79; H, 10.50; N, 4.92. Found: C, 85.07; H, 10.42; N, 4.92.

17α,20β-Dihydroxy-5α-pregnane-18-nitrile (7).—A solution of 0.5 g of osmium tetroxide in 10 ml of anhydrous ether was added to a solution of 0.4 g of **5** in 40 ml of anhydrous ether. The solution turned black on mixing and was left for 48 hr at 27°. After evaporation of the solvent, the residue was dissolved in 50 ml of ethanol and mixed with a solution of 2.5 g of sodium sulfite in 120 ml of water. It was refluxed for 2 hr and filtered while hot. The residue was washed with a large quantity of hot ethanol and then with ether. The combined filtrate and washings were taken to dryness and the solid was treated with water and filtered. After washing with water, the solid was purified by preparative tlc to give 0.3 g of **7**: mp 172–173°; $[\alpha]^{20}D$ +41° (c 0.11, $CHCl_3$); nmr 49.5 (19-H$_3$), 73 (21-H$_3$, J = 6.0 Hz), 260 Hz (20-H, quartet, J = 6.0 Hz).

Anal. Calcd for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03; N, 4.23. Found: C, 76.24; H, 9.93; N, 4.31.

17α,20β-Dihydroxypregn-4-en-3-one-18-nitrile (8).—A solution of 0.5 g of 6[16] in 40 ml of anhydrous ether was hydroxylated with OSO_4 as described for **7**. Purification by preparative tlc gave 0.3 g of **8**: mp 241–242° after recrystallization from hexane–benzene–ethanol; $[\alpha]^{20}D$ +89° (c 0.32, $CHCl_3$); ν_{max}^{KBr} 3520, 3415, 2225, 1655, 1620 cm^{-1}; nmr 74 (19-H$_3$), 74 (21-H$_3$, doublet, J = 6.0 cps), 261 (20-H$_3$, quartet, J = 6.0 Hz), 345 Hz (4-H).

Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.26; H, 8.27; N, 4.13.

17-Oxo-5α-androstane-18-nitrile (9).—To a solution of 0.25 g of **7** in 50 ml of ethanol, there was added 10 ml of 10% aqueous $HIO_4 \cdot 2H_2O$. The solution was stirred with a magnetic stirrer for 12 hr and evaporated to dryness. The residue was washed with water and filtered giving 0.22 g of material showing one spot on tlc. Recrystallization from hexane gave the analytical sample: mp 139–141°; $[\alpha]^{20}D$ +42° (c 0.26, $CHCl_3$); ν_{max}^{KBr} 2230, 1770 cm^{-1}; nmr 51 Hz (19-H$_3$).

Anal. Calcd for $C_{19}H_{27}NO$: C, 79.95; H, 9.53; N, 4.91 Found: C, 79.85; H, 9.38; N, 5.06.

17β-Hydroxy-5α-androstane-18-nitrile (10).—A stirred solution of 0.18 g of **9** in anhydrous ether–tetrahydrofuran was cooled in ice and 0.8 g of LiAl(t-BuO)$_3$H was added. After 3 hr under ice cooling the excess reagent was decomposed with 5% acetic acid and the solution was extracted with ether. Evaporation of the solvent gave 0.15 g of solid which showed mainly one spot on tlc. Purification with preparative tlc and recrystallization from hexane gave the analytical sample: mp 180–183°; $[\alpha]^{20}D$ +13° (c 0.2, $CHCl_3$) (lit.[10b] mp 180°; $[\alpha]D$ +7° when prepared in another way); ν_{max}^{KBr} 3280 (broad), 2235 cm^{-1}; nmr 50 Hz (19-H$_3$).

Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 80.06; H, 9.49; N, 4.72.

17β-Hydroxyandrost-4-en-3-one-18-nitrile (11).—The product from periodate cleavage (*cf.* compound **9**) of **8** was purified by preparative tlc. A stirred ice-cold solution of 0.08 g of the cleavage product and 0.5 g of LiAl(t-BuO)$_3$H in 2 ml of tetrahydrofuran was stirred for 3 hr. The excess reagent was decomposed with 5% acetic acid and the solution was extracted with ether. The residue obtained on evaporation of ether showed mainly one tlc spot. It was dissolved in 20 ml of chloroform and stirred with 1 g of MnO_2 for 18 hr. The MnO_2 was filtered off and washed with chloroform several times. The combined chloroform solution was evaporated to dryness. The residue showed mainly one spot on tlc. Purification by preparative tlc gave 0.07 g of **11**: mp 193–194°; $[\alpha]^{20}D$ +149° (c 0.2, $CHCl_3$) (lit.[10b] mp 188°; $[\alpha]D$ +5° when prepared in another way).

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 75.98; H, 8.23; N, 4.90.

17-Oxo-5α-androstan-18-carboxamide (12).—To 0.1 g of **9** there was added 1.5 ml of concentrated H_2SO_4 and 0.2 ml of water. This mixture, under nitrogen, was heated in an oil bath kept at 87° for 2.5 hr. It was cooled and poured into ice–water. The resulting precipitate was filtered and washed with water several times. Purification by preparative tlc gave 0.07 g of **12**: mp 167–168°; $[\alpha]^{20}D$ −38° (c 0.2, $CHCl_3$); ν_{max}^{KBr} 3500, 3460, 3400, 3300, 3180, 1740, 1690, 1630, 1600 cm^{-1}; nmr 47 Hz (19-H$_3$).

Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.62. Found: C, 75.38; H, 9.48; N, 4.83.

17β-Hydroxy-5α-androstane-18-carboxamide (13).—The product, obtained from LiAl(t-BuO)$_3$H reduction (*cf.* compound **11**) of 0.03 g of **12**, was purified by preparative tlc followed by recrystallization from hexane–benzene giving material of mp 211–213°; $[\alpha]^{20}D$ −11° (c 0.046, $CHCl_3$); ν_{max}^{KBr} 3450–3150 (broad), 1655, 1605 cm^{-1}; nmr 46 Hz (19-H$_3$).

Anal. Calcd for $C_{19}H_{31}NO_2$: N, 4.59. Found: N, 4.68.

13,17-Seco-5α,13ξ-androstan-17-oic Acid 18-Nitrile (14).—A solution of 0.1 g of **9** and 0.1 g of KOH in methanol was refluxed under nitrogen for 18 hr. On acidification with acetic acid, solid material precipitated which was purified by preparative tlc. Recrystallization from hexane–benzene gave the analytical sample: mp 166–168°; $[\alpha]^{20}D$ −48° (c 0.14, $CHCl_3$); nmr 43, 47.5 (both due to 19-H$_3$), 457 Hz (COOH, disappeared on addition of D_2O).

Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.62. Found: C, 75.09; H, 9.42; N, 4.67.

17β-Hydroxy-17α-methyl-5α-androstane-18-nitrile (15) and 17α-Hydroxy-17β-methyl-5α-androstane-18-nitrile (16).—To a solution of 0.1 g of **9** in 5 ml of anhydrous tetrahydrofuran and 5 ml of anhydrous ether, there was added slowly 3 ml of an ethereal 3 M methylmagnesium bromide solution. After refluxing for 10 hr, the reaction mixture was poured into ice–water and acidified with HCl to pH 1. It was extracted with ether and the combined extract was washed with water until the washings were neutral. Evaporation of the solvent gave a solid which showed (three) spots on tlc. Purification by preparative tlc gave, as the major product, 0.04 g of **15**: mp 169–170°; $[\alpha]^{20}D$ −13° (c 0.19, $CHCl_3$); ν_{max}^{KBr} 3455, 2240 cm^{-1}; nmr 50.5 (19-H$_3$); 75 Hz (17α-CH$_3$).

Anal. Calcd for $C_{20}H_{31}NO$: C, 79.68; H, 10.36; N, 4.65. Found: C, 79.73; H, 10.45; N, 4.75.

A second product, weighing 0.02 g, was identified as **16**: ν_{max}^{KBr} 3480, 2235 cm^{-1}; nmr 50 (19-H$_3$), 90.5 Hz (17β-CH$_3$).

Anal. Calcd for $C_{20}H_{31}NO$: C, 79.68; H, 10.36; N, 4.65. Found: C, 79.35; H, 10.13; N, 4.97.

A very small amount of **9** was recovered.

20-Oxopregna-3,5-diene-18-nitrile 3-Methyl Ether (17).—A solution of 2.0 g of 3,20-dioxopregn-4-ene-18-nitrile[16] and 0.10 g of p-toluenesulfonic acid in 20 ml of 2,2-dimethoxypropane and 20 ml of dimethylformamide was heated under reflux for 6 hr. After cooling, the solution was made alkaline with dilute NaOH solution and poured into ice–water. Recrystallization of the precipitated product from methylene chloride gave 1.8 g of sample: mp 202–207°; $[\alpha]^{20}D$ −51° (c 1, $CHCl_3$); nmr 60 (19-H$_3$), 132 (21-H$_3$), 214 Hz (3-CH$_3$O).

Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 76.97; H, 8.51; N, 4.26.

20-Oximinopregn-3,5-diene-18-nitrile 3-Methyl Ether (18).—A solution of 1.2 g of **17** and 1.2 g of hydroxylamine hydrochloride in pyridine was kept for 18 hr at 27° and poured into an ice–water mixture, and the resulting precipitate was collected. Recrystallization resulted in 0.90 g of analytical sample: mp 204–205°; $[\alpha]^{20}D$ −103° (c 1, $CHCl_3$); ν_{max}^{KBr} 3440, 3200, 2225, 1655, 1630 cm^{-1}; nmr 60.5 (19-H$_3$), 119 (21-H$_3$), 215 Hz (3-CH$_3$O).

Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.23; H, 8.36; N, 8.07.

3-Oxo-17β-acetamidoandrost-4-ene-18-nitrile (19.)—A solution of 0.5 g of **18** in 2.0 ml of pyridine was cooled in an ice bath and 1 ml of cold phosphorus oxychloride was added dropwise, while maintaining the temperature below 15°. After 3 hr, the mixture was poured into cold dilute HCl. This solution was extracted with methylene chloride and the combined extracts were washed with water and dried (Na_2SO_4). When the gummy residue from evaporation of the dried solvent was chromatographed on alumina, 0.20 g of 3,20-dioxopregn-4-ene-18-nitrile was recovered together with 0.06 g of **19**: mp 294–296°; $[\alpha]^{20}D$ +15° (*c* 1, $CHCl_3$); ν_{max}^{KBr} 3340, 2225, 1685, 1663, 1610, 1535 cm^{-1}; nmr 74 (19-H_3), 123 (CH_3CO–), 257 (17α-H, two broad peaks), 368 Hz (17β-NH, two broad peaks).

Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.84; H, 8.09; N, 8.45.

17β-Aminoandrost-4-en-3-one-18-nitrile Hydrochloride (20).—To a solution of 0.27 g of **18** in 2 ml of ethanol and a small amount of tetrahydrofuran, there was added 2 ml of concentrated HCl. The solution was refluxed for 24 hr and poured into ice–water. The precipitate which formed (0.1 g) was filtered and shown to be starting material. The filtrate was evaporated to dryness under vacuum giving 0.15 g of almost pure **20**. Recrystallization from methylene chloride gave a hygroscopic sample: mp 240°; $[\alpha]^{20}D$ +90° (*c* 0.082, $CHCl_3$).

Anal. Calcd for $C_{19}H_{29}N_2OCl$: N, 8.37; Found: N, 8.60.

Androst-4,16-dien-3-one-18-nitrile (21) and 17α-Hydroxyandrost-4-en-3-one-18-nitrile (22).—To a stirred, ice-cold solution of 0.15 g of **20** in 2 ml of 50% acetic acid, there was added, dropwise, a solution of 0.5 g of $NaNO_2$ in 2 ml of 50% acetic acid. After 18 hr at 27° the solution was made alkaline and extracted with ether. The ethereal extract was mixed with 2 ml of 5% methanolic KOH solution and stirred for 0–5 hr. After addition of water and back extraction with ether, the combined ethereal extracts were evaporated to dryness giving solid material. Purification by preparative tlc resulted in two products. The major product (0.04 g) was shown to be **21**: mp 128–130° after recrystallization from hexane–benzene; $[\alpha]^{20}D$ +224° (*c* 0.19, $CHCl_3$).

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.82; H, 8.16; N, 5.19.

The minor product (25 mg) was **22** as indicated by the doublet of the 17β proton. Recrystallization from hexane–benzene gave the analytical sample: mp 183–185°.

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.33; H, 7.67; N, 5.89.

3,20-Bismethylenedioxypregn-5-ene-18-nitrile (23).—3,20-Dioxopregn-4-ene-18-nitrile[16] (0.80 g) was dissolved in 15 ml of hot ethylene glycol. The solution was acidified with 0.10 g of *p*-toluenesulfonic acid and very slowly distilled at 1.5 mm at 70° for 3 hr. The resulting suspension was made alkaline with a small amount of methanolic KOH and poured into an excess of ice-water. Recrystallization of the preciptated product from methylene chloride–hexane gave the analytical sample: mp 195–197°; $[\alpha]^{20}D$ −32° (*c* 1, $CHCl_3$); nmr 64 (19-H_3), 79 (21-H_3), 235 (20-ketal-H_4, slightly broad), 241 Hz (3-ketal-H_4).

Anal. Calcd for $C_{25}H_{35}NO_4$: C, 72.61; H, 8.53; N, 3.39. Found: C, 72.86; H, 8.26; N, 3.68.

Registry No.—**1**, 14418-17-8; 20α-hydroxy-5α-pregnane nitrite, 16797-50-5; **4**, 16778-28-2; **5**, 16778-29-3; **7**, 16778-30-6; **8**, 16778-31-7; **9**, 13583-64-7; **10**, 13583-63-6; **11**, 16778-34-0; **12**, 16797-45-8; **13**, 16797-46-9; **14**, 16797-49-2; **15**, 16777-99-4; **16**, 16778-00-0; **17**, 16778-01-1; **18**, 16778-02-2; **19**, 16778-03-3; **20**, 16778-04-4; **21**, 16797-47-0; **22**, 16778-05-5; **23**, 16778-06-6.

The Action of Bromine on a Chol-7-enic Acid Derivative

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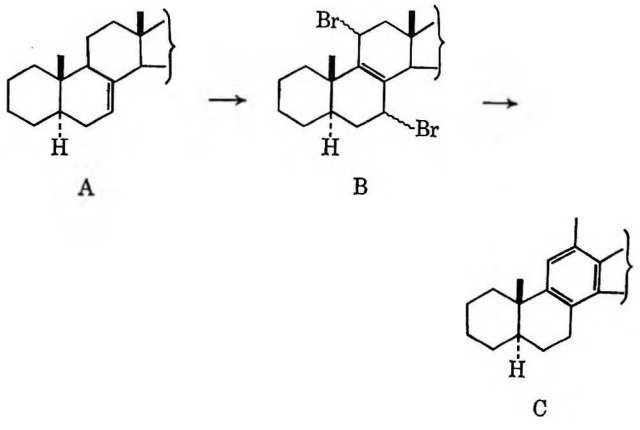
Received March 7, 1968

The behavior of a ring A/B *cis*-fused steroid unsaturated at C-7 toward bromine differs from that of the corresponding unsaturated ring A/B *trans*-fused steroids. On treatment with bromine, methyl 3α-ethoxycarbonyloxychol-7-enate yields methyl 14ξ-bromo-3α-ethoxycarbonyloxychol-7-enate. This allylic halide on dehydrobromination with silver acetate or alumina gives methyl 3α-ethoxycarbonyloxychola-7,14-dienate, and on debromination with zinc gives a mixture of methyl 3α-ethoxycarbonyloxychol-7-enate and methyl 3α-ethoxycarbonyloxychol-8-enate.

It has been shown[1] that bromine reacts with Δ^7-unsaturated steroids having rings A/B *trans*-fused (general part structure A) to yield, as major products, the 7,11-dibromo-Δ^8-unsaturated derivatives (part structure B) which are readily transformed into ring C benzenoid steroids (part structure C).[2,3] To ascertain if this route is feasible for the preparation of ring C benzenoid steroids in which rings A/B are *cis*-fused, we have examined the action of bromine on a Δ^7-unsaturated steroid derived from cholic acid.



Methyl cholate was selectively and quantitatively converted into the 3-ethoxycarbonyl derivative (**1**)[4] which was then dehydrated by the action of phosphorus oxychloride in pyridine to yield the known $\Delta^{7,11}$-diene (**2**)[5,6] (Scheme I). It has been reported[6] that the diene (**2**) undergoes selective hydrogenation of the Δ^{11}-ethylenic bond with platinum catalyst in acetic acid solution to yield the desired ester, methyl 3α-ethoxycarbonyloxychol-7-enate (**4**). In our hands, however, these condi-

(1) C. F. Hammer and R. Stevenson, *Steroids*, **5**, 637 (1965).

(2) C. F. Hammer, D. S. Savage, J. B. Thomson, and R. Stevenson, *Tetrahedron*, **20**, 929 (1964).

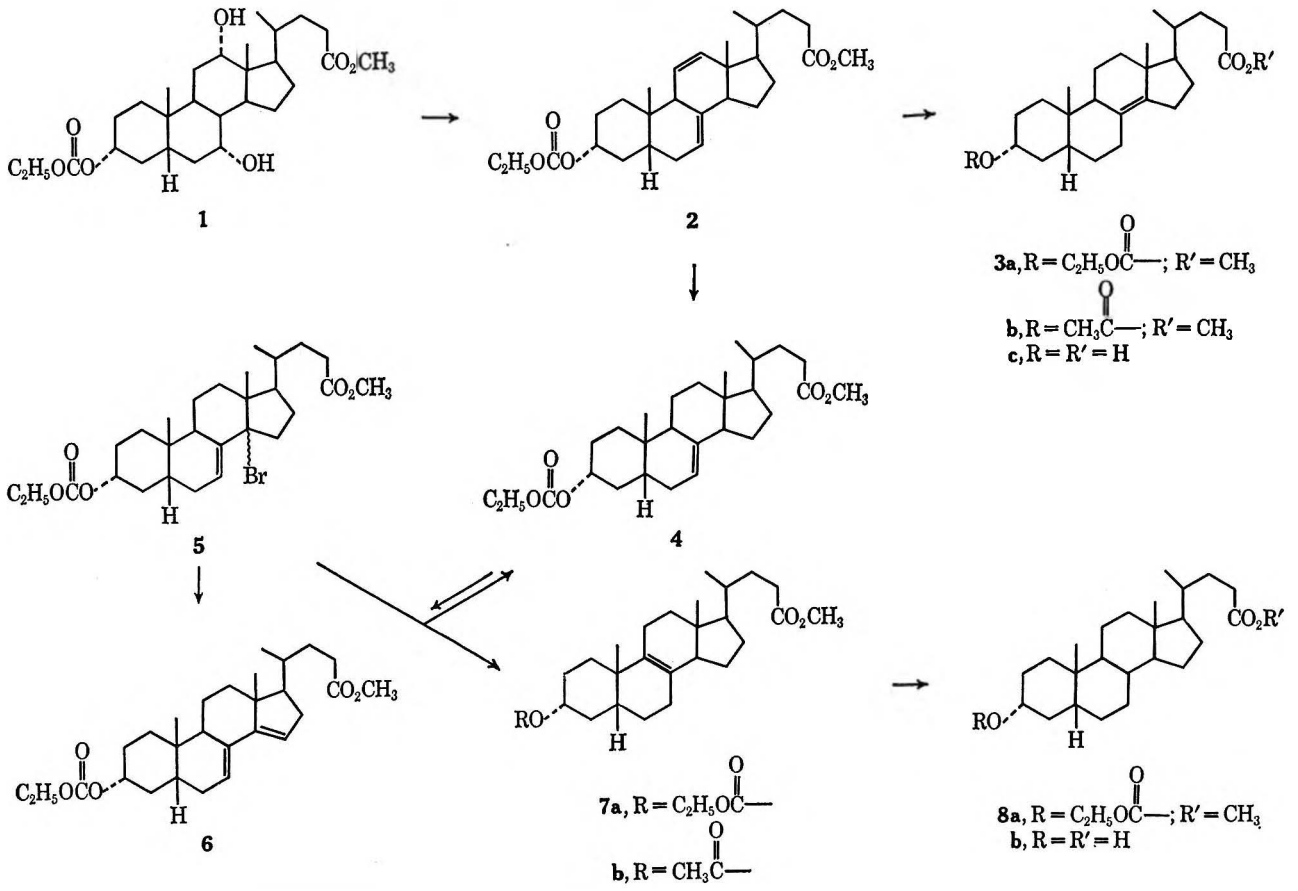
(3) T. N. Margulis, C. F. Hammer, and R. Stevenson, *J. Chem. Soc.*, 4396 (1964).

(4) L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.*, **71**, 3935 (1949).

(5) K. Yamasaki and I. Ushizawa, *Proc. Jap. Acad.*, **28**, 546 (1952).

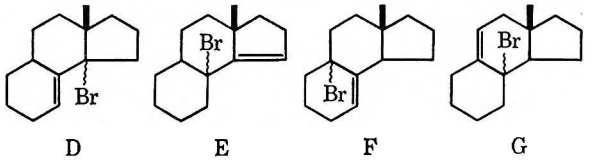
(6) F. Nakada, *Steroids*, **2**, 45 (1963).

SCHEME I



tions resulted in isolation of the $\Delta^{8(14)}$ isomer (**3a**).[7] In contrast, when the reduction was performed in ethyl acetate solution with palladium–carbon catalyst, the Δ^{7} isomer (**4**) was readily obtained. (See Scheme I.)

Treatment of this methyl chol-7-enate derivative (**4**) with bromine, using the procedures developed for ergostene and cholestene analogs,[1,8] yielded a rather unstable product (solutions in the common solvents rapidly darkened) which gave a positive Beilstein test and a positive unsaturation test with tetranitromethane. Elemental analysis indicated an empirical formula $C_{28}H_{43}BrO_5$, which is in marked contrast to the behavior of Δ^{7}-A/B *trans* systems, in which two bromine atoms are introduced into the ring system. The similarity of the ultraviolet spectrum (λ 254 mμ, ϵ 6900) to that reported[1] for 7,8,22,23-tetrabromoergost-14-en-3β-yl acetate (λ 253 mμ, ϵ 7600) suggested that the halogen atom was situated in an allylic position. This conclusion, coupled with evidence from the integrated nmr spectrum that the bromination product had *one* vinyl proton, led us to regard one of the compounds represented by part structure (D, E, F, G) as most probable.



D E F G

A distinction among these was sought by identification of the products of dehydrobromination and of debromination.

The allyl bromide underwent dehydrobromination on treatment with silver acetate to yield a product whose ultraviolet spectrum (λ 248 mμ, ϵ 11,500) indicated the presence of a cisoid heteroannular diene chromophore and which was accordingly formulated as methyl 3α-ethoxycarbonyloxychola-7,14-dienate (**6**). Evidence in support of this structure was obtained by catalytic hydrogenation to yield the known methyl 3α-ethoxycarbonyloxychol-8(14)-enate (**3a**), further characterized by hydrolysis to 3α-hydroxychol-8(14)-enic acid (**3c**). The diene (**6**) could also be simply obtained by filtration of the allyl bromide through chromatographic alumina. The identification of the dehydrobromination product (**3a**) established that no molecular rearrangement had occurred during the bromination or dehydrobromination steps, and also rendered part structures F and G unlikely representations of the allyl bromide.

Debromination of the allyl bromide in acetic acid by zinc dust yielded a sharp-melting product, $C_{28}H_{44}O_5$. The complexity of the nmr spectrum, particularly in the methyl group resonance region, indicated however that the product was a mixture. Catalytic hydrogenation of the mixture in a solution of acetic acid and hydrochloric acid, conditions devised to isomerize Δ^{7}, Δ^{8}, and $\Delta^{8(14)}$ double bonds to the Δ^{14} position where reduction is known to occur,[9] yielded methyl 3α-ethoxycarbonyloxycholanate (**8a**), characterized by hydrolysis to cholanic acid (**8b**). This finding suggested that the debromination mixture consisted of ethoxycarbonyloxy esters of isomeric methyl cholenates. Since the inte-

(7) F. Nakada, *Steroids.*, **2**, 403 (1963).

(8) R. C. Anderson, R. Stevenson, and F. S. Spring, *J. Chem. Soc.*, 2901 (1952).

(9) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 425–427.

grated nmr spectrum of the debromination product revealed only a fraction of one vinyl proton, this could best be interpreted as the mixture being constituted of two alkenes, one of which had a trisubstituted and the other a tetrasubstituted double bond. A mixture of Δ^7 or Δ^{14} and Δ^8 or $\Delta^{8(14)}$ isomers would most reasonably satisfy this requirement. The expected C-18 and C-19 methyl group resonances of these four isomers (Δ^7, Δ^8, $\Delta^{8(14)}$, and Δ^{14}) were calculated using the characteristic substituent frequency shift data compiled by Zürcher[10] and are tabulated as τ values (Table I). Since the

TABLE I

RESONANCE, τ

	Δ^7	Δ^8	$\Delta^{8(14)}$	Δ^{14}
C-18	9.47	9.43	9.17	9.10
C-19	9.07	8.93	9.17	9.05

methyl group region of the nmr spectrum of the debromination product had signals at τ 9.46, 9.37, 9.13 and 8.97, this implied that the mixture consisted of the Δ^7 and Δ^8 isomers and, from the intensities, in a ratio of approximately 1:2, respectively. This was firmly established by crystallization of a mixture of authentic methyl 3α-ethoxycarbonyloxychol-7-enate (**4**) and methyl 3α-ethoxycarbonyloxychol-8-enate (**7a**) in a ratio of 1:2 to give the sharp melting product, identical with that obtained by zinc debromination of the allylic bromide which is consequently formulated as methyl 14-bromo-3α-ethoxycarbonyloxychol-7-enate (**5**).

The failure of the chol-7-enic acid derivative to yield on bromination the corresponding 7,11-dibromochol-8-enic acid, the precursor necessary for aromatization of ring C led us to seek successfully alternative pathways to achieve this objective.[11] Further interest in the development of routes to ring C aromatic steroids, related particularly to steroid hormones, is evident in two recent communications,[12,13] in both of which the ring C aromatic hormone analog products lack asymmetry at C-5 and hence complement the series.

Experimental Section

Melting points were determined using a Gallenkamp melting point apparatus. Rotations were measured in chloroform solution and ultraviolet absorption spectra in ethanol solution unless otherwise stated. Nuclear magnetic resonance spectra were determined in deuteriochloroform solution with tetramethylsilane as an internal standard, using a Varian 4300 B spectrometer at 60 Mc.

Methyl 3α-Ethoxycarbonyloxy-7α,12α-dihydroxycholanate (1).—Ethyl chloroformate (30 ml) was added to a solution of methyl cholate (20 g) in pyridine (50 ml) and the mixture was allowed to stand at room temperature for 1 hr, then worked up in the usual way *via* ether. Crystallization from ether yielded **1** (21.8 g), mp 176–178° (lit.[4,5] mp 176–178°).

Methyl 3α-Ethoxycarbonyloxychola-7,11-dienate (2).—Phosphorus oxychloride (53 g) was added to a solution of methyl 3α-ethoxycarbonyloxy-7α,12α-dihydroxycholanate (10 g) in pyridine (80 ml) and the mixture was kept at 50° for 24 hr, then cooled, diluted with ice water (100 ml), and extracted with ether. Evaporation of the washed and dried extract yielded an oil that crystallized from ether–methanol to yield the diene as plates (5.1 g), mp 105–107° (lit.[5] mp 105–108°).

Methyl 3α-Ethoxycarbonyloxychol-8(14)-enate (3a).—Platinum dioxide (20 mg) was added to a solution of the diene **2**, (100 mg) in acetic acid (10 ml). The mixture was stirred for 4 hr under a hydrogen atmosphere, filtered, and evaporated under reduced pressure to yield a colorless oil, which crystallized on standing. Recrystallization from methanol gave methyl 3α-ethoxycarbonyloxychol-8(14)-enate as plates (80 mg): mp 113–115°; $[\alpha]_D$ +57° (*c* 1.0) (lit.[7] mp 115–117°; $[\alpha]_D$ +60°).

Methyl 3α-Ethoxycarbonyloxychol-7-enate (4).—Palladium-on-carbon catalyst (10%, 1.9 g) was added to a solution of the diene **2** (2.0 g) in ethyl acetate (40 ml). This mixture was stirred for 4 hr under a hydrogen atmosphere, filtered and evaporated. Recrystallization of the solid residue from methanol gave methyl 3α-ethoxycarbonyloxychol-7-enate as plates (1.85 g): mp 135–136°; $[\alpha]_D$ +69° (*c* 1.0) (lit.[6] mp 135–136°; $[\alpha]_D$ +70°).

Methyl 14ξ-Bromo-3α-ethoxycarbonyloxychol-7-enate (5).—A solution of bromine (360 mg) in acetic acid (1.1 ml) was added to a solution of methyl 3α-ethoxycarbonyloxychol-7-enate (420 mg) in ether (35 ml) at 0°, the mixture rapidly cooled to −60°, then allowed to regain room temperature over 2 hr with frequent shaking. The resultant crystalline precipitate was collected and washed with cold ether to give **methyl 14ξ-bromo-3α-ethoxycarbonyloxychol-7-enate:** mp 134–135° dec; $[\alpha]_D$ −103° (*c*, 1.1); λ (isooctane) 254 mμ (ϵ 6900). The nmr spectrum gives a multiplet signal at τ 4.93 (vinyl proton) with integrated intensity equivalent to one proton. The compound gives positive tetranitromethane and Beilstein tests. Warming solutions in the common recrystallizing solvents caused rapid decomposition (considerable darkening of solutions after 1–2 hr at room temperature).

Anal. Calcd for $C_{28}H_{43}BrO_5$: C, 62.27; H, 8.03; Br, 14.83. Found: C, 61.97; H, 8.31; Br, 15.01.

Methyl 3α-Ethoxycarbonyloxychola-7,14-dienate (6). A.—Silver acetate (80 mg) was added to a solution of methyl 14ξ-bromo-3α-ethoxycarbonyloxychol-7-enate (75 mg) in isooctane (20 ml) and the suspension vigorously stirred at room temperature for 20 hr. It was then filtered, the filtrate evaporated to dryness and the residue crystallized from methanol to give **methyl 3α-ethoxycarbonyloxychola-7,14-dienate** as needles (52 mg): mp 97–99°; $[\alpha]_D$ +115° (*c* 0.7); λ 248 mμ (ϵ 11,500). The nmr spectrum gives multiplet signals at τ 4.97 and 4.33, each of integrated intensity equivalent to one proton.

Anal. Calcd for $C_{28}H_{42}O_5$: C, 73.31; H, 9.24. Found: C, 72.95; H, 9.15.

B.—The monobromide (**5**) was chromatographed on alumina (Spence, Type H) and the column eluted with chloroform. Evaporation of the eluate (50 ml) yielded an oil (56 mg) which crystallized from methanol to give the diene (**6**) as needles: mp and mmp 97–99°; $[\alpha]_D$ +111° (*c* 0.6); λ 248 mμ (ϵ 11,700); and infrared spectrum identical with that obtained by method A.

Catalytic Hydrogenation of Methyl 3α-Ethoxycarbonyloxychola-7,14-dienate (6).—To a solution of the diene (50 mg) in acetic acid (10 ml) was added platinum dioxide (20 mg), the mixture stirred for 2 hr under a hydrogen atmosphere, filtered, concentrated to small volume (*ca.* 3 ml) and diluted with water. The crystalline precipitate was recrystallized from methanol to give methyl 3α-ethoxycarbonyloxychol-8(14)-enate (**3a**) as needles (35 mg): mp 114–116°; $[\alpha]_D$ +55° (*c* 1.0).

3α-Hydroxychol-8(14)-enic Acid (3c).—Methyl 3α-ethoxycarbonyloxychol-8(14)-enate (30 mg) was dissolved in 5% methanolic potassium hydroxide solution (5 ml), left at room temperature overnight, then worked up in the usual way. Crystallization of the product from methanol gave 3α-hydroxychol-8(14)-enic acid (15 mg) as prisms: mp 165–166°; $[\alpha]_D$ +57° (*c* 0.8) (lit.[7] mp 165–166°; $[\alpha]_D$ +54°).

Action of Zinc on Methyl 14ξ-Bromo-3α-ethoxycarbonyloxychol-7-enate.—Zinc dust (500 mg) was added to a solution of the bromo ester (**5**, 100 mg) in acetic acid (30 ml), the mixture stirred at 50° for 3 hr, then cooled, filtered and the filtrate concentrated under reduced pressure (to *ca.* 3 ml). The concentrate was diluted with water, extracted with ether and the extract washed with sodium bicarbonate solution and water. Evaporation of the dried ($MgSO_4$) extract gave a colorless oil which crystallized from methanol to yield a mixed crystal of **methyl 3α-ethoxycarbonyloxychol-7-enate** (**4**) and **methyl 3α-ethoxycarbonyloxychol-8-enate** (**7a**) as needles (70 mg): mp 139–140°;

(10) R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961); **46**, 2054 (1963). For the 3α-ethoxycarbonyloxy group, the values 0.5 and 1.5 cps are used for the C-18 and C-19 protons, respectively.

(11) D. Levy and R. Stevenson, *Tetrahedron Lett.*, 3063 (1966).

(12) A. J. Birch and G. S. R. Subba Rao, *ibid.*, 857 (1967).

(13) T. B. Windholz, B. Arison, R. D. Brown, and A. A. Patchett, *ibid.*, 3331 (1967).

$[\alpha]_D$ + 40° (c 0.8); ultraviolet end absorption (ε 3650 at 210 mμ).

Anal. Calcd for $C_{28}H_{44}O_5$: C, 72.99; H, 9.63. Found: C, 72.95; H, 9.41.

The nmr spectrum included signals at τ 4.95 (multiplet, less than one proton), 8.97 and 9.13 (singlets, three proton total), 9.37 and 9.45 (singlets, three proton total).

Catalytic Hydrogenation of Methyl Cholenate Mixture (4 + 7a).—The mixture (25 mg) was dissolved in acetic acid (3 ml), concentrated hydrochloric acid (0.3 ml), and platinum dioxide (15 mg) added, and the mixture stirred vigorously for 2 hr under a hydrogen atmosphere. Filtration and dilution with water yielded methyl 3α-ethoxycarbonyloxycholanate (**8a**, 11 mg) as needles, mp 130–137° (lit.[14] mp 120–135°).

Hydrolysis of Methyl 3α-Ethoxycarbonyloxycholanate.—The ester (10 mg) was dissolved in 5% methanolic potassium hydroxide solution (3 ml), left at room temperature overnight, and worked up in the usual way. Crystallization of the product from aqueous methanol gave 3α-hydroxycholanic acid (**8b**) as prisms (6 mg): mp 181–182°; $[\alpha]_D$ +36° (c 0.5) (lit.[14] mp 182–183°; $[\alpha]_D$ + 32°).

Catalytic Hydrogenation of Methyl 3α-Acetoxychola-7,9(11)-dienate.—A solution of methyl 3α-acetoxychola-7,9(11)-dienate[15] (100 mg, mp 148–150°) in acetic acid (4 ml) was shaken with platinum dioxide (20 mg) for 1 hr under a hydrogen atmosphere. Filtration, concentration of the filtrate, and dilution with methanol yielded crystals which on recrystallization from methanol gave methyl 3α-acetoxychol-8-enate (**7b**) as plates: mp 143–145°; $[\alpha]_D$ + 55° (c 1.0); ultraviolet end absorption (ε 4200 at 210 mμ) (lit.[12] mp 144.5–146°; $[\alpha]_D$ +60°). Water was added to the mother liquor and, after cooling for several hours, methyl 3α-acetoxychol-8(14)-enate (**3b**) was collected as fine needles: mp 79–81°; $[\alpha]_D$ +50° (c 1.0); ultraviolet end absorption (ε 5900 at 210 mμ) (lit.[16] mp 81–82°; $[\alpha]_D$ +56°).

Authentic Mixture of 4 and 7a.—Methyl 3α-acetoxychol-8-enate was hydrolyzed with methanolic potassium hydroxide solution and converted into methyl 3α-ethoxycarbonyloxychol-8-enate by successive treatment with diazomethane and ethyl chloroformate in the standard manner. The methyl ester (**7a**) so obtained (10 mg) was mixed with the methyl ester (**4**, 5 mg) and the mixture dissolved in methanol. Concentration yielded the mixed crystals as needles, mp 139–140°, identical with that (**4** + **7a**) obtained by the action of zinc on **5**.

Registry No.—**3a**, 16797-63-0; **4**, 16797-64-1; **5**, 16797-65-2; **6**, 16797-66-3; **7a**, 16797-67-4; **7b**, 16797-68-5; bromine, 7726-95-6; **3b**, 16797-69-6.

Acknowledgment.—The award of Research Grant AM-03439 from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service, to R. S. is gratefully acknowledged.

(14) F. Nakada and K. Yamasaki, *Steroids*, **1**, 131 (1963).

(15) L. F. Fieser, W.-Y. Huang, and J. C. Babcock, *J. Amer. Chem. Soc.*, **75**, 116 (1953).

(16) F. Nakada, R. Osawa, and K. Yamasaki, *Bull. Chem. Soc. Jap.*, **34**, 538 (1961).

The Dehydration of Coronopilin

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Received January 29, 1968

The dehydration of coronopilin (**1**) in sulfuric acid–acetic acid was known to yield coronophilic acid (**4**), but it also yields the isomer **10** in formic or trifluoroacetic acid. $\Delta^{1,2}$-Anhydrocoronopilin (**6**), the product of thionyl chloride–pyridine dehydration of **1**, has been shown not to undergo the rearrangement. A proposed mechanism for the rearrangement is supported by nmr and CD data, and the absolute configuration of isocoronophilic acid is shown to be that expressed in **10a**.

Sesquiterpene dilactones have been isolated from some collections of *Ambrosia psilostachya*,[1-3] and we we were interested in the chemical correlation of psilostachyin B (**5**)[3] with coronopilin (**1**) through the unknown $\Delta^{1,10}$-anhydrocoronopilin (**2**). The stereochemistry of **1**, a major sesquiterpene lactone in this species, has been completely elucidated through X-ray analysis and chemical correlations,[4] but it had also been correctly postulated earlier by Geissman and Turley[6] as a result of their study of the unusual rearrangement of **1** to coronopilic acid (**4**).

When this work was initiated, the dehydration of **1** without rearrangement had not been achieved and our first goal was therefore to complete such a reaction.

Discussion

It is now known[4] that thionyl chloride–pyridine treatment of **1** yields $\Delta^{1,2}$-anhydrocoronopilin (**6**) rather than the desired $\Delta^{1,10}$ isomer. We expected that acid treatment of **6** would shift the 1,2 double bond to the more substituted 1,10 position, but we were also concerned with the possibility that this latter compound would further rearrange to **4**, as described by Geissman and Turley in their study of the acid-catalyzed dehydration of **1**.[5] These authors postulated that **2** was the first intermediate formed in the treatment of **1** with acetic acid–sulfuric acid and that it efficiently yielded the cyclopropane derivative **3**, which further reacted with acid to yield their observed product **4**.

We therefore anticipated that acid treatment of **6** would yield **4** readily and that the difficulty in the work would lie in defining the conditions required for stopping the reaction after double-bond migration to **2**. Actually, a double-bond migration into conjugation within the five-membered ring was the only reaction which was observed when **6** was submitted to the conditions of the coronopilic acid rearrangement. The conjugated ketone which was isolated after treatment was identified as epiambrosin (**7**) by direct comparison. It is therefore probable that **6** is also one intermediate in the acid-catalyzed isomerization of ambrosin (**8**) to **7**.[4]

Our failure to achieve the conversion of **6** into **2** led us to reinvestigate the acid-catalyzed reaction of corono-

(1) T. J. Mabry, H. E. Miller, H. B. Kagan and W. Renold, *Tetrahedron*, **22**, 1139 (1966).

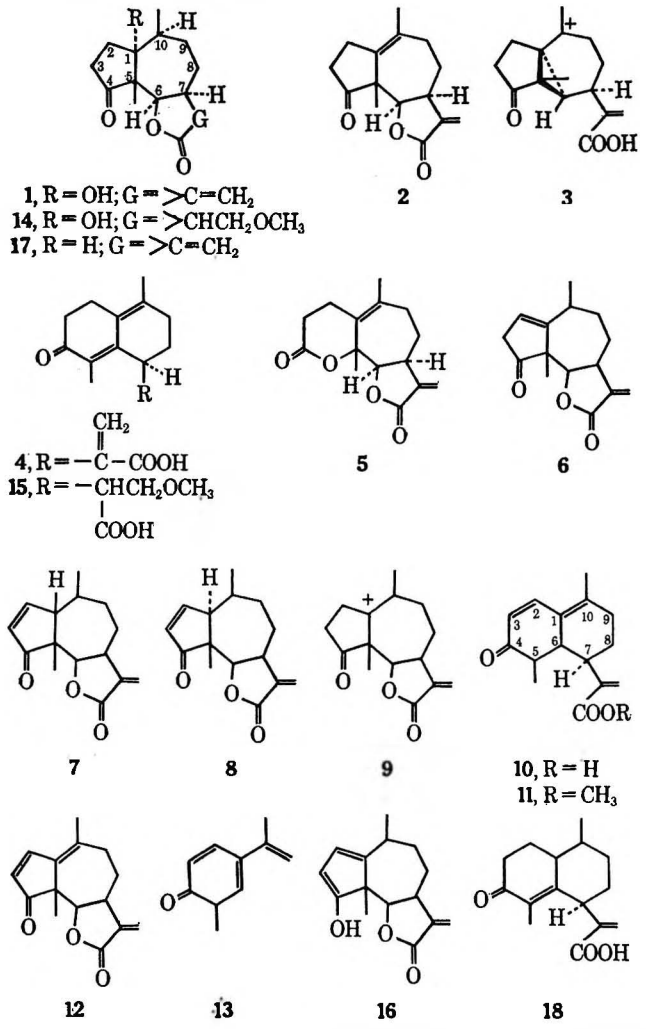
(2) H. B. Kagan, H. E. Miller, W. Renold, M. V. Lakshmikantham, L. R. Tether, W. Herz, and T. J. Mabry, *J. Org. Chem.*, **31**, 1629 (1966).

(3) T. J. Mabry, H. B. Kagan, and H. E. Miller, *Tetrahedron*, **22**, 1943 (1966).

(4) A. Romo de Vivar, L. Rodriguez, J. Romo, M. V. Lakshmikantham, R. N. Mirrington, J. Kagan, and W. Herz, *ibid.*, **22**, 3279 (1966).

(5) T. A. Geissman and R. J. Turley, *J. Org. Chem.*, **29**, 2553 (1964).

pilin. When **1** was treated with sulfuric acid in acetic acid as described by Geissman and Turley, coronopilic acid (**4**) was the only identified product. The reaction could be carried out in a sample tube at the temperature of the nmr probe, and its progress was followed continuously. The five-membered-ring vinyl protons of **6**, **7**, or **8** were not detected. Coronopilic acid itself was unstable under the conditions of the reaction, and after a maximum corresponding to the disappearance of **1**, its concentration decreased with time until the reaction mixture was completely black and the components could no longer be recognized.



We then turned to other media for the dehydration of **1**. No reaction was observed when a solution of **1** in 97% formic acid was allowed to stand for 15 hr at room temperature. When that solution was heated to 80° for 10 hr, all of the starting material disappeared. Neither **6** nor **7** was detected by nmr spectroscopy in the reaction mixture, and the acidic fraction proved to be a mixture of **4** (60%) and another product which was eventually shown to be **10** (40%).

Coronopilin was stable when heated for 18 hr at 60° in a 50% solution of trifluoroacetic acid in acetic acid. When it was heated in pure trifluoroacetic acid, a rearrangement identical with that observed in formic acid took place, and a mixture of **4** (60%) and **10** (40%) could be isolated in over 50% yield. This rearrangement was not observed when **6** was treated in these same two acids. Instead, some double-bond migration into conjugation took place.

The mixture of **4** and **10** crystallized easily, but neither component could be obtained in pure form upon recrystallization of the mixture under a variety of conditions. A small amount of the new acid **10**, mp 168–170°, pure on the basis of its nmr spectrum, was finally obtained after column chromatography of the mixture over silica gel G and recrystallization. The isomer **4** and most of **10** were lost in this process. The new acid, isocoronopilic acid (**10**), was shown by mass spectroscopy (on the methyl ester) to have the same molecular weight as **4**. Its nmr spectrum showed methylene vinyl protons at 5.73 and 6.61 ppm as broad singlets, with a shape comparable to those in **4**, departing from the sharp doublets always associated with the rigid lactone ring structure in **1** and related sesquiterpene lactones. A low field doublet (one proton) at 7.44, in conjunction with a doublet at 5.94 ppm (one proton, J = 10 cps), indicated an α,β-unsaturated ketone. The presence of a third double bond in the molecule was disclosed by a methyl peak at 1.90 ppm. Since another methyl group appeared as a doublet at 1.02 ppm (J = 6 cps), a rearrangement of the ring system must have taken place in the conversion of **1** into **10**, and the formula **10** accounts for all the analytical results on isocoronopilic acid. The most intense peak in the mass spectrum of methyl isocoronopilate (**11**) had m/e 148, which is due to the product (**13**) of a retro-Diels–Alder reaction. The experimental value for the ultraviolet absorption maximum in ethanol [λ_{max} 304 nm (ϵ 15,300) with a shoulder at 230 nm] matches perfectly the calculated value.[6] In contrast, the same chromophore in the unrearranged ring system of anhydroparthenin (**12**) has a band at λ_{max} 296 nm (ϵ 12,500).[7]

A derivative of coronopilin was prepared in order to study on another example this unusual rearrangement. The crystalline product **14** was obtained as a mixture of isomers by the base-catalyzed addition of methanol onto the exocyclic double bond of **1**. This adduct was converted into the corresponding coronopilic acid derivative **15** upon treatment with sulfuric acid in acetic acid, and, as expected, the increased bulk of the 7 substituent in this compound compared with **4** resulted in a slightly lower value (306 nm, ϵ 14,900) of the absorption maximum. The isocoronopilic acid derivative was not observed when this rearrangement was carried out in formic or trifluoroacetic acid.

Mechanism of the Acid-Catalyzed Dehydration of Coronopilin.—Several possibilities exist, which would explain the absence of **10** in Geissman and Turley's conditions for the dehydration of **1**: (a) **10** is not formed at all in these conditions; (b) **10** and **4** are both formed, but the former is unstable and yields unidentified neutral products, thus leaving **4** as the only isolated acid; (c) **10** and **4** are both formed, but **10** readily isomerizes into **4**; (d) **10** is the primary product in the reaction, but it isomerizes into **4**.

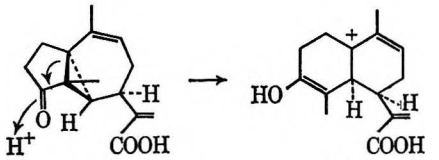
(6) The observed uv absorption maximum of **4** (310 nm)[5] is much lower than the calculated value of 337 nm. Steric interaction between the 5-methyl and the 7 substituent is probably responsible for this effect. Decoupling experiments performed on **4** at 100 Mc showed that the coupling constants between H_7 and both H_8's are smaller than 5 cps. This is a clear confirmation of the axial character of the C-7 side chain in **4**. If present in **10**, such an interaction (although necessarily of a different magnitude because of the difference in the geometry at C-5) does not affect significantly the electronic system of the dienone.

(7) W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Amer. Chem. Soc.*, **84**, 2601 (1962).

In order to shed some light on the process, a mixture of **4** and **10**, obtained from the reaction in formic acid, was subjected to Geissman and Turley's conditions for 1 hr. After work-up, the only acidic material was found to be **4**. When pure **10** was treated in the same manner, no acidic compound could be isolated. These experiments rule out the third and fourth hypotheses but do not allow one to decide between the first and the second. Similarly, the presence of **10** in trifluoroacetic acid and in formic acid might have resulted either from the concurrent formation of both products **4** and **10** or from partial isomerization of **4**. This latter hypothesis was not supported by the evidence, since pure **4** could be treated in the conditions of the reaction in these two media and it could be recovered without formation of **10**.

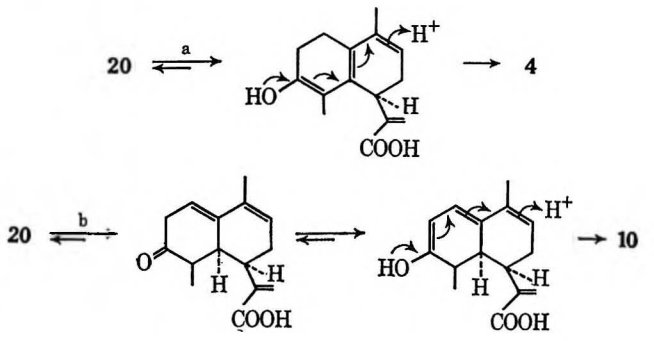
It is therefore tempting to postulate that in all cases the acid-catalyzed dehydration of **1** follows a single mechanism leading to both **4** and **10**, but that occasionally the latter compound is further degraded in the medium and escapes detection.

A mechanism accounting for the simultaneous formation of **4** and **10** incorporates the essential features of Geissman and Turley's proposal. Initial dehydration of **1** to **2** is followed by proton loss to **19**. Protonation of **19** at the ketone yields the bicyclic enol **20**, from



19 **20**

which loss of a proton may occur in two different manners, leading to coronopilic acid **4** (path a) as well as to isocoronopilic acid **10** (path b).



In support of this mechanism, we observed that the presence of the 1-hydroxyl was essential for the rearrangement to take place. Damsin (**17**), which contains all the stereochemical features of **1** but lacks the tertiary hydroxyl,[8] was treated for several days in the conditions of the coronopilic acid rearrangement. The solution became black, but **18** was not detected in the solution by nmr spectroscopy.

Our failure to observe the isomerization of **6** to **4** could have been taken as evidence against the initial formation of **2** in the acid treatment of **1**, since the 1 double bond could reasonably be expected to shift to the more substituted 10 position. However, the experimental result is easily explained if protonation of **6** takes place initially at the ketone rather than at the double bond, yielding first the enol **16** and finally the observed conjugated ketone.[9]

It must be noted that our proposed mechanism for the formation of **4** and **10** preserves the integrity of the asymmetric center at C-7 in both products, which therefore must be optically active. It was indeed observed that both coronopilic acid ($[\alpha]D$ −441°, c 0.58 in $CHCl_3$) and its isomer ($[\alpha]D$ −325°, *c* 0.50 in $CHCl_3$) had very large specific rotations. There is only one asymmetric center at C-7 in **4**, whereas there are three such centers in **10**. As the center next to the carbonyl is easily racemized in acid, one can only deduce from the presence of optical activity in **10** that the centers C-6 and C-7 had not both been epimerized.

Finally, in an attempt to locate the centers which had been protonated during the rearrangement, the dehydration of **1** was carried out in deuterated trifluoroacetic acid. Comparison of the nmr spectra of the isolated acids with those obtained in the normal medium showed incorporation of deuterium at C-3 and C-5 in **10** and at C-3 (2 atoms) in **4**. In particular, a proof that H-6 was not affected in **10** was found in the fact that it appeared as a doublet at 2.65 ppm. This clearly showed that deuterium had been incorporated at C-5 but not at C-6 or C-7. Integration of the spectra indicated that incorporation had taken place elsewhere, probably at the allylic positions, but the signals were not resolved sufficiently to allow the exact location of the label. When the same mixture of **4** and **10** prepared in normal acid was treated in deuterated trifluoroacetic acid, deuterium was incorporated at C-3 in **4** and at C-5 in **10**. In addition, some incorporation took place at saturated positions. The lack of incorporation of deuterium at C-3 in **10** in the latter experiment, coupled with the presence of label at that position in the former, demonstrated that enolization of the ketone toward C-3 had taken place before formation of **10**. The ease of enolization of **1** was shown by carrying out the rearrangement in deuterated trifluoroacetic acid to very small conversion. The nmr spectrum of the starting material showed some deuterium incorporation, in particular at the ring methylene protons which gave resonance at the lowest field. These are probably the C-3 protons.

The presence of optical activity in **4**, coupled with the results of the deuterium incorporation showing no label at C-7, allows us to conclude that formula **4** represents the absolute configuration of coronopilic acid. These results determined only the absolute configuration at the unreacted C-7 in **10**, and the configuration at the other asymmetric centers in isocoronopilic acid remained to be demonstrated.

Stereochemistry of Isocoronopilic Acid.—Since the absolute configuration at C-7 in **10** is known from that in **1**, the configuration at C-5 and C-6 relative to that at C-7 will determine the absolute stereochemistry of isocoronopilic acid.

No label was incorporated at C-6 in the deuterated acid treatment of **1** and the stereochemistry at this center must therefore be accessible from mechanistic considerations alone. The hypothesis of a backside attack by the electrons of the 1,10 double bond during the lactone ring opening in **2** fixes the stereochemistry of

(8) M. Suchý, V. Herout, and F. Šorm, *Collect. Czech. Chem. Commun.*, **28**, 2257 (1963).

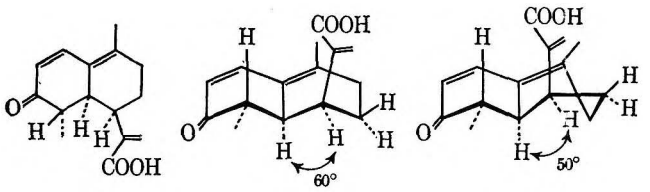
(9) Protonation at the ketone also explains why anhydroparthenin (**12**) does not undergo the rearrangement and is stable to acid.

the substituents on the cyclopropane as indicated in **3** and in **19**; C-5 is above the plane of the B ring soon to be formed, and H_6 is almost in that plane. After ketone protonation and bond breaking between C-1 and C-5, it is clear that H_6 will necessarily be *below* the B ring and axial, as expressed in **20**.

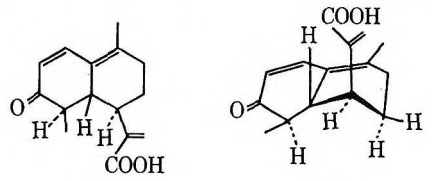
It is reasonable to postulate that the configuration at the equilibrable C-5 will be such that the methyl substituent will suffer minimum 1,3 interactions. Since the configurations at C-6 and C-7 are such that H_6 and the large C-7 substituent are both axial, the C-5 methyl will therefore be equatorial and α, as expressed in **10a** which must therefore represent the complete stereochemistry of isocoronopilic acid.[10]

The structural assignment was substantiated by the results of nmr measurements. Double resonance nmr experiments performed at 100 Mc allowed the determination of the coupling constants: $J_{H_5H_6} = 14$ cps, $J_{H_6H_7} = 4.8$ cps, and $J_{H_7H_6} = 7$ cps. These coupling constants clearly indicate that H-5 and H-6 are both axial and that H_7 is equatorial, in support of the structure **10a** derived from mechanistic considerations.

Inspection of a model of **10a** shows that the A ring will necessarily be in a half-chair conformation in order to have H_5 axial, but that the B ring may have either a half-chair or a half-boat conformation. In the former case (**10b**), the dihedral angle between H_6 and H_7 is about 60°, while in the latter case (**10c**) that angle is about 50°. The observed coupling constant of 4.8 cps is reasonable in either case and does not allow one to distinguish between these conformations.



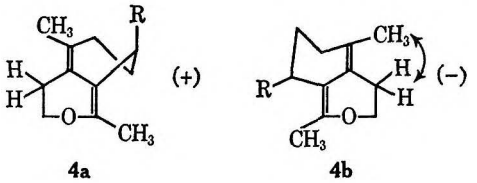
10a **10b** **10c**



10d **10e**

It must be noted that the alternative structure **10d**, where the angular hydrogen is β, possesses only one conformation (**10e**) in which the H_5 (axial), H_6 (axial), H_7 (equatorial) relationship is satisfied, but this conformation must be ruled out since the dihedral angle between H_6 and H_7 is 90° and should have resulted in no measurable coupling between these protons in the nmr spectrum.

In the absence of suitable models of known configuration, the interpretation of the observed circular dichroism is hazardous. However, its application to the simpler coronopilic acid **4** may be checked against the structure derived from the nmr data and the study of models. Of the two conformations possessing an axial C-7 side chain, **4a** appears energetically favored because the interaction between the C-10 methyl and C-2 proton indicated in **4b** is minimized



4a **4b**

Application of the CD rules for enones[11] predicts a positive value for **4a** and negative one for **4b**. The observed value was positive and gives some confidence that the rule may be applied to the more complex isomer **10**. Application of the dienone rule should give a negative dichroism for **10e** and a positive dichroism for **10b** and **c**. The experimental value was positive and therefore rules out **10e**.

In conclusion, the mechanistic proposal as well as the interpretation of the physical data point to **10a** for the absolute configuration of isocoronopilic acid.[12] The data presently available does not allow a choice between **10b** and **10c** for the actual conformation of **10a**.

Experimental Section

The nmr spectra were determined on Varian A-60 or A-60A spectrometers in chloroform and are described in parts per million downfield from an internal standard of tetramethylsilane. The ir spectra were measured in a Beckman IR-5 and the uv spectra were recorded with Beckman DB or Bausch and Lomb 505 spectrometers. The melting points were determined with a Fisher-Johns apparatus and are not corrected.

Acid-Catalyzed Isomerization of 6.—The dehydration of **1** with thionyl chloride in pyridine was carried out as described.[5] A solution of 0.100 g of **6** in 2.5 ml of acetic acid and 0.25 ml of sulfuric acid was heated for 1 hr at 80°. The dark solution was diluted with water and extracted with ethyl acetate which was then washed with sodium bicarbonate and with water. The neutral fraction was shown by nmr spectroscopy to be an almost equimolar mixture of **6** and **7**. This latter compound was isolated in low yield by preparative tlc over silica gel with chloroform–ethyl acetate (3:1). It crystallized, mp 146–148°, upon seeding with an authentic sample of epiambrosin[4] with which it was identical in all respects.

Rearrangement of 1 in Formic Acid.—A solution of **1** (1.488 g) in 20 ml 97% formic acid was heated at 80° for 10 hr. Water was added to the brown solution, which was then extracted with ethyl acetate. The organic phase was extracted with bicarbonate. The acidic fraction consisted of 0.836 g of solid which was analyzed by nmr spectroscopy to be about 60% **4** and 40% **10**.

Rearrangement of 1 in Trifluoroacetic Acid.—A solution of 0.219 g of **1** in 2 ml of trifluoroacetic acid was heated in a closed vial at 60° for 7.5 hr. After dilution with water the mixture was extracted with ethyl acetate, which was in turn extracted with bicarbonate. After acidification of the aqueous layer and usual work-up, there was obtained 0.122 g of solid, analyzed by nmr spectroscopy to be about 60% **4** and 40% **10**.

The reaction in deuterated acid was carried out under identical conditions. The acid was prepared by careful addition of the calculated amount of deuterium oxide to trifluoroacetic anhydride.

Isocoronopilic Acid (10).—A mixture of **4** and **10** (0.836 g) obtained in formic acid was placed on a 15 × 2 cm column of silica gel G (from Merck Co.) packed in chloroform. Upon elution with the same solvent a crystalline material was obtained in the fourth and fifth 25-ml fractions. After two recrystallizations from ethyl acetate there was obtained 0.046 g of **10**, mp

(10) The mechanistic argument is based on the assumption that no carbonium ion is formed at C-6 by lactone ring opening prior to cyclopropane formation. This point has already been discussed[5] and our finding that damsin (**17**) did not undergo any rearrangement despite the large relief of steric interaction to be gained gives stronger support to this assumption.

(11) G. Snatzke, *Tetrahedron*, **21**, 413, 421, 439 (1965).

(12) It is interesting to find the larger C-6 substituent axial and the smaller equilibrable C-4 substituent equatorial as one would have been tempted to predict the alternative relationship.

168–170°, pure according to nmr data. No other product could be eluted from the column.

The nmr spectrum of **10** (100 Mc) showed the following signals: methyls, C-5 at 1.02 (d, J = 6 cps) and C-10 at 1.9 (s); ring methylenes between 1.72 and 2.3 (complex); ring methines, H_6 at 2.50, H_8 at 2.65, H_7 at 3.41 with $J_{H_5H_6}$ = 14 cps, $J_{H_6H_7}$ = 4.8 cps, and $J_{H_7H_8}$ = 7 cps; vinyl protons, exocyclic at 5.70 (s) and 6.58 (s), H_2 at 7.41, and H_3 at 5.90 ppm ($J_{H_2H_3}$ = 10 cps).

In double resonance experiments at 100 Mc, the protons at C-5 and C-6 gave partially overlapping, complex signals centered at 2.5 and 2.65, respectively, while H_7 appeared as a poorly resolved doublet at 3.41. Upon irradiation at H_7 the vinyl signals were not affected but H_6 was converted into a doublet with $J_{H_5H_6}$ = 14 cps. The area near the vinyl methyl at 1.90 was also affected, indicating the general location of the C-8 protons. The location of H_5 was ascertained by irradiating at 2.50, which converted the C-5 methyl doublet into a singlet. Conversely, irradiation at the C-5 methyl converted the complex H_5 signal into a doublet with $J_{H_5H_6}$ = 14 cps. Irradiation at H_6 sharpened H_7 into a peak with a half width of 7 cps, while irradiation at H_8 near 1.90 converted H_7 into a doublet with $J_{H_6H_7}$ = 4.8 cps. Finally, from the half width measurement of the H_7 signal (about 7 cps), one finds that $J_{H_7H_8}$ is not more than 7 cps.

Circular dichroism values in dioxane were as follows: 371 (+2.46), 353 (+4.06), 342 (+3.91), 298 (−14.90), 229 (−1.99), positive at shorter wavelengths; in ethanol, they were 344 (+5.65), 302 (−15.53), and 229 (−1.62), strongly positive at shorter wavelengths. The same solutions showed uv maxima at 298 and 230 (infl) in dioxane and at 304 and 230 nm (infl) in ethanol For comparison, in ethanol a sample of **4** containing about 20% **10** gave values of 344.5 (+4.98), 304 (−20.86), and 237 (−1.56), strongly positive at shorter wavelengths.

The methyl ester was obtained by diazomethane treatment and had mol wt 260 (mass spectroscopy). A rotation was determined on a mixture of **4** and **10** which was made 50% in each component by a preliminary treatment on a smaller column of silica gel. The observed value was $[\alpha]_D$ −383° (c 0.11, in $CHCl_3$), which corresponds to −325° for **10**. The ir spectrum of **10** in $CHCl_3$ showed absorptions at 5.9, 6.2, 6.18, and 6.31 μ.

Acid Treatment of 4 and 10.—All the acid treatment experiments on **4** and **10** were performed in nmr sample tubes kept at the appropriate temperature. After the proper reaction time the nmr spectrum was recorded, the acidic products in the reaction mixture were isolated and they were also examined by nmr spectroscopy.

Adduct 14.—A solution of 0.629 g of **1** in 15 ml of methanol was treated with a few drops of 0.1 N sodium hydroxide. After 4 hr at room temperature, the solution was diluted with water and extracted with chloroform. A quantitative yield of adduct [mol wt 296 (mass spectroscopy)] was obtained upon recrystallization of the extract from methanol. The melting point (203–235°) was raised to 235–237°, $[\alpha]_D$ 23.8 ± 2° (c 0.3, dioxane), after several recrystallizations. The nmr spectrum showed prominent signals at 1.18 (s, C-5 methyl), 1.21 (d, J = 8 cps, C-10 methyl), 3.38 (s, $-OCH_3$), 3.67 (d, J = 5 cps, $-CH_2-O-$), 4.96 ppm (d, J = 9 cps, H_8). In addition to the broad melting range, the presence of a mixture of isomers (probably at C-11) was suggested by the lack of sharpness of the 1.21 and 4.96 ppm peaks, which could be due to almost superimposed signals from both isomers.

Acid Treatment of 14. A. In Acetic Acid–Sulfuric Acid.—Two drops of sulfuric acid was added to a solution of 0.047 g of **14** in 10 ml of acetic acid. The solution was heated to 80° for 30 min. After addition of water it was worked up as usual. The acidic fraction was crystallized from ether–hexane and yielded 0.009 g of **15**: mp 176–177°; λ_{max} 212 nm (ϵ 7900), 243 (5300) and 306 (14,900). The nmr spectrum indicated two CH_3's at 1.8 ppm, characteristic for the coronopilic acidlike structure.

B. In Formic Acid.—A solution of 0.300 g of **14** in 5 ml of 97% acid was heated to 80° for 30 min. After the usual work-up, 0.064 g of acid was obtained. Its nmr spectrum and melting point were identical with those of the above products. Contrary to the results observed with **1**, the dienone isomer was not detected.

Registry No.—**1**, 2571-81-5; **10a**, 16526-71-9; **15**, 16526-72-0.

Acknowledgments.—Part of this work was carried out at the University of Texas in the laboratory of Dr. T. J. Mabry, whom we sincerely thank. We are indebted to Drs. T. J. Mabry, W. Herz, and H. E. Miller for help and useful discussions during the course of this work, Dr. R. Wolff for mass spectral studies, Dr. G. Snatzke for the circular dichroisms and their interpretation, and Mrs. L. Lacombe for the decoupling experiments. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. A NATO grant to H. B. K. and support from the Robert A. Welch Foundation are also gratefully acknowledged.

Preparation and Reactions of a 3-Chlorocoumarin Photodimer

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Received February 2, 1968

The preparation of a head-to-tail 3-chlorocoumarin photodimer is described. Attempts to convert this dimer into the corresponding cyclobutadienoid system are discussed.

Both the direct and sensitized photodimerization of coumarin have been reported in the literature. Anet[1] reported that direct irradiation of coumarin in ethanol solution produces the *cis* head-to-head dimer (**1**) while Schenck[2] showed that irradiation in the presence of benzophenone gives the *trans* head-to-head dimer (**2**) along with a trace of the *trans* head-to-tail dimer (**3**). Hammond[3] reinvestigated these reactions and concluded that the direct irradiation proceeds through interaction of excited coumarin singlet whereas the sensitized irradiation involves excited-triplet coumarin. The effect of various solvents on the direct, unsensitized dimerization was later studied by Morrison.[4] He found that in nonpolar solvents the *trans* head-to-head dimer (**2**) is formed to the virtual exclusion of the *cis* head-to-head dimer (**1**). The ratio of **2** to **1** decreases in polar solvents and is reversed in methanol. Morrison suggests that **1** is formed from a singlet excimer, whereas **2** arises *via* a monomeric triplet species. These solvent effects are similar to those found independently by

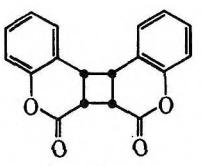
(1) R. Anet, *Can. J. Chem.*, **40**, 1249 (1962).

(2) G. O. Schenck, I. von Wiluchi, and C. H. Krauch, *Ber.*, **95**, 1409 (1962).

(3) G. S. Hammond, C. A. Stout, and Angelo A. Lamola, *J. Amer. Chem. Soc.*, **86**, 3103 (1964).

(4) H. Morrison, H. Curtis, and T. McDonell, *ibid.*, **88**, 5415 (1966).

Krauch[5] who has also isolated the *cis* head-to-tail dimer (**4**) from the nonsensitized irradiation. This compound shows a solvent dependency analogous to **1**.



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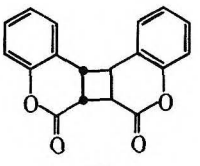

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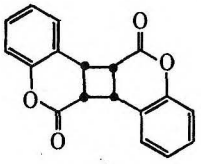

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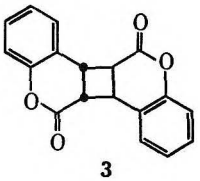
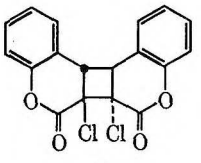
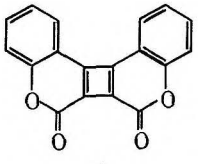


3

We have investigated the sensitized photodimerization of 3-chlorocoumarin in the hope of obtaining the *trans* head-to-head dimer (**5**) which might yield the cyclobutadienoid system **6** under the proper reaction conditions.

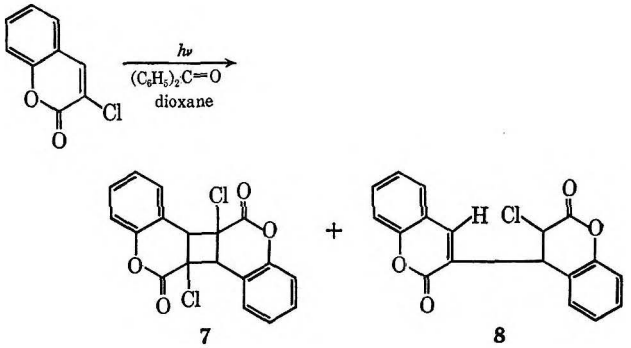


5



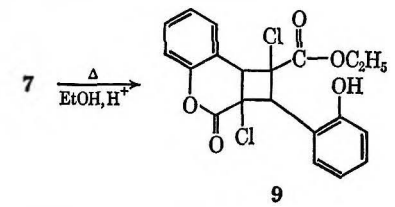
6

The irradiation of 3-chlorocoumarin was carried out in the presence of benzophenone. Two photolysis products were obtained from this sensitized reaction. The major product was shown to be the head-to-tail 3-chlorocoumarin dimer (**7**). The minor product was isolated and identified as 3′-chloro-3′,4′-dihydro-3,4′-bicoumarin (**8**).



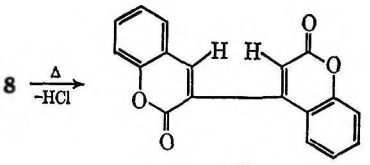
7 **8**

During the course of the separation of **7** and **8**, it was found that, if the 3-chlorocoumarin dimer (**7**) is heated in ethanol in the presence of a trace amount of acid, one of the lactone rings undergoes ethanolysis to give **9**. It was on the basis of the nmr spectrum of **9** that the dimer (**7**) was initially assigned the head-to-tail structure. The spectrum shows two cyclobutane hydrogens at τ 4.50 and 4.88, each as a singlet. Therefore, these hydrogens are uncoupled and most probably not on adjacent carbon atoms as they would have to be if the ethanolysis product were formed from a head-to-head dimer. Thus far attempts to determine whether the dimer is *cis* or *trans* head-to-tail have been inconclusive.[6,7]



9

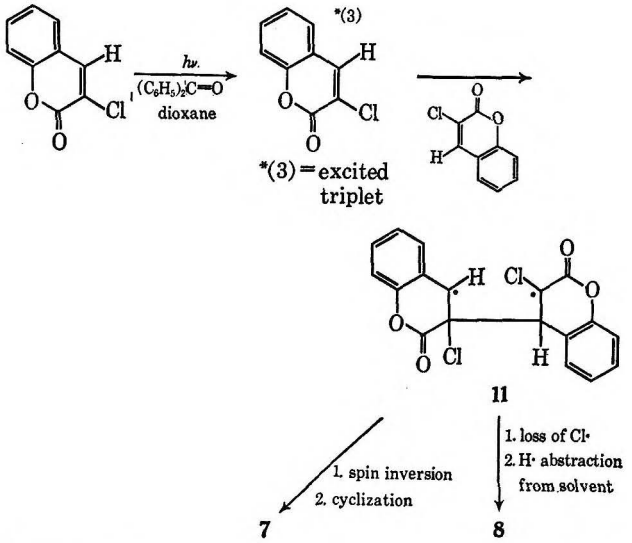
The structure of the minor product (**8**) was determined from its spectral data. The nmr spectrum of **8** showed one β-coumarin hydrogen at τ 2.20, and two ring hydrogens at 4.70 and 5.08, each as a doublet (J = 7 cps). Heating **8** beyond its melting point resulted in the evolution of hydrogen chloride and the formation of 3,4′-bicoumarin (**10**). The orientation of this bicoumarin, which can be established from its nmr spectrum, further verifies the structure assigned to the minor product (**8**). The nmr spectrum of **10** showed one β-coumarin hydrogen at τ 2.08 (singlet) and one α-coumarin hydrogen at 4.33 (singlet).



10

In an attempt to determine whether the minor product (**8**) is a primary or secondary photolysis product, the sensitized irradiation of the dimer (**7**) was carried out. One might consider the formation of **8** from **7** proceeding through an initial homolytic cleavage of the cyclobutane ring. No evidence was found for the formation of **8** from irradiation of the dimer (**7**). Thus, it appears that **8** is a primary photolysis product. A possible mechanism for its formation is shown in Scheme I. The diradical intermediate **11** may be a common precursor to both **7** and **8**.

SCHEME I

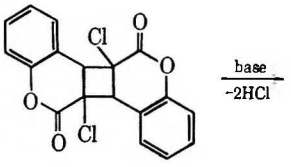


(5) C. H. Krauch, S. Farid, and G. O. Schenck, *Chem. Ber.*, **99**, 625 (1966).

(6) The possibility of this photodimer (**7**) having *trans*-ring fusions is considered highly unlikely. No compounds of this type have been isolated from the photodimerization studies of coumarin.[1-5]

(7) An attempt to prepare the desired *trans* head-to-head dimer (**5**) by direct photolysis produced the same dimer (**7**) as obtained by photosensitization.

The chemical literature contains many examples of attempts to prepare substituted cyclobutadienes. The synthesis of cyclobutadienoid systems in which the instability of the four-membered system is diminished by some structural or electronic feature has been somewhat successful.[8] The head-to-tail 3-chlorocoumarin dimer (**7**) is a possible intermediate in the preparation of the cyclobutadienoid system (**12**). Treatment of the dimer with base under the proper conditions might yield **12** with the elimination of 2 mol of hydrogen chloride. It is possible that **12** would be stable owing to some contribution of structure **13** to the resonance hybrid.



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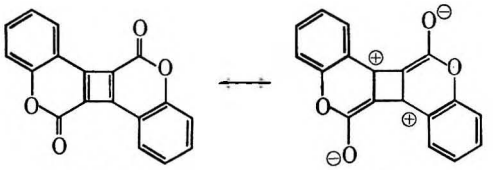
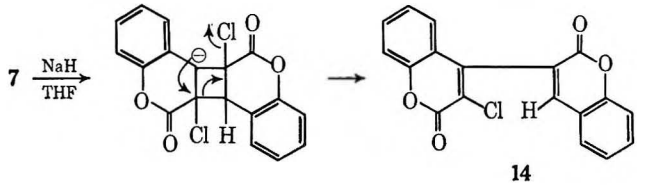


12 **13**

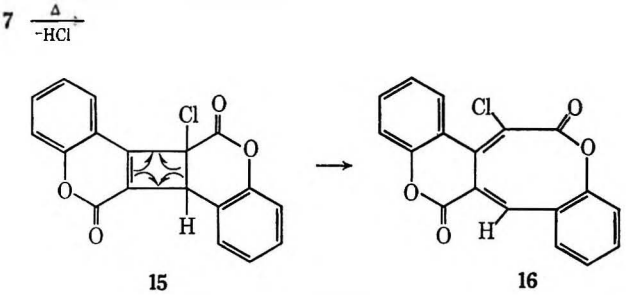
Several attempts were made to prepare **12** with different dehydrohalogenating agents as well as by pyrolysis. In no case was the synthesis of **12** accomplished; however, other interesting reaction products were obtained.

Treatment of the 3-chlorocoumarin dimer (**7**) with sodium hydride resulted in the elimination of 1 mol of hydrogen chloride to give 3′-chloro-3,4′-bicoumarin (**14**). The same product was also obtained by treatment of the dimer with triethylamine. The structure of the product was determined from its uv, ir, nmr, and mass spectrum. The uv spectrum of the product is quite similar to that of 3,4′-bicoumarin (**10**). The reaction most likely proceeds by the pathway



14

Another approach to the synthesis of **12** was by pyrolysis of **7**. On heating **7**, it was observed that the compound gave off hydrogen chloride at its melting point. Pyrolysis of **7** at 280° gave a new compound, however, with the elimination of only 1 mol of hydrogen chloride. This new material is believed to be the substituted eight-membered-ring lactone **16**. Again the structure of the product is based upon the analysis, nmr, ir, uv, and mass spectrum (see Experimental Section). The uv spectrum of the product (**16**) was quite significant. It showed uv max (CH_3OH) 291 mμ (ε 16,600) and 327 mμ (ε 18,800), while the 3′-chloro-3,4′-bicoumarin (**14**) gave uv max (CH_3OH) 284 (ε 20,000) and 315 mμ (ε 15,100). Thus the new material (**16**), compared with **14**, shows a shift to longer wavelengths for its uv maxima. In compound **14** there are two coumarin chromophores connected by an essential single bond and it appears that there is steric inhibition of coplanarity with essentially no interaction between the two chromophores.[9] In the case of **16**, it is expected that this molecule would have an extra double bond in conjugation with one of the carbonyl groups, thus giving rise to the longer wavelength absorption. The reaction probably proceeds by initial loss of hydrogen chloride to give a cyclobutene intermediate (**15**) which then rearranges to the product.



15 **16**

In conclusion, attempts to prepare the cyclobutadienoid system **12** have thus far been unsuccessful. However, the possibility remains that with the proper dehydrohalogenating agent the compound may be isolated or trapped.

Experimental Section[10]

Irradiation Apparatus.—Irradiations were carried out using an immersion apparatus supplied by the Hanovia Lamp Division of Englehard Industries. The lamp used was a 450-W, medium-pressure mercury arc, type no. 679A-10. Cylindrical glass filters were placed inside the lamp well.

Material.—Benzophenone from Eastman Organic Chemicals and 3-chlorocoumarin from Aldrich Chemical Co. were used without additional purification. Sodium hydride was supplied by Metal Hydrides, Inc. Dioxane and tetrahydrofuran from Matheson Coleman and Bell were used. The dioxane was purified by distillation from the sodium ketyl of benzophenone and stored frozen under nitrogen. Tetrahydrofuran was distilled from lithium aluminum hydride.

Irradiation of 3-Chlorocoumarin.—A solution of 4.2 g (0.023 mol) of 3-chlorocoumarin, 0.50 g (0.003 mol) of benzophenone, and 25 ml of dioxane was prepared in a Pyrex test tube. Nitrogen gas was bubbled through the solution and the test tube was sealed and taped to the outside of the cylindrical reaction well of the immersion apparatus. The test tube was then irradiated for 30 hr. The solvent was removed on the rotating evaporator and the residue was recrystallized from benzene to give 1.5 g (36%) of the head-to-tail 3-chlorocoumarin dimer (**7**), mp 266°. The infrared spectrum of the dimer contained strong carbonyl absorption at 1757 cm^{-1}. The nmr spectrum contained two cyclobutane hydrogens at τ 5.08 (single peak) and eight aromatic hydrogens at 2.63 (multiplet).

Anal. Calcd for $C_{18}H_{10}O_4Cl_2$: C, 59.9; H, 2.8; Cl, 19.6. Found: C, 60.1; H, 3.2; Cl, 19.6.

The minor reaction product (**8**) was isolated by stripping the benzene filtrate to a minimum volume and cooling. Using this procedure, 0.50 g (13%) of 3′-chloro-3′,4′-dihydro-3,4′-bicoumarin (**8**) was isolated. The material was recrystallized from ethanol to give pure product, mp 217°. The infrared spectrum contained strong carbonyl absorption at 1776 and 1712 cm^{-1}. The nmr spectrum showed the β-coumarin hydrogen at τ 2.20

(8) For a review, see P. Cava and M. J. Mitchell, "Organic Chemistry. V. 10 Cyclobutadiene and Related Compounds," Academic Press Inc., New York, N. Y., 1967, pp 1–84.

(9) This conclusion is based on a comparison of the uv spectrum of **14** with those of coumarin and 3-chlorocoumarin.

(10) Nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Infrared spectra were determined on a Perkin-Elmer Infracord spectrophotometer. Ultraviolet spectra were measured in methanol on a Cary Model 11 MS spectrophotometer. Mass spectra were determined on a AEIMS9 mass spectrometer. Melting points were determined in a capillary tube in a Mel-Temp apparatus and are uncorrected.

(singlet), two ring hydrogens at 4.70 and 5.08, each as a doublet (J = 7 cps), and eight aromatic hydrogens centered at 2.70 (multiplet). The uv spectrum showed uv max (CH_3OH) 280 mμ mμ (ε 14,300) and 314 mμ (ε 9400).

Anal. Calcd for $C_{18}H_{11}O_4Cl$: C, 66.2; H, 3.4; Cl, 10.8. Found: C, 65.9; H, 3.7; Cl, 10.8.

1,3-Dichloro-2,4-bis(O-hydroxyphenyl)-1,3-cyclobutanecarboxylic Acid Ethyl Ester δ-Lactone (9).—To 30 ml of ethanol was added 0.5 g (0.0015 mol) of the head-to-tail 3-chlorocoumarin dimer and 0.3 ml of 12 *N* HCl. This mixture was heated at reflux until all of the material went into solution. The ethanol was evaporated and the residue recrystallized from benzene to give 0.40 g (71%) of a white solid, mp 191–193°. The infrared spectrum showed hydroxyl absorption at 3448 cm^{-1} and carbonyl absorption at 1754 and 1727 cm^{-1}. The nmr spectrum contained two cyclobutane hydrogens at τ 4.50 and 4.88 (singlets), two methylene hydrogens at 5.97 (quartet), three methyl hydrogens at 9.02 (triplet), and eight aromatic hydrogens at 2.70 (multiplet).

Anal. Calcd for $C_{20}H_{16}O_5Cl_2$: C, 59.0; H, 4.0; Cl, 17.4. Found: C, 58.9; H, 4.2; Cl, 17.5.

3,4′-Bicoumarin (10).—In a Pyrex test tube was placed 1.0 g (0.003 mol) of 3′-chloro-3′,4′-dihydro-3,4′-bicoumarin (8). The test tube was then heated at 250° in a Wood's metal bath for 20 min. After cooling, the solid material in the test tube was removed and recrystallized from benzene. Approximately 300 mg (34%) of a solid white precipitate, mp 255–257°, was obtained. The infrared spectrum showed strong absorption at 1724, 1608, 1449, and 1376 cm^{-1}. Th uv spectrum of the material showed uv max (CH_3OH) 282 mμ (ε 18,400) and 313 mμ (ε 13,900). The nmr spectrum contained one β-coumarin hydrogen at τ 2.08 (singlet), one α-coumarin hydrogen at 4.33 (singlet), and eight aromatic hydrogens centered at 3.03 (multiplet).

Anal. Calcd for $C_{18}H_{10}O_4$: C, 74.5; H, 3.5. Found: C, 74.9; H, 3.6.

Sensitized Irradiation of the Head-to-Tail 3-Chlorocoumarin Dimer (7).—A solution containing 0.70 g (0.002 mol) of the head-to-tail 3-chlorocoumarin dimer, 0.20 g (0.001 mol) of benzophenone, and 150 ml of dioxane was prepared and added to the outside vessel of the 450-W, medium-pressure mercury arc irradiation apparatus. After flushing with nitrogen, the solution was irradiated for 45 hr. The solvent was then removed on the rotating evaporator. The infrared spectrum of the residue indicated that no amount of 3′-chloro-3′,4′-dihydro-3,4′-bicoumarin (8) was formed.

3′-Chloro-3,4′-bicoumarin (14).—In 15 ml of tetrahydrofuran was dissolved 1.0 g (0.003 mol) of the head-to-tail 3-chlorocoumarin dimer. The mixture was then added to a suspension of 0.25 g (0.006 mol) of sodium hydride (54.7%) in 5 ml of tetrahydrofuran. The mixture was stirred for 1 hr and then 1 *N* hydrochloric acid added to neutralize any unreacted sodium hydride. A yellow oil formed which was extracted with chloroform and the chloroform solution dried over anhydrous sodium sulfate. The chloroform was stripped off and the residue recrystallized from benzene. A white solid precipitate was formed, 250 mg (28%), mp 256–258°. The infrared spectrum showed strong absorption at 1721, 1608, and 1447 cm^{-1}. The nmr spectrum contained one β-coumarin hydrogen at τ 2.08 (singlet) and eight aromatic hydrogens centered at 2.50 (multiplet). The uv spectrum showed uv max (CH_3OH) 284 mμ (ε 20,000) and 315 mμ (ε 15,100). The compound gave a molecular ion at m/e 324 (326).

Anal. Calcd for $C_{18}H_9O_4Cl$: C, 66.6; H, 2.8; Cl, 10.9. Found: C, 66.4; H, 2.9; Cl, 11.4.

α-Chloro-2,3-dihydro-3-o-hydroxybenzylidene-2-oxo-4H-2-benzopyran-$\Delta^{4,\alpha}$-acetic Acid Lactone (16).—In a Pyrex test tube was placed 1.0 g (0.003 mol) of the heat-to-tail 3-chlorocoumarin dimer. The test tube was then heated at 290° for 20 min in a Wood's metal bath. The evolution of hydrogen chloride was easily detected with litmus paper. After heating, the test tube was cooled and the contents recrystallized from benzene to yield 270 mg (30%) of a light tan solid, mp 279°. The infrared spectrum showed strong absorption at 1724, 1610, 1560, and 1485 cm^{-1}. The nmr spectrum contained one β-coumarin hydrogen at τ 2.12 (singlet) and eight aromatic hydrogens centered at 2.55 (multiplet). The uv spectrum showed uv max (CH_3OH) 291 mμ (ε 16,600) and 327 mμ (ε 18,800). The compound gave a molecular ion at m/e 324 (326).

Anal. Calcd for $C_{18}H_9O_4Cl$: C, 66.6; H, 2.8; Cl, 10.9. Found: C, 66.2; H, 3.3; Cl, 10.7.

Registry No.—**7**, 16666-82-3; **8**, 16666-83-4; **9**, 16666-84-5; **10**, 16666-85-6; **14**, 16666-86-7; **16**, 16666-87-8.

Acknowledgments.—We thank Mr. L. Brancone and staff for the microanalyses, Mr. W. Fulmor and staff for the ultraviolet and nmr spectra, and Dr. J. Karliner for the mass spectra.

Bile Acids. XXIV. Raney Nickel in the Preparation of Allocholanic Acids[1]

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Received February 21, 1968

Treatment of methyl polyhydroxy-5β-cholanoates, such as methyl cholate (I) or methyl chenodeoxycholate (XI), with Raney nickel in boiling *p*-cymene provided a mixture of 5α-cholanoates now separated and characterized as the 3,7-diketones (III and XIII), the 7-deoxy derivatives (II and XII), and the methyl 3-ketoallocholanoates (IV and XIV, respectively). Methyl deoxycholate (X) and methyl lithocholate (XVI) afforded the corresponding 3-keto-5α-cholanoates, II and XII, respectively; reduction provided the isomeric hydroxyallocholanoates, VIII and IX and XVII and XVIII. Treatment of methyl 7β-tritiocholate (XX) with Raney nickel gave tritiated IV (XXIII) and II (XXI); the amount of tritium retained in *p*-cymene was equivalent to that lost in the formation of the diketone III.

During a study of the metabolism of cholestanol-4-^{14}C in our laboratory[2-4] a new method of synthesis of allocholic acid[1c] and allochenodeoxycholic acid[5] was developed. The first step in this method provides a mixture of products after treatment of methyl cholate (I) or methyl chenodeoxycholate (XI) with Raney nickel in boiling *p*-cymene. After chromatography on alumina these mixtures yielded three major compounds from distinct fractions (A, B, and C) in each case.

(1) (a) This investigation was supported in part by the National Institutes of Health (Grant No. HE-07878 and AM-09992). (b) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966. (c) For Paper XXIII in this series, see M. N. Mitra and W. H. Elliott, *J. Org. Chem.*, **33**, 175 (1968). (d) The following abbreviations have been used: tlc, thin layer chromatography; plc, preparative layer chromatography; glpc, gas–liquid partition chromatography; R_t, retention time relative to methyl deoxycholate (methyl 3α,12α-dihydroxy-5β-cholanoate; absolute time = 29 min.).

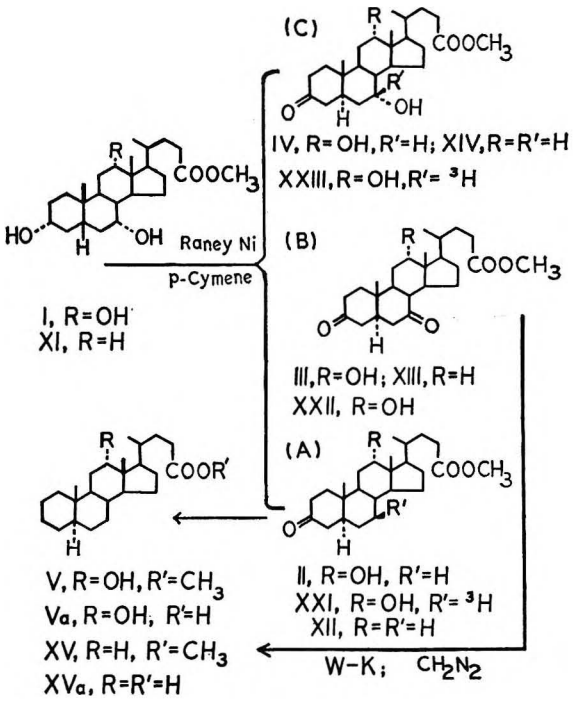
(2) H. J. Karavolas, W. H. Elliott, S. L. Hsia, E. A. Doisy, Jr., J. T. Matschiner, S. A. Thayer, and E. A. Doisy, *J. Biol. Chem.*, **240**, 1568 (1965).

(3) H. J. Karavolas and W. H. Elliott, "The Biliary System," W. Taylor, Ed., F. A. Davis Co., Philadelphia, Pa., 1965, pp 175–181.

(4) S. A. Ziller, Jr., and W. H. Elliott, *Fed. Proc.*, **25**, 221 (1966).

(5) S. A. Ziller, Jr., M. N. Mitra, and W. H. Elliott, *Chem. Ind.* (London), 999 (1967).

While the products from fractions C were identified as methyl 3-keto-7α,12α-dihydroxy-5α-cholanoate[1c] (IV) from I and methyl 3-keto-7α-hydroxy-5α-cholanoate[5] (XIV) from XI, the synthetic precursors of allocholic and allochenodeoxycholic acids, respectively, the products from fractions A and B have now been identified and found to be useful starting materials for the preparation of a number of allocholanic acids.



After treatment of methyl cholate (I) with freshly prepared Raney nickel in boiling *p*-cymene for 10 hr, separation of the nickel and *p*-cymene, and chromatography of the residue on alumina,[1c] fraction A was purified by plc on silica gel H to provide methyl 3-keto-12α-hydroxy-5α-cholanoate[6] (II) in 20–22% yield. II may also be prepared directly from methyl deoxycholate (X) in 45% yield by the above reaction.

After plc of fraction B on silica gel H methyl 3,7-diketo-12α-hydroxy-5α-cholanoate (III) was obtained in crystalline form in 18–20% yield. Reduction of either II or III by the Wolff–Kishner method (W–K) followed by diazomethylation provided the same known compound, methyl 12α-hydroxy-5α-cholanoate[1c] (V), whereas on oxidation with chromic acid II or III afforded methyl 3,12-diketo-5α-cholanoate[7] (VI) or methyl 3,7,12-triketo-5α-cholanoate[1c] (VIII), respectively. The above chemical degradation supports the structure of III.

The mass spectrum of III (Figure 1) exhibits a rather weak mass peak (*m/e* 418, 4.9%) and the fragments M − 18, 27.3%, M − 36, 10.5%, M − (18 + 31), 6.3%, M − 73, 7.3%, and M − (18 + 73), 6.6%; base peak, *m/e* 285, M − (18 + 115), is a fragment in which the C_5 side chain and a molecule of water have been lost from the parent ion. The mass spectrum of methyl 3,7-diketo-12α-hydroxy-5β-cholanoate is similar to that of III.

On reduction with sodium borohydride compound II yielded a mixture of methyl allodeoxycholate[6] (VIII) in 12% yield and its 3β isomer (IX) in 72% yield, which was conveniently separated by acetic acid partition chromatography.[8] Catalytic hydrogenation of II in the presence of platinum, however, gave 28% of VIII and 48% of IX.

In an analogous manner fraction A obtained by chromatographic separation of the mixture of products from treatment of methyl chenodeoxycholate (XI) with Raney nickel in boiling *p*-cymene was purified by plc on silica gel H; methyl 3-keto-5α-cholanoate[9] (XII) was obtained in 20–25% yield. Fraction B from XI gave methyl 3,7-diketo-5α-cholanoate (XIII) in 15–18% yield. The structure of XIII was established by physical and chemical means. Both XII and XIII on W–K reduction yielded allocholanic acid.[10] Oxidation of an authentic sample of methyl 3-keto-7α-hydroxy-5α-cholanoate[5] with chromic acid provided a compound identical with XIII. These observations along with mass spectral data confirmed the structure of XIII.

The mass spectrum of XIII (Figure 1) exhibits a strong mass peak (*m/e* 402, 56%), the usual fragments of keto bile acid esters [M − 18, M − 32, M − (18 + 31), M − 73], and the fragments *m/e* 287 [M − 115] and *m/e* 269 [M − (115 + 18)]. The major fragment, *m/e* 192, retains the carbonyl groups of rings A and B, and is apparently stabilized as the enolic triene. The spectrum is significantly different from that of methyl 3,7-diketo-5β-cholanoate or III.

Although the melting point of XIII (158–159°) is close to that of VI (162–163°), the specific rotations are different and are in agreement with calculated values as shown in Table I. The calculated values are based on a sample of methyl allocholanoate, $[\alpha]^{25}D$ +22 ± 1° (*c* 0.49, in chloroform) as reported[1c] and the values as tabulated by Klyne.[11,12]

TABLE I
MOLECULAR ROTATION OF METHYL DIKETO-5α-CHOLANOATES

	MD, deg	
Diketo-5α-cholanoate	Calcd	Found
3,12- (VI)	+423	+358
3,7- (XIII)	−80	−87
12α-Hydroxy-3,7- (III)	+13	0

Methyl 3-keto-5α-cholanoate (XII) was also obtained by treatment of methyl lithocholate (XVI) with Raney nickel in boiling *p*-cymene. On catalytic reduction of XII in the presence of platinum a mixture of methyl allolithocholate[13] (XVII) and its 3β isomer[14]

(6) H. Danielsson, A. Kallner, and J. Sjövall [*J. Biol. Chem.*, **238**, 3846 (1963)] prepared II from methyl 3-keto-12α-hydroxy-5β-cholanoate by treatment with Raney nickel in boiling *p*-cymene. They reported, for II, mp 134–136°, $[\alpha]D$ +56.8°; for VIII, mp 174–176°, $[\alpha]D$ +35.6°; for VIIIa, mp 214–215°, $[\alpha]D$ +42°; for IX, mp 137–138°, $[\alpha]D$ +41°; for IXa, mp 228°.

(7) A. F. Hofmann and E. H. Mosbach [*ibid.*, **239**, 2813 (1964)] reported mp 157–160° for VI.

(8) J. T. Matschiner, T. A. Mahowald, W. H. Elliott, E. A. Doisy, Jr., S. L. Hsia, and E. A. Doisy, *ibid.*, **225**, 771 (1957).

(9) H. Wieland, E. Dane, and C. Martius [*Z. Physiol. Chem.*, **215**, 15 (1933)] reported mp 114° and mp 184° for XII and XIIa, respectively.

(10) L. F. Fieser and Mary Fieser ("Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 54) reported mp 94° for XV and mp 173° and $[\alpha]D$ +22° for XVa.

(11) W. Klyne, "The Chemistry of Steroids," Methuen and Co. Ltd., London, 1960, p 55.

(12) D. H. R. Barton and W. Klyne, *Chem. Ind.* (London), 755 (1948).

(13) (a) L. Ruzicka, M. Oberlin, H. Wirz, and J. Mayer [*Helv. Chim. Acta*, **20** 1283 (1937)] reported mp 169–170° for XVII. (b) I. G. Anderson and G. A. D. Haslewood [*Biochem. J.*, **85**, 236 (1962)] reported mp 161–164° for XVII.

(14) A. Stoll and J. Renz [*Helv. Chim. Acta*, **24**, 1380 (1941)] reported mp 150–151° and $[\alpha]D$ +23° for XVIII.

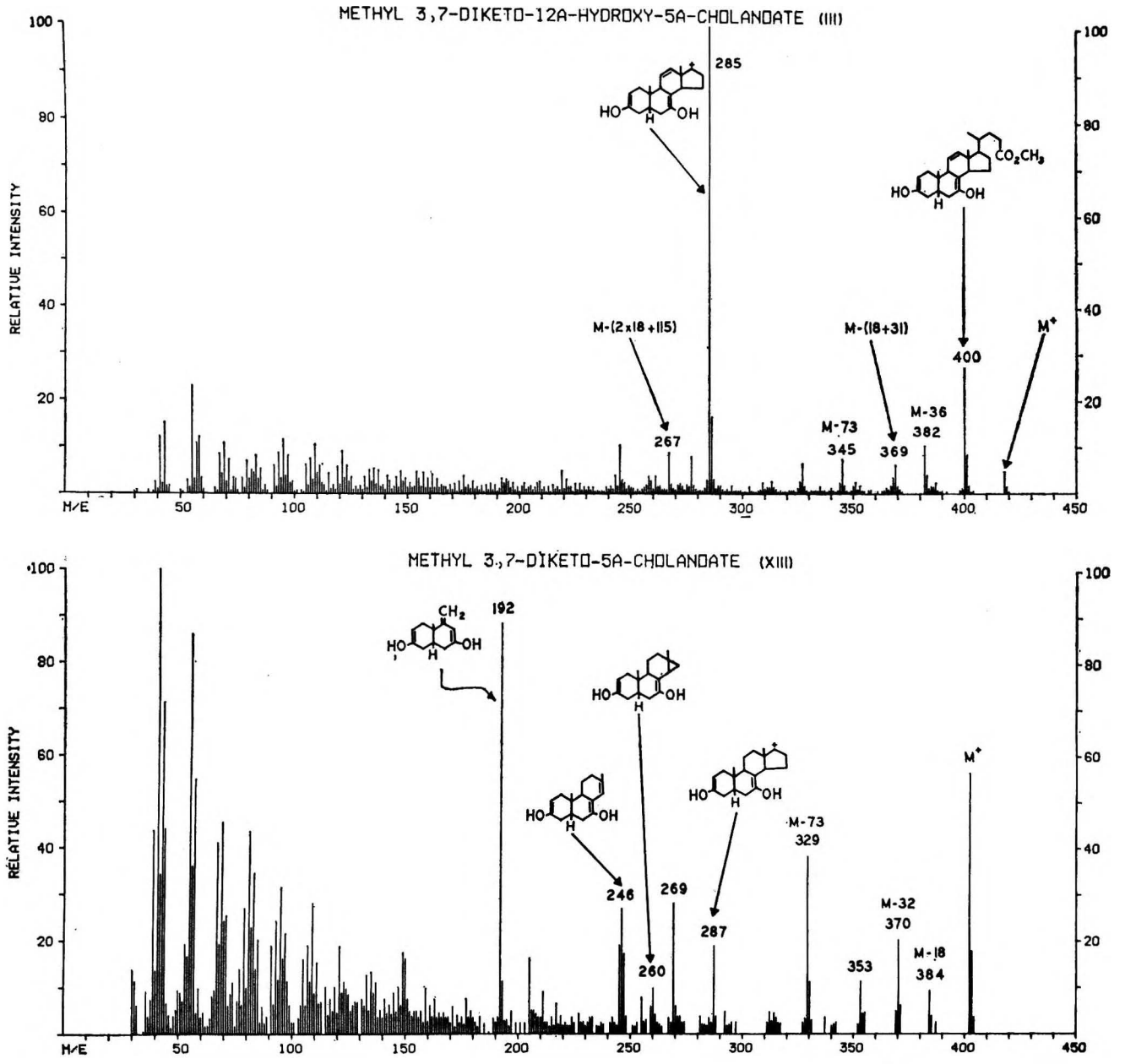


Figure 1.—Mass spectra of methyl 3,7-diketo-12α-hydroxy-5α-cholanoate (III) and methyl 3,7-diketo-5α-cholanoate (XIII) were determined with an LKB Model 9000 mass spectrometer with the direct probe at 75 and 105°, respectively. Other conditions were ion source, 270°; ionizing energy, 70 eV; ionizing current, 60 μA. The structures drawn for the fragment ions are purely formal.

(XVIII) was obtained in a ratio of approximately 1:2. The isomers XVII and XVIII were easily separated by plc.

As obtained, compounds II, III, XII, and XIII are always associated with the corresponding 5β isomers before purification by plc. The separation of 5α from 5β isomers is effected by taking advantage of their differences in R_f values with different concentrations of acetone in benzene (Table II).

TABLE II

R_f VALUES OF METHYL CHOLANOATES

	% acetone in benzene	5α	5β
3-Keto-12α-hydroxy (II)	20	0.49	0.40
3,7-Diketo-12α-hydroxy (III)	20	0.30	0.33
3-Keto (XII)	5	0.60	0.62
3,7-Diketo (XIII)	20	0.70	0.74

The allo (5α) compounds differed from the normal (5β) compounds in their behavior in glpc as indicated by their different relative retention times given in the Experimental Section.

After completion of the identification of the various compounds formed in the Raney nickel reaction with methyl cholate or methyl chenodeoxycholate, an investigation was undertaken to elucidate the mechanism by which elimination of the 7α-hydroxy group takes place in I or XI. Methyl cholate was preferentially oxidized at position 7 with N-bromosuccinimide using the method of Fieser and Rajagopalan.[15] After purification by plc methyl 7-keto-3α,12α-dihydroxy-5β-cholanoate[16] (XIX) was reduced with sodium borotri-

(15) L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.*, **71**, 3935 (1949).

(16) I. Tanasescu, E. Ramontian, I. Ganea, and F. Hodosan, *Rev. Chim. Acad. Rep. Populaire Roumaine*, **2**, 157 (1957), cited in H. Van Belle, "Cholesterol, Bile Acids and Atherosclerosis," North-Holland Publishing Co., Amsterdam, 1965, p 43.

tide to provide methyl 3α,7α,12α-trihydroxy-7β-tritio-5β-cholanoate (XX). The mobility of XX agreed with I (R_f 0.23 in 50% acetone–benzene) as opposed to methyl 3α,7β,12α-trihydroxy-5β-cholanoate (R_f 0.16 in 50% acetone–benzene). Since approximately 5% of the tritium was retained after preferential oxidation of XX with N-bromosuccinimide at position 7, XX must contain about 95% of the tritium at the 7β position.

The tritiated methyl cholate (XX) was mixed with methyl cholate, heated with Raney nickel in *p*-cymene in the usual way, and the products XXI, XXII, and XXIII corresponding to II, III, and IV, respectively, were isolated in the pure state. From the specific activities of these products (Table III) it is clear that tritium has been retained completely in XXI and XXIII, and that the activity retained in XXII is essentially that introduced elsewhere in the molecule during reduction of XIX with borotritide.

TABLE III

RETENTION OF TRITIUM AFTER RANEY NICKEL REACTION

Compd	Specific activity, dpm/mg — First crystn	Second crystn	% tritium
XX (calcd)	2.74×10^6		
XX	2.66×10^6	2.69×10^5	100
XXI	2.57×10^5	2.58×10^5	96
XXII	0.10×10^5	0.09×10^5	4
XXIII	2.65×10^5	2.60×10^6	98

From these results it is evident that III is not an intermediate in the formation of II or IV from methyl cholate (I); thus, the 7α-hydroxyl group may have been eliminated as water with an adjacent proton, followed by saturation of the double bond to provide XXI or II. *p*-Cymene recovered from the above reaction was found to retain about 20% of the total tritium present in XX (1.07×10^8 dpm). Further studies on the mechanism of the Raney nickel reaction are in progress.

Experimental Section

The procedures and conditions for the determination of melting points, optical rotations, infrared and mass spectrometry, and thin layer, preparative layer, and gas chromatography have been described.[1c] Radioactivity was measured in a Model 3314 Tricarb liquid scintillation spectrometer as reported;[17] counting efficiency was 20% as determined with tritiated water as internal standard.

Raney Nickel Catalyst.—W-2 catalyst was prepared from Raney catalyst powder (No. 2813, W. R. Grace and Co., Chattanooga, Tenn.) according to the method of Mozingo.[18]

Action of Raney Nickel on Methyl Cholate.—Dry purified methyl cholate (mp 156–157°, 10.0 g) was heated for 10 hr with freshly prepared Raney nickel catalyst (*ca.* 25 g) in refluxing *p*-cymene as reported.[1c] After removal of the catalyst and the solvent, the residue was chromatographed on neutral Woelm alumina deactivated with 12% water. Elution of the column and evaporation of the solvents provided the following three major fractions: (A) eluted with hexane–benzene, 2:1 (2.8 g); (B) with hexane–benzene, 1:1 (3.1 g); (C) with benzene and benzene–ethyl acetate, 9:1 (1.7 g).

Methyl 3-Keto-12α-hydroxy-5α-cholanoate[6] (II).—Fraction A was purified by plc with 20% acetone in benzene on 20 plates (20 cm × 40 cm) coated with silica gel II. The upper bands of solids on the plates corresponding to R_f 0.49 were removed and extracted with acetone. After evaporation of the solvent 2.2 g of crystalline residue was crystallized from acetone–hexane as stout needles[6] of II: mp 144–145°; $[\alpha]^{25}D$ +51.7 ± 0.5° (*c* 1.0); R_t 2.23 (R_t for methyl 3-keto-12α-hydroxy-5β-cholanoate 1.18); ir 3401, 1706, 1068, 1043, 958, 893, 852 cm^{-1}.

Methyl 3,7-Diketo-12α-hydroxy-5α-cholanoate (III).—Fraction B was purified by plc with 25% acetone in benzene in a similar manner. In this case the lower bands of solids on the plates were removed and extracted with acetone. After removal of the solvent 2.04 g of crystalline residue was crystallized from acetone–hexane to afford soft shining needles of III: mp 178°; $[\alpha]^{25}D$ 0 ± 0.5° (*c* 1.0); R_t 7.14 (R_t for methyl 3,7-diketo-12α-hydroxy-5β-cholanoate, 5.05); ir 3496, 3355, 1739, 1709, 1075, 952, 893 cm^{-1}.

Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.65; H, 9.16.

On hydrolysis with 5% potassium hydroxide III yielded the corresponding acid, 3,7-diketo-12α-hydroxy-5α-cholanoic acid: mp 222–223°; ir 3472, 1709, 1207, 1077, 952 cm^{-1}.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.09; H, 9.06.

W-K Reduction of II.—Reduction of 100 mg of II was carried out[19] in a mixture of 1 ml of 85% hydrazine hydrate, 500 mg of potassium hydroxide, and 5 ml of triethylene glycol. The reduction product (98 mg) was crystallized from acetone–hexane as plates of 12α-hydroxy-5α-cholanoic acid (Va): mp 199°; $[\alpha]^{25}D$ +42.1 ± 0.5° (*c* 1.0); ir 3378, 1712, 1093, 1030, 884 cm^{-1} (lit.[1c] mp 199°; $[\alpha]^{25}D$ +42.2°).

Methylation of Va with diazomethane yielded needles of V: mp 118° (acetone–hexane); $[\alpha]^{25}D$ +41.5 ± 1° (*c* 1.0); R_t 0.37; ir 3436, 1736, 1160, 936, 886 cm^{-1} (lit.[1a] mp 118–119°; $[\alpha]^{26}D$ +41.6 ± 1°).

W-K Reduction of III.—Reduction of 34 mg of III was carried out as above. The product (30 mg) had the same R_f value as that obtained from II in analytical tlc with a mixture of isooctane, ethyl acetate, acetic acid (50:50:0.7). On crystallization from acetone–hexane shining plates of 12α-hydroxy-5α-cholanic acid[1c] (Va) were obtained: mp 198–199°; $[\alpha]^{25}D$ +42.3 ±0.5° (*c* 0.98). The infrared spectrum was comparable with that of a sample obtained by reduction of II.

On methylation with diazomethane, Va obtained from III gave the same methyl ester (V): mp 119°; R_t 0.37.

Oxidation of III.—A solution of III (62 mg) in 0.6 ml of acetic acid was oxidized with chromic anhydride (20 mg in 0.6 ml of acetic acid) for 2 hr at room temperature. The product (50 mg) was purified by plc with 20% acetone in benzene, and finally crystallized from acetone–hexane as fine needles of methyl 3,7,12-triketo-5α-cholanoate (VII): mp 198–199°; $[\alpha]^{25}D$ +29.0 ± 1° (*c* 1.0, in chloroform); R_t 9.24; ir 1736, 1706, 1282, 811 cm^{-1} (lit.[1c] mp 198–199°; $[\alpha]^{25}D$ +29.1 ± 1°).

Oxidation of II (50 mg) was accomplished with chromic acid as above. After crystallization from aqueous acetone shining flakes of methyl 3,12-diketo-5α-cholanoate[7] (VI) were obtained: mp 162–163°; $[\alpha]^{25}D$ +88.0 ± 1.5° (*c* 0.55); R_t 3.52 (R_t for methyl 3,12-diketo-5β-cholanoate 2.86); ir 3472, 1709, 1207, 1077, 952 cm^{-1}.

Action of Raney Nickel on Methyl Deoxycholate.—A mixture of methyl deoxycholate (X) (4.0 g, mp 82°), freshly prepared Raney nickel (*ca.* 10 g), and 60 ml of freshly distilled *p*-cymene was heated as before. After removal of the nickel and the solvent, the resulting solid residue (3.5 g) was chromatographed on Woelm alumina deactivated with 12% water. The column was eluted with successive quantities of hexane, mixtures of hexane and benzene, and benzene. The fraction eluted with hexane–benzene (2:1) yielded a residue (2.9 g) containing mainly methyl 3-keto-12α-hydroxy-5α-cholanoate as shown by analytical tlc. After purification by plc with 20% acetone in benzene and crystallization from acetone–hexane, stout needles of II were obtained:[6] mp 145–146°; $[\alpha]^{25}D$ +51.2 ± 0.5° (*c* 1.0); R_t 2.23.

Reduction of II with Sodium Borohydride.—II (100 mg) was dissolved in methanol (5 ml) and treated with powdered sodium borohydride (50 mg) for 0.5 hr at room temperature. The mixture was diluted with water and acidified, and the product was extracted with ether. After evaporation of the ether the residue (99.0 mg) was purified by acetic acid partition chromatography.[8] Methyl allodeoxycholate[6] (VIII) (16 mg) was eluted with hexane: shining needles (aqueous methanol): mp 177–178°; $[\alpha]^{25}D$ +43.3 ± 1° (*c* 0.48); R_t 1.07; ir 3058, 3378, 1730, 1028, 905 cm^{-1}. On hydrolysis with 5% methanolic potassium hydroxide VIII yielded allodeoxycholic acid[6] (VIIIa), mp 215–216°.

(17) P. D. Ray, E. A. Doisy, Jr., J. T. Matschiner, S. L. Hsia, W. H. Elliott, S. A. Thayer, and E. A. Doisy, *J. Biol. Chem.*, **236**, 3158 (1961).

(18) R. Mozingo in "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p 181.

(19) Huang-Minlon, *J. Amer. Chem. Soc.*, **71**, 3301 (1949).

On elution with 20% benzene in hexane, methyl 3β,12α-dihydroxy-5α-cholanoate[6] (IX) (78 mg) was obtained: shining flakes (aqueous methanol); mp 137–138° (sintering at 90°); $[\alpha]^{25}D$ +35.2 ± 1° (c 0.33); R_t 1.16; ir 3424, 3333, 1718, 1312, 1041, 902, 890 cm^{-1}. Hydrolysis of IX with 5% methanolic potassium hydroxide afforded 3β,12α-dihydroxyallocholanoic acid[6] (IXa), mp 231–232°.

Catalytic hydrogenation of II (100 mg) was carried out in the presence of Adams catalyst in glacial acetic acid containing a few drops of concentrated hydrochloric acid. After the reduction, methyl allodeoxycholate (VIII, 28 mg) and methyl 3β,12α-dihydroxy-5α-cholanoate (IX, 47 mg) were separated by acetic acid partition chromatography,[3] crystallized from aqueous methanol and identified in the usual manner.

Action of Raney Nickel on Methyl Chenodeoxycholate.—Methyl chenodeoxycholate[20] (mp 89–90°, 9.5 g) (XI) was heated for 10 hr in boiling *p*-cymene in the presence of freshly prepared Raney nickel (*ca.* 18 g) in the usual manner. After separation of the Raney nickel and *p*-cymene, the semisolid (8.21 g) was chromatographed over alumina deactivated with 12% water. Three major fractions were collected: (A) with hexane–benzene, 4:1 (3.0 g); (B) with hexane–benzene, 2:1 (2.0 g); and (C) with benzene and benzene–ethyl acetate, 9:1 (2.2 g).

Methyl 3-Keto-5α-cholanoate (XII).—Fraction A was purified by plc with 4% acetone in benzene and provided a crystalline residue of XII (2.3 g). Crystallization from aqueous methanol afforded shining plates of methyl 3-keto-5α-cholanoate[9] (XII): mp 113–114°; $[\alpha]^{25}D$ +40.5 ± 1° (c 0.99); R_t 1.06 (R_t for methyl 3-keto-5β-cholanoate 1.00); ir 1739, 1715, 1228, 985 cm^{-1}.

Hydrolysis of XII with 5% methanolic potassium hydroxide provided the corresponding 3-keto-allocholanoic acid:[9] mp 183–184°; $[\alpha]^{25}D$ +32.6 ± 0.5° (c 0.98).

Methyl 3,7-Diketo-5α-cholanoate (XIII).—Fraction B was purified by plc with 10% acetone in benzene to provide 1.6 g of crystalline residue. After crystallization from acetone–hexane stout needles of methyl 3,7-diketo-5α-cholanoate (XIII) were obtained: mp 160–161°; $[\alpha]^{25}D$ −21.6 ± 2.0 (c 1.0); R_t 3.96 (R_t for methyl 3,7-diketo-5β-cholanoate 2.90); ir 1736, 1706, 1319, 1162, 977, 906, 894 cm^{-1}.

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51; mol wt, 402. Found: C, 74.53; H, 9.40; mol wt, 402 (mass spectrometry).

W–K Reduction of XIII.—Compound XIII (100 mg) was reduced by the W–K method using 5 ml of triethylene glycol, 500 mg of potassium hydroxide, and 1 ml of 85% hydrazine hydrate. The reduction product (99 mg) on crystallization from aqueous acetone provided shining flakes of allocholanoic acid[10] (XVa): mp 172–173°; $[\alpha]^{25}D$ +22.2 ± 1° (c 0.50, in chloroform).

After methylation with diazomethane, purification of the product by plc in benzene, and crystallization from aqueous methanol, shining flakes of methyl allocholanoate[10] (XV) were obtained: mp 93°; $[\alpha]^{25}D$ +22.1 ± 1° (c 0.49, in chloroform).

W–K Reduction of XII.—Reduction of 100 mg of XII by the W–K method in the usual way yielded allocholanoic acid (XVa) identical with that obtained from XIII.

Oxidation of Methyl 3-Keto-7α-hydroxy-5α-cholanoate.[5]—Oxidation of XIV (50 mg) with chromic anhydride (50 mg) in acetic acid provided 40 mg of product which was crystallized from aqueous methanol as XIII: mp 162–163°; $[\alpha]^{25}D$ −21.6 ± 2.0° (c 1.0). The infrared spectrum was comparable with that of methyl 3,7-diketo-5α-cholanoate obtained directly from XI by the action of Raney nickel.

Catalytic Hydrogenation of XII.—Compound XII (108 mg) was hydrogenated in the presence of Adams catalyst in glacial acetic acid solution containing a few drops of hydrochloric acid. The product of reduction was purified by plc in 17% acetone in benzene. The upper band in plc corresponding to R_f 0.72 yielded methyl allolithocholate[13] (XVII) (24 mg), which was crystallized from aqueous methanol as shining flakes: mp 167–168°; $[\alpha]^{25}D$ +22.5 ± 1° (c 0.85, in chloroform); R_t 0.50 (R_t for methyl lithocholate 0.50); ir 3225, 1736, 1275, 1034,10 02, 956, 894 cm^{-1}.

The lower band in plc corresponding to R_f 0.57 yielded methyl 3β-hydroxy-5α-cholanoate[14] (XVIII, 47 mg) which formed needles from aqueous methanol: mp 150–151°; $[\alpha]^{25}D$ +24.3 ± 0.5° (c 1.0); R_t 0.53; ir 3494, 1712, 1297, 1051, 1002, 952, 893 cm^{-1}.

Action of Raney Nickel on Methyl Lithocholate.—After refluxing methyl lithocholate[21] (XVI) (1.0 g, mp 129–130°) in *p*-cymene with freshly prepared Raney nickel (*ca.* 3.0 g), and removal of the nickel and solvent, the crude reaction product (800 mg) was taken up in ether and washed with water. The residue obtained after removal of the ether was crystallized from aqueous methanol to provide shining plates of methyl 3-keto-5α-cholanoate[9] (XII) in 65% yield: mp 113–114°; R_t 1.06.

On hydrolysis of XII with 5% methanolic potassium hydroxide 3-ketoallocholanoic acid[9] was obtained, mp 183–184°.

Methyl 7-Keto-3α,12α-dihydroxy-5β-cholanoate (XIX).—Methyl cholate (200 mg) was oxidized with N-bromosuccinimide (175 mg) in a mixture of 25 ml of dioxane and 4 ml of water at room temperature for 1 hr.[15] The residue from oxidation (196 mg) was purified by plc with 35% acetone in benzene. The major product was crystallized from acetone–hexane as needles of methyl 7-keto-3α,12α-dihydroxy-5β-cholanoate[16] (XIX): mp 153–154°; $[\alpha]^{25}D$ +0.3 ± 1° (c 0.99); R_t 3.51.

Methyl Cholate-7β-^{3}H (XX).—To a solution of 56 mg of XIX in 5 ml of methanol was added a few milligrams of sodium borotritide (New England Nuclear Corp.). The mixture was allowed to stand at room temperature for 0.5 hr and was then diluted with water and acidified. The resulting precipitate was separated and purified by plc on silica gel H with 50% acetone in benzene. The residue (30 mg) was acetylated with acetic anhydride (2 ml) and pyridine (1 ml), crystallized, and hydrolyzed with methanolic potassium hydroxide to remove tritium bonded to oxygen. The tritiated cholic acid thus obtained was methylated with diazomethane, and the product (25.0 mg) again purified by plc with 50% acetone in benzene. After crystallization from a mixture of acetone and hexane, crystals of methyl cholate-^{3}H (XX) were obtained, mp 154–155°. After successive crystallizations from acetone–hexane, the specific activities of XX and of the mother residue were 5.27×10^7 and 5.20×10^7 dpm/mg, respectively.

A sample of XX (0.837 mg) was mixed with methyl cholate (I) and oxidized with N-bromosuccinimide as described before. The product was purified by plc and crystallized from acetone–hexane to provide methyl 7-keto-3α,12α-dihydroxy-5β-cholanoate, mp 154°. The specific activities of the diluted tritiated methyl cholate and the oxidized product were 5.1×10^5 and 0.28×10^5 dpm/mg, respectively. Thus, 5.5% of the tritium in XX was not located at position 7.

Action of Raney Nickel on Tritiated Methyl Cholate.—A mixture of 2.089 mg of XX and 399.3 mg of I (Table III) was heated in boiling *p*-cymene with freshly prepared Raney nickel for 10 hr and the reaction product (304 mg) separated into the major compounds XXI, XXII, and XXIII as described above. The purity of these compounds was checked by analytical tlc; the specific activities after successive crystallizations from acetone–hexane are given in Table III. *p*-Cymene was recovered by steam distillation, dehydrated thoroughly with anhydrous sodium sulfate, and radioactivity was determined from an aliquot in the scintillation counter; 0.21×10^8 dpm were found in the total *p*-cymene.

Registry No.—III, 16656-66-9; free acid of III, 16656-67-0; XIII, 16656-68-1.

Acknowledgment.—We are pleased to acknowledge the expert technical assistance of Miss Mei Mei Mui and Rev. Lawrence B. Walsh, C. M., and valuable discussion with Dr. Stephen A. Ziller, Jr. Cholic and deoxycholic acids were generously provided by Dr. Conrad deFiebre, The Wilson Laboratories, Chicago, Ill.

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The Isolation from Tobacco of 2-Hydroxy-2,6,6-trimethylcyclohexylideneacetic Acid γ-Lactone and Its Synthesis

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Received November 8, 1967

A C_{11} lactone has been isolated in minute quantities from the neutral fraction of the steam volatiles from tobacco, and its structure has been shown by physical methods and synthesis to be 2-hydroxy-2,6,6-trimethylcyclohexylideneacetic acid γ-lactone.

During a preliminary stage of cigarette manufacture, hogsheads of tobacco are treated with steam in order to make the tobacco leaf more pliable. The compound, $C_{11}H_{16}O_2$ (I), was obtained from the neutral oxygenated fraction of the tobacco volatiles found in the condenser water from this process. This compound has also been obtained from bright and Turkish tobaccos in yields of 2×10^{-4} and 6×10^{-4}%, respectively.

The molecular formula of I was determined on the basis of high-resolution mass spectral data and elemental analysis. The high-resolution mass spectrum[2] afforded a molecular weight of 180.1718; the theory for $C_{11}H_{16}O_2$ is 180.1724. Combustion analyses[3] were consistent with the formula $C_{11}H_{16}O_2$. The presence of a carbonyl function and a double bond was deduced from the following data: infrared bands[4] of I at 1761 cm^{-1} (carbonyl) and 1637 cm^{-1} (double bond). No hydroxyl function was observed in the infrared spectrum. Evidence that the carbonyl function was not an aldehyde or ketone was furnished by the resistance of the carbonyl moiety toward silver oxide oxidation, 2,4-dinitrophenylhydrazone, oxime, and semicarbazone formation. Further support for this conclusion was obtained when a qualitative determination[1b] of the optical rotatory dispersion (700–300 mμ) of I failed to show any Cotton effect.

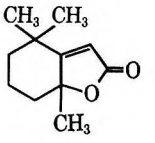
The absorption maximum,[5] in cyclohexane, at 208 mμ (log ε 4.05), is consistent with an α,β-unsaturated γ-lactone structure. Catalytic hydrogenation of I afforded a dihydro derivative II which showed no maximum in the ultraviolet spectrum and exhibited a carbonyl absorption at 1770 cm^{-1} in the infrared spectrum. A molecular weight of 182 was found for the dihydro derivative by mass spectral analysis.

The nuclear magnetic resonance spectrum[6] of I shows signals for a total of 16 protons. Three methyl groups (three three-proton singlets at τ 8.78, 8.73, and 8.50), a complex pattern in the 8.0–8.5 region, and a vinyl hydrogen (one-proton singlet at 4.48) were observed. The spectrum of the hydrogenated compound II did not show any signals in the vinyl region. Instead, a complex multiplet (about three protons), attributable to the methylene hydrogens α to the lactone carbonyl and the methine hydrogen at the ring junction, appeared at τ 7.4–8.1, the most intense peak at 7.6 accounting for ~1.3 protons. The methyl signals were somewhat displaced compared to those in I, appearing at τ 9.07, 8.94, and 8.45.

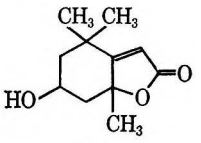
Various attempts were made to hydrolyze I without success. The compound is unchanged upon heating for several hours in methanolic potassium hydroxide, ethylene glycol–potassium hydroxide, or aqueous sulfuric acid.

Based on the physical data reported above and since the high-resolution mass spectrum afforded a strong $[M - (CH_3CO)]^+$ ion species, suggesting a saturated methylene group adjacent to the ring lactone function, two structures, I and XVI, were considered in the early stages of this investigation. Since the difficulty of isolation of I precluded degradative work, definitive evidence for the structure of the tobacco lactone was sought by the synthesis of both compounds depicted by structures I and XVI.

Compound I, which has the trimethylcyclohexanone ring of the higher terpenoids, is related to the compound loliolide (III), isolated from *Lolium perenne*[7] and



I



III

Digitalis purpurea,[8] whose structure has been recently confirmed by Horii, *et al.*[9]

Sakan and coworkers[10a] report the isolation of a lactone of structure I from the essential oil of the leaves of

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(2) Mass spectra were determined on either a Consolidated 21-103B, or, in the case of high-resolution spectra, a Consolidated 21-110 instrument. They will be reported in detail in a subsequent publication.

(3) Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(4) Infrared spectra were determined as thin films (liquids) and in KBr (solids) using either a Perkin-Elmer Model 21 or 221 spectrophotometer.

(5) Ultraviolet spectra were determined in cyclohexane solution using an Applied Physics Model 14 spectrophotometer in the wavelength range of 200–400 mμ.

(6) Nuclear magnetic resonance spectra were determined using Varian Associates A-60 and HA-100 instruments using $CDCl_3$ as the solvent and TMS as the reference compound.

(7) R. Hodges and A. L. Porte, *Tetrahedron*, **20**, 1463 (1964).

(8) T. Wada, *Chem. Pharm. Bull.* (Tokyo), **12** (9), 1117 (1964); **13** (1), 43 (1965).

(9) Z. Horii, T. Yagami, and M. Hanaoka, *Chem. Commun.*, **18**, 634 (1966).

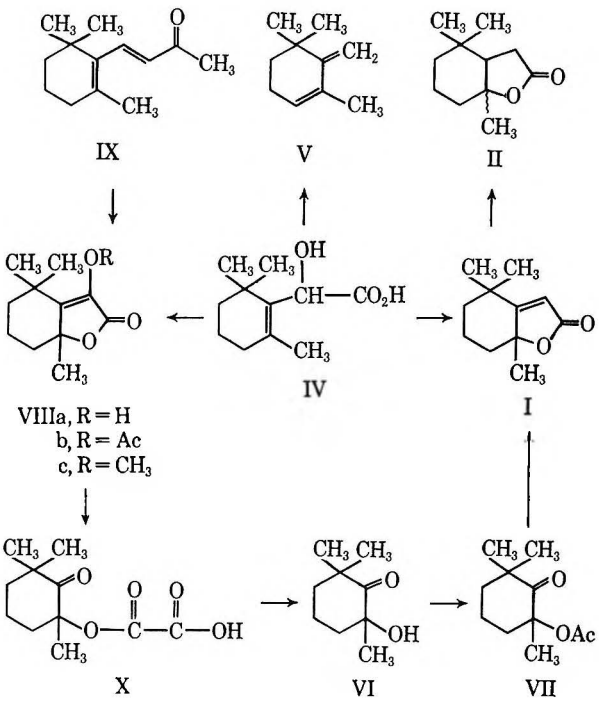
(10) (a) T. Sakan, S. Isoe, and S. B. Hyeon, *Tetrahedron Lett.*, 1623 (1967); (b) M. Mousseron-Canet, J. C. Mani, and J. P. Dalle, *Bull. Soc. Chim. Fr.*, 608 (1967); (c) J. Bricout, R. Viani, F. Müggler-Chavan, J. P. Marion, D. Reymond, and R. H. Egli, *Helv. Chim. Acta*, **50**, 1517 (1967). Since the completion of this work the three publications above appeared. The latter two, unavailable to us when the manuscript was prepared, were kindly pointed out by a reviewer. The reviewer also mentions the wide variation in the ultraviolet data and the noticeable differences in the infrared spectra reported. Correspondence with these authors establishes that the value reported by Sakan[10a] should be 214 mμ for the ultraviolet absorption. We assume both Sakan and Mousseron used ethanol as solvent as our material (I), we have since determined, has absorption maximum, in ethanol, at 214 mμ (log ε 4.03).

Actinidia polygama. Mousseron[10b] reports the isolation of I from the base-catalyzed rearrangement products obtained from the photooxidation of both β-ionone and β-cyclocitrylideneacetic acid methyl ester. The isolation of I from black tea is further reported by Bricout[10c] and coworkers. The physical property data from these publications and ours differ. The ultraviolet absorption values reported are 208, 217, and 241 mμ. These values appear widely separated for solvent differences if indeed the solvents were different. There are noticeable differences in the infrared spectra reported also. The carbonyl absorptions reported are 1745, 1750, and 1761 cm^{-1} while the double bond absorptions reported are 1625, 1630, 1637, and 1650 cm^{-1}. These values would appear to be greater than experimental error.

The lactone I readily prepared starting with the known 2,6,6-trimethylcyclohexene-1-glycolic acid (IV)[11] which is obtained from 2,2,6-trimethylcyclohexanone. Treatment of the glycolic acid with aqueous sulfuric acid afforded the desired lactone I in approximately 35% yield (as determined by vpc) as well as varied amounts of the diene pyronene V.[12] Heating of the glycolic acid at 200–220° afforded the lactone in high yield without contamination by the diene component. Alternately, the lactone could be prepared from the known hydroxytrimethylcyclohexanone VI. Preparation of the acetate VII followed by base-catalyzed ring closure[13] afforded the lactone I in 13% yield. Treatment of the intermediate glycolic acid IV with chromic anhydride–pyridine mixture afforded the "hydroxyionolactone" VIIIa, which is also obtained by the permanganate oxidation[14] of β-ionone (IX). Conversion of "hydroxyionolactone" prepared from the glycolic acid into its acetate and methyl ether gave the known compounds VIIIb and VIIIc,[14b] whose physical properties were identical with materials prepared from "hydroxyionolactone" synthesized from β-ionone. Treatment of "hydroxyionolactone" VIIIa with ozone[15] afforded in high yield the expected derivative X, which, upon basic hydrolysis, afforded the known keto alcohol VI.[16] No characterizable products, however, could be obtained upon similar treatment of the lactone I under a variety of conditions. The interrelationships existing in the above synthetic procedures are depicted in Scheme I.

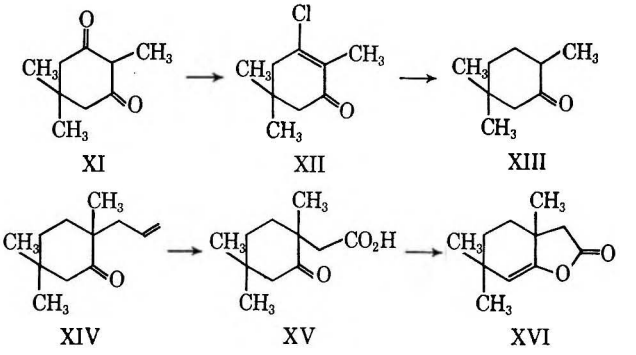
The synthesis of 1,4,4-trimethylcyclohexan-2-one-acetic acid enol lactone (XVI) was effected starting with the known 2,5,5-trimethylcyclohexane-1,3-dione (XI)[17] prepared from dimedone. Treatment of this β-diketone with phosphorus trichloride[18] gave the 3-chlorocyclohexenone XII in 67% yield. Catalytic hydrogenation of XII afforded the trimethylcyclohexanone XIII, which was further alkylated with allyl bromide to obtain 3-(1,4,4-trimethylcyclohexan-2-one)-prop-1-ene

SCHEME I



(XIV). Subsequent oxidation of XIV with ozone afforded the keto acid XV, which was converted into the enol lactone XVI upon treatment with acetic anhydride. The reaction sequence leading to the enol lactone XVI is shown in Scheme II.

SCHEME II



Experimental Section

Melting points and boiling points are not corrected. Gas chromatographic separations were effected using a F & M Model 500 chromatographic unit fitted with a 3/8 in. × 10 ft copper column containing 20% Carbowax 20M on 60–80 mesh Chromosorb P. The helium carrier gas flow was 100 ml/min and the unit was programmed from 100 to 225° at 5.6°/min.

Isolation of Lactone I from *N. Tabacum*.—Shredded leaves (2 lb) of *N. Tabacum* were extracted in a Soxhlet extractor with 3000 ml of methylene chloride. The cooled extract was dewaxed using cold acetone. After removal of solvent under reduced pressure, the residue was dissolved in ether. The ethereal solution was then extracted with cold 1 *N* hydrochloric acid followed by cold 1 *N* sodium hydroxide solution. The remaining neutral extract was washed with water and dried and the solvent was removed under reduced pressure. The residual material (10–12 g), in a minimum of hexane, was adsorbed on 300–500 g of silicic acid and eluted gradiently with acetone–hexane, with 150 ml aliquots being taken. The compound I was found in highest concentration in fraction 11 (5% acetone–95% hexane) as verified by vpc. Repeated trapping of the appropriate peak (26-min retention time under our standard conditions) on the gas chromatographic unit afforded 1–2 μl of the desired lactone

(11) J. D. Chanley, E. Chow, and H. Sobotka, *J. Amer. Chem. Soc.*, **77**, 6056 (1955), in which the compound is misnamed 2,2,6-trimethylcyclohexene-1-glycolic acid.

(12) G. Ohloff, *Ann.*, **627**, 79 (1959).

(13) H. G. Lehmann, *Angew. Chem. Intern. Ed. Engl.*, **4**, 783 (1965).

(14) (a) Tieman, *Ber.*, **31**, 857 (1898); (b) C. J. W. Brooks, G. Eglinton, and D. S. Magrill, *J. Chem. Soc.*, 308 (1961).

(15) Ozone was generated using a laboratory Welsbach ozonator.

(16) C. L. Stevens and A. J. Weinheimer, *J. Amer. Chem. Soc.*, **80**, 4072 (1958).

(17) (a) T. G. Halsall and D. B. Thomas, *J. Chem. Soc.*, 2431 (1956); (b) R. D. Desai, *ibid.*, 1079 (1932); (c) E. G. Meek, J. H. Turnbull, and W. Wilson, *ibid.*, 811 (1953).

(18) R. L. Frank and H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **72**, 1645 (1950).

I from 200 μl of the crude column chromatographic fraction. The analytical sample was prepared by a second rectification of the material by vpc.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.90, 73.07; H, 9.16, 9.31.

2-Hydroxy-2,6,6-trimethylcyclohexylideneacetic Acid γ-Lactone (I). Procedure 1.—2,6,6-Trimethylcyclohexene-1-glycolic acid (IV, 50 μl)[11] was added to 100 ml of 50% v/v aqueous sulfuric acid and the mixture heated under reflux for 2 hr. The cooled solution was extracted with three 100-ml portions of ether. The extracts were washed with 25 ml of 5% aqueous sodium hydroxide and to neutrality with water. The solution was dried and filtered and the solvent was removed; 5-μl samples of the residue were trapped from the gas chromatographic unit. The infrared, ultraviolet, and high resolution mass spectra of the synthetic compound were identical with those of the natural product. An additional material (*ca.* 35% of the total) having a retention time of 22 min was identified as pyronene[12] by comparison of their infrared spectra.

Procedure 2.—2,6,6-Trimethylcyclohexene-1-glycolic acid (IV, 3.7 g) in an evacuated tube was heated at 219° for 1 hr in a bath of phenethyl alcohol. After cooling, the contents of the tube were dissolved in ether and the solution was washed with aqueous sodium bicarbonate, saturated sodium chloride solution, and water. The dried solution was evaporated under reduced pressure to obtain 3.0 g of a tan oil. Distillation gave 2.1 g of a colorless liquid, bp 108–109° at 800 μ, which crystallized on cooling: mp 42–43°; ir 1761 cm^{-1} (strong, α,β-unsaturated lactone carbonyl), 1637 cm^{-1} (weak, double bond).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.12; H, 8.83.

Procedure 3.—6-Hydroxy-2,2,6-trimethylcyclohexanone (VI, 292 mg)[16] was dissolved in 2 ml of isopropenyl acetate containing a crystal of *p*-toluenesulfonic acid. After the solution was allowed to stand overnight, the volatile material was removed under reduced pressure and the residue was dissolved in ether. The ethereal solution was washed with aqueous sodium bicarbonate, saturated sodium chloride solution, and water. After drying, removal of the solvent afforded 222 mg of VII as an oil: ir 1736 cm^{-1} (strong, ester function), 1712 cm^{-1} (strong, ring ketone).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.80; H, 9.23.

The keto acetate (100 mg) was dissolved in 2 ml of toluene and 50 mg of potassium *t*-butoxide added. After the mixture was allowed to stand overnight, ether was added; the mixture was washed with water. Removal of the solvent under reduced pressure afforded a clear oil (20 mg) whose major peak (~90%) on vapor phase chromatography afforded the lactone I, identified by mass, infrared and nmr analyses.

2-Hydroxy-2,6,6-trimethylcyclohexylacetic Acid γ-Lactone (II).—The hydrogenation of natural lactone I was effected using platinum oxide catalyst in glacial acetic acid and a Parr laboratory shaker at room temperature and a pressure of 20–25 lb of hydrogen for 1 hr. The product was isolated by vpc trapping. The product exhibited a molecular ion of 182 in the mass spectrum; no absorption in the ultraviolet; ir 1770 cm^{-1} (strong, lactone carbonyl), no absorption in the double-bond region.

2-Hydroxy-2,6,6-trimethylcyclohexanone Oxalate (X).—"Hydroxyionolactone" (VIIIa, 1.50 g), prepared from β-ionone,[14] was dissolved in 50 ml of anhydrous ethyl acetate. Ozone–oxygen[16] (~3% ozone) was passed into the ice-cooled solution until an excess was indicated by the KI–H_3BO_3 trap. The solution was then transferred to the Parr bottle along with 300 mg of PtO_2 and hydrogenated overnight at 40-lb pressure. The catalyst was removed by filtration and the solution was evaporated to afford 1.45 g of an oil which crystallized on standing. Recrystallization of the solid material from ether–hexane (ice cold) gave 600 mg of 2-hydroxy-2,6,6-trimethylcyclohexanone oxalate (X), mp 103–104°, with a second crop of ~100 mg recoverable from the mother liquor. The analytical sample exhibited in the ir spectrum (Nujol) a broad band at 3700–2400 cm^{-1} (acid and hydrogen-bonded carbonyl), 1782 and 1680 cm^{-1} (strong, carbonyl functions).

Anal. Calcd for $C_{11}H_{16}O_6$: C, 57.88; H, 7.07. Found: C, 57.91; H, 7.29.

2-Hydroxy-2,6,6-trimethylcyclohexanone (VI).—To 10 ml of methanol containing 0.663 mg of potassium hydroxide was added 201 mg of keto ester X. After the solution was allowed to stand overnight, the mixture was filtered and extracted with cold ether. The ether solution was washed with 5% aqueous sodium hydroxide and to neutrality with water. Evaporation of the dried solution afforded 103 mg of an oil: ir 3420 cm^{-1} (strong, OH stretch), 1698 cm^{-1} (very strong, six-membered ring carbonyl), 1156 cm^{-1} (strong, *t*-hydroxyl).

Treatment of the keto alcohol with pyridine–acetic anhydride afforded the acetate VII whose infrared and mass spectra were identical with those of the compound prepared above.

Oxidation of 2,6,6-Trimethylcyclohexene-1-glycolic Acid (IV).—Chromium trioxide (87 mg) was dissolved in 5 ml of pyridine, cooled to 0° and a cooled solution of the glycolic acid (174 mg) in 3 ml of pyridine was added. The mixture was left in the refrigerator overnight and then stirred at room temperature an additional 3 hr. Water (10 ml) was added and the mixture was extracted with ether. The ether layer was extracted with 5% aqueous hydrochloric acid followed by washing with water. Evaporation of the solvent afforded a dark brown residue, which was further extracted with boiling heptane to obtain 19 mg of a solid, mp 125–130°. The infrared spectrum of this material was identical[14b] with that of material prepared from β-ionone (mp 129–131°). The acetate exhibited the following characteristics: mp 70–71°; λ_{max} 216 mμ (ε 13,300); ν_{max} 1780 cm^{-1} (broad, very strong, carbonyls) and 1680 cm^{-1} (unsaturation) [lit.[14b] mp 66–67°; λ_{max} 216.5 mμ (ε 14,000); ν_{max} 1787 cm^{-1} (very strong) and 1776 cm^{-1} (very strong), γ-lactone and enolic acetate carbonyl]. The methyl ether exhibited the following characteristics: λ_{max} 227 mμ; ν_{max} 1763 cm^{-1} (very strong, lactone carbonyl) and 1663 cm^{-1} (strong, double bond) [lit.[14b] λ_{max} 226 mμ (ε 11,000); ν_{max} 1763, 1660, 2868, and 2845 cm^{-1}].

2,5,5-Trimethyl-3-chlorocyclohex-2-en-1-one (XII).—2,5,5-Trimethylcyclohexane-1,3-dione (XI) was prepared by the methylation of dimedone.[17] The reaction of XI with phosphorus trichloride was effected under the conditions described by Frank and Hall.[18]

2,5,5-Trimethylcyclohexanone (XIII).—A solution of 2,5,5-trimethyl-3-chlorocyclohex-2-en-1-one (XII, 23.4 g) in 200 ml of glacial acetic acid containing 11.3 g of anhydrous sodium acetate was shaken with 1.5 g of 5% palladium–carbon catalyst at room temperature and 25 lb of hydrogen. The catalyst was removed by filtration and the acetic acid was removed under reduced pressure. The residue was dissolved in ether. The resultant solution was washed with dilute sodium hydroxide solution and water. After drying, the solvent was removed. Distillation of the residue afforded 15.9 g of 2,5,5-trimethylcyclohexanone: bp 51–52° (4 mm) [lit. bp 71–73° (12 mm)[17a] and 79–80° (21 mm)[19]].

3-(1,4,4-Trimethylcyclohexan-2-one)prop-1-ene (XIV).—2,5,5-Trimethylcyclohexanone (XIII, 20.5 g) in 50 ml of dry ether was added to an ether suspension of lithamide (prepared from 1.06 g of lithium and 500 ml of anhydrous ammonia followed by replacement of the ammonia with 300 ml of dry ethyl ether). The mixture was heated at the reflux temperature for 3 hr, cooled to 0° and allyl bromide (18 g in 40 ml ether) was added in one portion. The mixture was heated at the reflux temperature for 3 hr, cooled and water was added to dissolve the precipitated salts. The ether layer was washed with water and dried. Removal of the solvent under reduced pressure afforded a residual oil (25.0 g) which was vacuum distilled to obtain 10.6 g of XIV: bp 86–89° (4.5 mm); ir 1718 cm^{-1} (strong, ketone) and 1647 cm^{-1} (unsaturation).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.95; H, 11.18. Found: C, 79.81, 79.71; H, 11.30, 11.06.

The thiosemicarbazone derivative had mp 124–125°.

Anal. Calcd for $C_{13}H_{23}N_3O$: C, 61.62; H, 9.15; N, 16.58; S, 12.66. Found: C, 61.49; H, 9.08; N, 16.37; S, 12.85.

1,4,4-Trimethylcyclohexan-2-oneacetic Acid (XV).—3-(1,4,4-Trimethylcyclohexan-2-one)prop-1-ene (XIV, 8.0 g) was dissolved in 250 ml of methylene chloride, the solution was cooled to −60 to −65° and a 3% ozone–oxygen mixture was passed through the solution for 15 min. Glacial acetic acid (175 ml) was added to the warmed (30°) solution and the methylene dichloride was removed under diminished pressure. The acetic acid solution of the ozonide was added over 20 min to a cooled solution (0°) of 150 ml of water, 1 ml of concentrated sulfuric acid, and 10 ml of 29% hydrogen peroxide. The oxidizing mixture was heated at the reflux temperature for 1.5 hr and then allowed to stand overnight at room temperature. The

(19) F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959).

mixture was evaporated to dryness under reduced pressure. The residue was extracted with ether and the ether solution was extracted with two 30-ml portions of 5% sodium hydroxide. The combined base extract was neutralized in the cold with 5% hydrochloric acid and reextracted into ether. The ether solution was washed with water and dried. Removal of the solvent under reduced pressure afforded 7.7 g of an oil. Low-boiling material was distilled to 128° (0.2 mm) and the residue (5.0 g) was crystallized from ether to obtain XV: mp 71–77°; ir 3700–2400 cm^{-1} (broad band, acid hydroxyl) and 1721 cm^{-1} (strong, ketone); analytical sample, mp 77–78°.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.42; H, 9.05.

The thiosemicarbazone derivative had mp 185–186°.

Anal. Calcd for $C_{12}H_{21}N_3SO_2$: C, 53.11; H, 7.80; N, 15.48; S, 11.82. Found: C, 53.35; H, 7.62; N, 15.32; S, 11.63.

1,4,4-Trimethylcyclohexan-2-oneacetic Acid Enol Lactone (XVI).—1,4,4-Trimethylcyclohexan-2-oneacetic acid (XV, 200 mg) was heated for 12 hr in 5 ml of acetic anhydride containing 100 mg of anhydrous potassium acetate. The solution was cooled and water was added. The resultant acetic acid solution was extracted with ether; the combined ether extracts were washed with saturated sodium bicarbonate and water. Removal of the solvent under reduced pressure afforded 165 mg of an oil. The analytical sample was obtained by adsorption of the material on Florisil (30:1) followed by elution with benzene: ir 1802 cm^{-1} (strong, lactone carbonyl), 1701 cm^{-1} (unsaturation); mp 44.5–45°.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.11; H, 8.88.

The nmr spectrum showed the following: three methyl singlets at τ 9.01 (3 H), 8.93 (3 H), and 8.80 (3 H); singlets at τ 7.63 (2 H) and 5.03 (1 H); and two multiplets centered at τ 8.41 (2 H) and 8.31 (2 H).

Registry No.—I, 15356-74-8; II, 16778-27-1; VI, 7500-42-7; VII, 16797-54-9; X, 16797-55-0; XIV, 16778-23-7; thiosemicarbazene derivative of XIV, 16778-24-8; XV, 16778-25-9; thiosemicarbazene derivative of XV, 16797-44-7; XVI, 16778-26-0.

Pyrimidine Nucleosides. I. The Synthesis of 6-Methylcytidine, 6-Methyluridine, and Related 6-Methylpyrimidine Nucleosides[1]

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Received March 13, 1968

The first successful synthesis of 6-methylpyrimidine nucleosides has been realized. 6-Methylcytidine (VIII) and 6-methyl-2′-deoxycytidine (XI) have now been prepared by direct utilization of 6-methylcytosine (IV) *via* silylation and subsequent treatment with the appropriate acetohalo sugar in acetonitrile. Conversion of 6-methylcytidine into 6-methyluridine (IX) has been achieved in 65% yield. This direct glycosidation procedure applied to 6-methyluracil gave 6-methyl-3-β-D-ribofuranosyluracil (IIa) as the major product. Utilization of this general method has resulted in preparation of 5,6-dimethyluridine (XIII). A new route to the synthesis of 6-methylcytosine (IV) is reported.

Although thymidine, 5-methyl-2′-deoxycytidine,[2] 5-methylcytidine,[3,4] and 5-methyluridine[4,5] have been isolated from various sources of nucleic acid and each has been synthesized chemically[6,7] the corresponding 6-methylpyrimidine nucleosides are unknown. Various unsuccessful attempts to prepare N_1-glycosyl derivatives of 6-methyluracil have been recorded[8,9] and date back to the work of Fischer.[10] The only direct N_1-glycosidation of a 6-substituted uracil, cytosine, or thymine derivative disclosed in the literature is the preparation of orotidine reported by Curran and Angier[11] by coupling the mercury derivative of *n*-butyl orotate. In this latter instance the yield reported was very low and 3-β-D-ribofuranosylorotic acid was the main product.[11]

Newmark and Goodman[8] utilized 6-methyl-2,4-diethoxypyrimidine and 6-methyl-2-ethylthio-4-ethoxypyrimidine in an unsuccessful attempt to prepare 6-methylpyrimidine *N*-glycosides by the Hilbert–Johnson method.

Recent success in utilizing trimethylsilyloxypyrimidine derivatives[12,13] in a *modified* Hilbert–Johnson procedure[14] suggested a reinvestigation of the problem of the synthesis of 6-methylpyrimidine nucleosides. The readily available 6-methyluracil was converted into 6-methyl-2,4-bis(trimethylsilyloxy)pyrimidine (I) with hexamethyldisilazane.[12] Treatment of I with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in acetonitrile gave a 16% yield of crystalline 3-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-6-methyluracil (II). Treatment of II with sodium methoxide gave a 66% yield of 3-β-D-ribofuranosyl-6-methyluracil (IIa) (see Scheme I).

Assignment of glycosidation at N_3 was made on the basis of the significant bathochromic shift of 25 mμ in basic solution accompanied by a substantial increase in ϵ_{max} which is characteristic of N_3-substituted uracils.[15–17]

Treatment of I with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide under similar conditions yielded after fractionation a homogeneous syrup, 3-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-methyluracil (III) which exhibited a coupling constant $J_{1',2'}$ of less than 1 cps for $H_{1'}$ which established the anomeric config-

(1) This work was supported by Research Grants CA-08109 and CA-08109-02 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) J. W. Littlefield and D. B. Dunn, *Nature*, **181**, 254 (1958); see also C. A. Dekker and D. T. Elmore, *J. Chem. Soc.*, 2864 (1951).

(3) J. W. Littlefield and D. B. Dunn, *Biochem. J.*, **70**, 642 (1958).

(4) R. H. Hall, *Biochemistry*, **4**, 661 (1965).

(5) D. B. Dunn, *Biochim. Biophys. Acta*, **38**, 176 (1960).

(6) J. J. Fox, D. Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *J. Amer. Chem. Soc.*, **81**, 178 (1959).

(7) J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, *ibid.*, **78**, 2117 (1956).

(8) P. Newmark and I. Goodman, *ibid.*, **79**, 6446 (1957).

(9) J. J. Fox and I. Wempen, *Advan. Carbohyd. Chem.*, **14**, 335 (1959).

(10) E. Fischer and B. Helferich, *Ber.*, **47**, 210 (1914).

(11) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **31**, 201 (1966).

(12) E. Wittenburg, *Z. Chem.*, **4**, 303 (1964).

(13) T. Nishimura and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **12**, 352, 357 (1964).

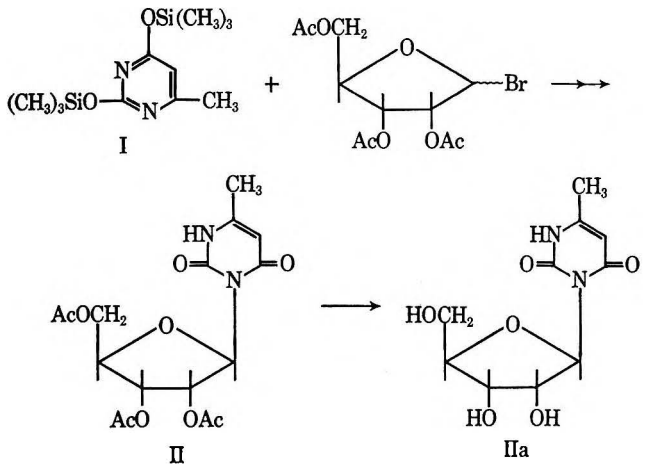
(14) M. G. Stout and R. K. Robins, *J. Org. Chem.*, **33**, 1219 (1968).

(15) D. Shugar and J. J. Fox, *Biochim Biophys. Acta*, **23**, 295 (1957).

(16) J. P. Scannell and F. W. Allen, *J. Org. Chem.*, **25**, 2143 (1960).

(17) M. Sano, *Chem. Pharm. Bull.* (Tokyo), **10**, 320 (1962).

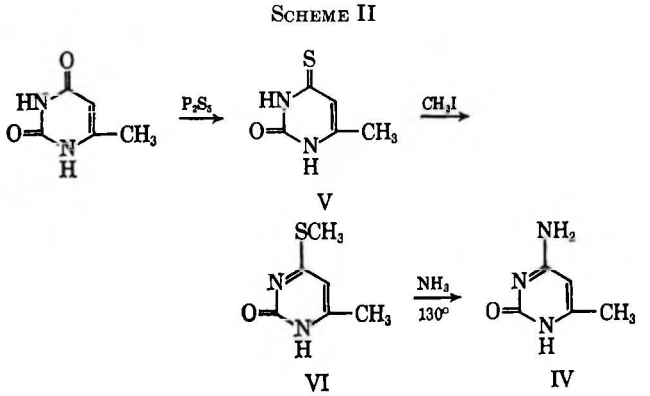
SCHEME I



uration[18] as β. Debenzoylation of III with methanolic ammonia gave a residual syrup which could not be crystallized but was acetylated to yield crystalline II in an over-all 18% yield from I. The identity of the product II obtained *via* 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide or *via* III established the β configuration for II.

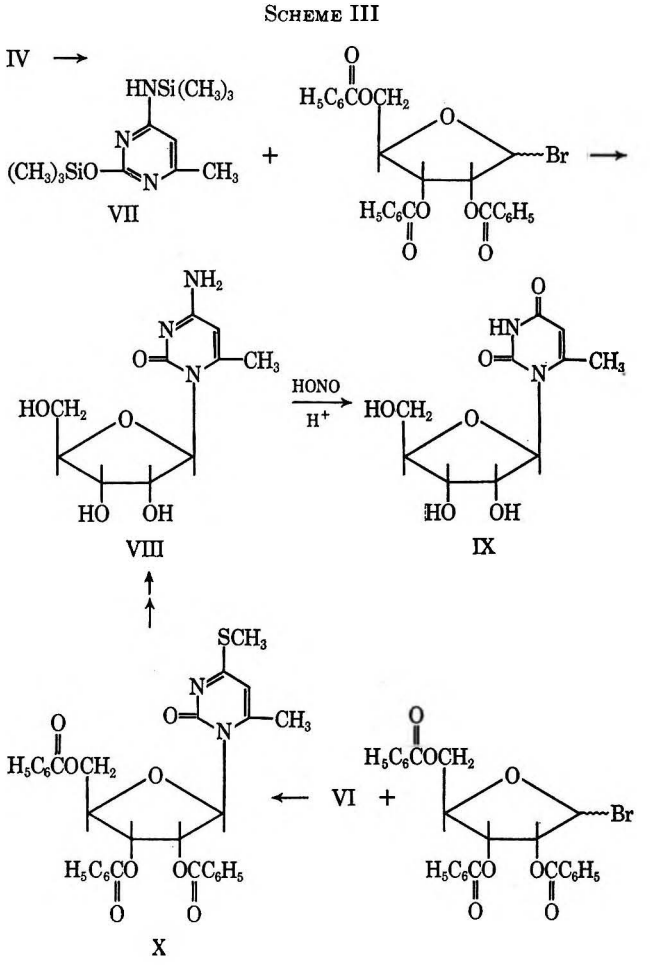
The isolation of the N_3-glycoside of 6-methyluracil is not wholly unexpected since the work of Curran and Angier[11] has shown that with a 6 substituent the mercury coupling procedure resulted in the 3-β-D-ribofuranosyl derivative as the major product. In the present study however, none of the desired 1-(β-D-ribofuranosyl)-6-methyluracil could be isolated from direct glycosidation of I. In view of these results 6-methylcytosine[19] (IV) was selected for further glycosidation studies. Since rather large quantities of 6-methylcytosine were required a new synthesis was devised in our laboratory which now makes 6-methylcytosine readily available from 6-methyluracil. 6-Methyluracil was treated with phosphorus pentasulfide in pyridine to yield 6-methyl-4-thio-2-pyrimidone (V) which was methylated with methyl iodide to provide 6-methyl-4-methylthio-2-pyrimidone (VI) in excellent yield. Replacement of the 4-methylthio group was accomplished with alcoholic ammonia at 130° to provide large white needles of 6-methylcytosine (IV) in excellent yield (Scheme II). Treatment of

SCHEME II



6-methylcytosine (IV) with hexamethyldisilazane gave an intermediate hexamethyldisilyl derivative VII which was utilized directly in the present study (Scheme III). Treatment of VII with 2,3,5-tri-*O*-benzoyl-D-

SCHEME III



ribofuranosyl bromide in acetonitrile gave a 40% yield of pure 6-methylcytidine (VIII) after chromatography and debenzoylation. Treatment of 6-methylcytidine in 2 *N* acetic acid in the presence of sodium nitrite gave 6-methyluridine (IX) in 65% yield. The 6-methylpyrimidine nucleosides VIII and IX were not hydrolyzed with 1 *N* sodium hydroxide at 100° for 2.5 hr and were resistant to 0.1 *N* hydrochloric acid at 100° for 2 hr. These conditions are known to hydrolyze *O*-glycosides.[20] The infrared spectrum of IX exhibited strong carbonyl absorption bands at 1660, 1675, and 1700, 1725 cm^{-1}, respectively. These data eliminate *O*-glycoside structures.[16]

Assignment of the D-ribose moiety to N_1 in 6-methylcytidine was made on the basis of ultraviolet absorption spectral data. The ultraviolet absorption spectra of 6-methylcytidine (VIII) closely resembles that of cytidine and at pH 11 exhibits a band at λ_{max} 271 mμ. This is vastly different from the spectrum of 3-methylcytosine which exhibits a band at λ_{max} 294 at pH 12. Similarly comparison of the ultraviolet absorption spectra of 6-methyluridine (IX) and uridine shows considerable similarity. 6-Methyluridine exhibits absorptions at $\lambda_{max}^{pH\ 1}$ 261 mμ (ϵ 11,200) and $\lambda_{max}^{pH\ 11}$ 262 mμ (ϵ 9400). The ultraviolet absorption spectra of

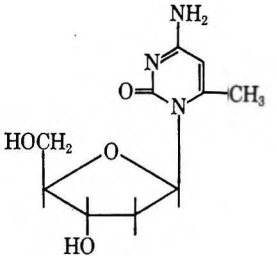
(18) K. L. Rhinehart, Jr., W. S. Chilton, M. Hickens, and W. J. von Phillips, *J. Amer. Chem. Soc.*, **84**, 3216 (1962); see also R. U. Lemieux and D. R. Lineback, *Ann. Rev. Biochem.*, **32**, 155 (1963).

(19) C. O. Johns, *Amer. Chem. J.*, **40**, 348 (1908).

(20) T. L. V. Ulbricht and G. T. Rogers, *J. Chem. Soc.*, 6125 (1965).

3-β-D-ribofuranosyluracil[16] on the other hand is characterized by a bathochromic shift in alkali from $\lambda_{max}^{pH\ 2}$ 261 mμ (ε 8000) to $\lambda_{max}^{pH\ 12}$ 292 mμ (ε 11,400) and is accompanied by a characteristic increase in the extinction coefficient. Assignment of β configuration to 1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-methylcytosine was made since this derivative in deuteriochloroform exhibited a sharp singlet at δ 5.91 due to $H_{1'}$ proton.[18] This established β configuration for both 6-methylcytidine (VIII) and 6-methyluridine (IX).

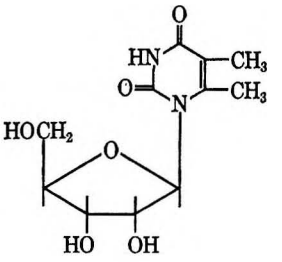
A second route to the synthesis of 6-methylcytidine (VIII) was from 6-methyl-4-methylthio-2-pyrimidone (VI) and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide which gave a crude syrup (X) which was treated with alcoholic ammonia at 80° to give a product (8% yield) identical with 6-methylcytidine (VIII) prepared from 6-methylcytosine (IV). The successful preparation of 6-methylcytidine suggested that this procedure might be applicable to the synthesis of 6-methyl-2′-deoxycytidine (XI).



XI

Thus 3,5-di-*O*-*p*-toluyl-2-deoxy-D-ribofuranosyl chloride[21] and the hexamethyldisilyl derivative VII were mixed in dry acetonitrile in the presence of molecular sieves. Chromatography of the crude reaction syrup on alumina gave two major fractions consisting of the β and α anomers, respectively. Treatment of the first fraction with methanolic ammonia yielded a 14% yield of crystalline 6-methyl-2′-deoxycytidine, the β anomer XI. Similar treatment of the second fraction yielded 1-(2′-deoxy-α-D-ribofuranosyl)-6-methylcytosine (XII). The assignment of anomeric configuration was readily made by a comparison of the pmr spectra of XI and XII measured in deuterium oxide with an internal standard of sodium 2,2-dimethyl-2-silapentane 5-sulfonate. The anomeric proton of XII consisted of a multiplet of four peaks centered at δ 6.33 ppm (width 14.2 cps, "$J_{H_{1'}}$" = 6.2 and 8.0 cps). The anomeric proton of XI exhibited a pseudo triplet centered at δ 6.22 ppm (width 13.5 cps, $J_{1',2'}$ = 6.7 cps). These data clearly allow assignment of XII as the α anomer and XI as the β anomer.[22-24] It is noteworthy that in the case of the present reaction procedure the β anomer predominated whereas with 3,5-di-*O*-*p*-toluyl-2-deoxy-D-ribofuranosyl chloride in the Hilbert–Johnson synthesis of 2′-deoxyribofuranosylpyrimidines the major, and often the sole product, is the α anomer.[24]

The importance of substituent groups in the pyrimidine ring on the orientation of the entering sugar moiety is illustrated by the fact that, although 2,4-bis(trimethylsilyloxy)-6-methylpyrimidine gave almost exclusively ribosidation at position N_3 when 2,4-bis(trimethylsilyloxy)-5,6-dimethylpyrimidine was employed, under similar conditions the main product was the N_1 isomer 5,6-dimethyluridine (XIII). Thus 2,3,5-tri-*O*-



XIII

acetyl-D-ribofuranosyl bromide and 2,4-bis(trimethylsilyloxy)-5,6-dimethylpyrimidine gave XIII in 17% over-all yield after removal of the acetyl groups. Structural assignment for XIII follows similar lines as discussed for 6-methyluridine (IX).

Nishimura and Iwai[13] report that acetohalogenosugars did not condense with trimethylsilyloxypyrimidines in boiling benzene or xylene and preferred fusion as a method of nucleoside formation.[13,25] The present work and employment of a similar procedure in the recent synthesis of 1-β-D-ribofuranosyl-2,4-quinazolinedione[14] is convincing evidence that in many instances the general method of pyrimidine nucleoside formation here described is to be preferred and often succeeds where older procedures fail. The extension of these procedures to other sugars and additional 6-substituted pyrimidines is a subject presently under detailed investigation in our laboratory.

Experimental Section

Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. Specific rotations were measured in a 2-dm tube with a Rudolph precision polarimeter. Proton magnetic resonance (pmr) spectra were measured with appropriate internal standards of tetramethylsilane or sodium-2,2-dimethyl-2-silapentane 5-sulfonate with a Varian A-60 nmr spectrometer. Detection of components on SilicAR 7GF (Mallinkrodt) and alumina HF 254 (Brinkmann) was by ultraviolet light. Solvent proportions were by volume. Evaporations were performed under diminished pressure at 35° with a Buchi "Rotovapor."

Trimethylsilyl derivatives of various pyrimidines were prepared using the general procedure of Wittenburg.[12] The pyrimidines were heated under reflux in an excess of hexamethyldisilizane with a catalytic quantity of ammonium sulfate under anhydrous conditions until complete solution was achieved. The time of heating varied from 1 or 2 hr to approximately 20 hr. The excess hexamethyldisilazane was removed by distillation under diminished pressure and the residue (oil or crystalline solid) was used directly without further purification.

6-Methyl-3-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuransoyl)uracil (II). Method 1.—To Tetra-*O*-acetyl-β-D-ribofuranose (21.2 g) in dry dichloromethane (100 ml) at −60° was added a solution of dry dichloromethane (originally 100 ml) which had been saturated at −60° with dry hydrogen bromide gas. The mixture was protected from moisture and allowed to warm to near room temperature. The solution was evaporated to near dryness and the resulting syrup was treated with azeotropically dried toluene and the excess toluene removed. To the residue was added crystalline 2,4-bis(trimethylsilyloxy)-6-methylpyrimidine (18 g) followed by 250 ml of dry "Nanograde" acetonitrile.[26] The re-

(21) M. Hoffer, *Ber.*, **93**, 2777 (1960).
(22) M. J. Robins and R. K. Robins, *J. Amer. Chem. Soc.*, **87**, 4934 (1965).
(23) T. Nishimura and B. Shimizu, *Chem. Pharm. Bull.*, **13**, 803 (1965).
(24) (a) K. J. Ryan, E. M. Acton, and L. Goodman, *J. Org. Chem.*, **31**, 1181 (1966); (b) M. Prystas, J. Farkas, and F. Šorm, *Collect. Czech. Chem. Commun.*, **30**, 3123 (1965).
(25) T. Nishimura, B. Shimizu, and I. Iwai, *Chem. Pharm. Bull.*, **11**, 1470 (1963); **12**, 1471 (1963); T. Nishimura and B. Shimizu, *ibid.*, **13**, 803 (1965).
(26) Purchased from Mallinkrodt Chemical Works, St. Louis, Mo.

action mixture was sealed and stirred until solution occurred. After 3 days at room temperature the mixture was evaporated to a syrup and excess sodium bicarbonate was added. Water (50 ml) and ethanol (50 ml) were added and the mixture was evaporated to dryness. Coevaporation with absolute ethanol removed the last traces of moisture. The residue was extracted several times with dichloromethane and the dichloromethane solution was evaporated to dryness.

The residual syrup was dissolved in benzene (70 ml) and applied to a column (5.0 × 48 cm) of alumina[27] prepacked in benzene. The material was washed onto the column with benzene (1500 ml). Elution was started with benzene–ethyl acetate (4:1, 2 l.) and then continued with ethyl acetate. One-hundred milliliter fractions were collected beginning with the benzene–ethyl acetate (4:1), and the fractionation was monitored by tlc on alumina HF 254 with ethyl acetate as developer. The fast-moving sugar degradation products were removed by elution with benzene–ethyl acetate (4:1) in the early fractions. Fractions 33–72 which contained a single nucleoside component were pooled and evaporated to dryness. Trituration with ether yielded 4.0 g (16%) of II, mp 157–159°. Recrystallization of this product from dichloromethane–ether yielded 3.70 g of pure material: mp 159–160°; $\lambda_{max}^{pH\ 1}$ 264 mμ (ε 9200), $\lambda_{min}^{pH\ 1}$ 233 (1500), $\lambda_{max}^{pH\ 11}$ 289 (10,400), $\lambda_{min}^{pH\ 11}$ 246 (1100); λ_{max}^{KBr} 1740 (OAc), 1720 (shoulder of peak at 1740), and 1650 cm^{-1} [C=O of 6-methyluracil moiety; 6-methyluracil has absorptions at 1720 and 1650 cm^{-1}]; pmr ($CDCl_3$), δ 2.08 (s, 9, OAc), 2.17 (s, 3, 6-CH_3), 4.00–4.63 (m, 3, 5′-CH_2OH overlapped by a sugar ring H), 5.48–5.84 (m, 3, 5-H and sugar ring H's), 6.45 (d, 1, 1′-H, $J_{1',2'}$ = 1.7 cps), 10.40 ppm (s, 1, 1-NH).

Anal. Calcd for $C_{16}H_{20}N_2O_9$: C, 49.99; H, 5.24; N, 7.29. Found: C, 49.77; H, 5.44; N, 7.46.

Method 2.—To tri-*O*-benzoyl-D-ribofuranosyl bromide prepared from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (20 g) was added 2,4-bis(trimethylsilyloxy)-6-methylpyrimidine (23 g) and dry acetonitrile (480 ml). The mixture was protected from moisture and stirred until solution was achieved. After 6 days at room temperature the solution was evaporated to a syrup. Sodium bicarbonate (excess), water and ethanol were added and the mixture was evaporated to dryness as in method 1. The residue was extracted with dichloromethane and the dichloromethane solution was evaporated to a syrup. A solution of the syrup in tetrahydrofuran (50 ml) was poured with stirring into pentane (1200 ml) to give a semisolid, yield 21.3 g. This material was dissolved in a small volume of benzene and applied to a column (5.0 × 48 cm) of alumina prepacked in benzene. Benzene (1500 ml) was added and the benzene fractions were discarded. The elution was effected in a manner similar to that outlined above for the acetylated nucleoside. The ethyl acetate fractions were pooled and evaporated to a yellow syrup (8.4 g) which was dissolved in a small volume of benzene and fractionated once more on another column (3.0 × 45 cm) of alumina. The appropriate fractions (as determined by tlc were pooled and evaporated to dryness to yield 5.98 g of homogeneous material). The pmr spectrum of this syrup in deuteriochloroform displayed peaks at δ 2.08 (s, 3, 6-CH_3), 4.52–4.90 (3, 5′-CH_2OH and a sugar ring H), 5.56 (s, 1, 5-H), 6.00–6.35 (m, 2, sugar ring H's), 6.68 (s, 1,1′-H, $J_{1',2'}$ < 1 cps), 7.12–7.70, 7.82–8.20 (m, 15, benzoate H's), 10.44 ppm (s, 1, 1-NH). The small value for $J_{1',2'}$ (<1 cps) of the pmr signal for the anomeric proton established the anomeric configuration as β. To the above syrup (4.98 g) was added a solution of methanol (150 ml) saturated at 0° with ammonia and the mixture sealed in a steel bomb and heated at 80° overnight. The solution was filtered and evaporated to dryness. The residue was stirred with dichloromethane and the resulting gummy solid was removed by filtration, yield 2.80 g. This solid was dissolved in acetic anhydride (20 ml)–pyridine (20 ml) and left at room temperature overnight. The solution was poured into water and ice and the mixture was extracted with dichloromethane. The dichloromethane extract was washed consecutively with two 100-ml portions of water, 1 *N* hydrochloric acid, aqueous sodium bicarbonate solution, and then finally with water. The dried ($MgSO_4$) solution was evaporated to dryness and the residue was crystallized from ether to yield 2.30 g (18%), mp 157–158°. Recrystallization produced pure material, mp 159–160°, which did not depress the melting point of the product prepared by method 1.

(27) Reagent aluminum oxide for chromatographic adsorption purchased from Merck and Co., Rahway, N. J.

6-Methyl-3-(β-D-ribofuranosyl)uracil (IIa).—To II (1.50 g) in anhydrous methanol (50 ml) was added sodium (0.2 g). The resulting solution was sealed and left at room temperature overnight. To the stirred solution diluted with methanol was added portionwise Dowex 50 (H^+, X4, 200–300 mesh) until the solution was no longer basic. The resin was removed by filtration and washed well with methanol. The filtrate and washings were evaporated to smaller volume and decolorized with charcoal. The solution was evaporated to a syrup which was crystallized slowly from isopropyl alcohol. The yield of IIa was 0.80 g (66%), mp 142–145°. Recrystallization from methanol–isopropyl alcohol produced pure material: mp 144–146°; $[\alpha]^{27}D$ −27.6 (c 1, water); λ_{max}^{KBr} 1650, 1725 cm^{-1} (C=O of 6-methyluracil moiety); $\lambda_{max}^{pH\ 1\ and\ pH\ 4}$ 265 mμ (ε 8700), $\lambda_{min}^{pH\ 1\ and\ pH\ 4}$ 235 (1500), $\lambda_{max}^{pH\ 11}$ 289 (9800), $\lambda_{min}^{pH\ 11}$ 244 (800), $\lambda_{max}^{pH\ 14}$ 289 (11,300), $\lambda_{min}^{pH\ 14}$ 247 (500); pmr (D_2O), δ 2.17 (s, 3, 6-CH_3), 3.60–4.15 (m, 3, 5-CH_2OH centered at 3.85 overlapped by 4′-H), 4.42 (t, 1, width 13.0 cps, $J_{3',2'}$ = 6.5 cps, 3′-H), 4.58–4.93 (2′-H overlapped by solvent centered at 4.72), 5.67 (s, 1, 5-H), 6.25 ppm (d, 1, $J_{1',2'}$ = 3.0 cps, 1′-H).

Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.61; H, 5.67; N, 10.65.

5,6-Dimethyluridine (XIII). Method 1.—To syrupy 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide prepared from tetra-*O*-acetyl-β-D-ribofuranose (10 g) was added crystalline 2,4-bis(trimethylsilyloxy)-5,6-dimethylpyrimidine (10 g) and dry acetonitrile (250 ml) and the mixture was stirred until solution occurred. After 3 days at room temperature the solution was evaporated to a syrup. This syrup was treated as in the synthesis of II, method 1, and the fractionation was monitered by tlc on alumina HF 254 with ethyl acetate–methanol (9:1) as developer. The crude carbohydrate fraction was eluted with benzene–ethyl acetate (4:1) and the crude nucleoside was then eluted with ethyl acetate. The ethyl acetate fractions were evaporated to dryness to yield 5.0 g of crude syrup which was again applied to an alumina column (3.2 × 48 cm) and the elution was achieved with benzene–ethyl acetate (4:1); 100-ml fractions were collected. Fractions 19–23 were pooled and evaporated to dryness. The residue was dissolved in methanol (50 ml) and the solution was saturated at 0° with ammonia. After remaining at room temperature overnight the solution was filtered and the filtrate evaporated to near dryness. The residue was crystallized from isopropyl alcohol to give crystals: mp 178–180°; yield 1.44 g (17%). Recrystallization from aqueous isopropyl alcohol produced pure material: mp 179–180°; $[\alpha]^{30}D$ −30.6° (c 1.47, water); λ_{max}^{KBr} 1650 and 1710 cm^{-1} (C=O of 5,6-dimethyluracil moiety, 5,6-dimethyluracil has the same absorptions); $\lambda_{max}^{pH\ 1\ and\ pH\ 4}$ 268 mμ (ε 10,400), $\lambda_{min}^{pH\ 1\ and\ pH\ 4}$ 236 (1700), $\lambda_{max}^{pH\ 11}$ 269 (7800), $\lambda_{min}^{pH\ 11}$ 246 (3800) and $\lambda_{max}^{pH\ 14}$ 271 (7600), $\lambda_{min}^{pH\ 14}$ 247 (3100); pmr (D_2O, CD_3COOD), δ 1.96 (s, 3, 5-CH_3), 2.40 (s, 3, 6-CH_3), 3.73–4.22 (m, 3, 5′-CH_2OH centered at 3.90 overlapped by 4′-H), 4.51 (t, 1, width 12.5, $J_{3',2'}$ = 6.0 cps, 3′-H), 4.92 (q, 1, width 10.0, $J_{2',3'}$ = 6.0 $J_{2',1'}$ = 3.7 cps, 2′-H), 5.79 (d, 1, $J_{1',2'}$ = 3.7 cps, 1′-H), 6.3–6.7 ppm (solvent).

Anal. Calcd for $C_{11}H_{16}N_2O_6$: C, 48.51; H, 5.92; N, 10.29. Found: C, 48.70; H, 6.15; N, 10.18.

Method 2.—Similar treatment of 2,4-bis(trimethylsilyloxy)-5,6-dimethylpyrimidine (14 g) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (prepared from 25 g of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose) gave after alumina chromatography a homogeneous syrup residue of 2′,3′,5′-tri-*O*-benzoyl-5,6-dimethyluridine which exhibited the following pmr spectrum in $CDCl_3$: 2.00 (s, 3, 5-CH_3), 2.30 (s, 3, 6-CH_3), 4.50–4.97 (m, 3, 5′,CH_2OH and a sugar ring H), 5.85 (s, 1, $J_{1',2'}$ < 1 cps, 1′-H), 6.12–6.30 (m, 2, sugar ring H's), 7.10–7.60 (m, 9, benzoate), 7.70–8.20 (m, 6, benzoate), 9.60 ppm (s, 1, 3-NH). The singlet at δ 5.85 ppm for the anomeric proton established the β configuration.[18] To this syrup was added methanol (200 ml) saturated with ammonia at 0° and the mixture was heated at 80° overnight in a steel bomb. The brown solution was filtered and evaporated to dryness. The residue was extracted with dichloromethane and the dichloromethane discarded. The residue was dissolved in acetic anhydride (50 ml)–pyridine (50 ml) and the solution was left at room temperature overnight. The solution was poured into water and ice and extracted with dichloromethane. The extract was washed consecutively with three portions of 1 *N* hydrochloric acid, water, aqueous sodium bicarbonate, and two portions of water. The dried ($MgSO_4$) solution was evaporated to dryness and the residue was dissolved in methanol (70 ml) saturated at 0° with ammonia. After standing overnight

the reaction solution was filtered and the filtrate was evaporated to dryness. The residue was crystallized from methanol–isopropyl alcohol to yield 1.50 g (11%), mp 179–180°. This product was identical with that prepared by method 1.

6-Methylcytidine (VIII) from 6-Methyl-4-methylthio-2-pyrimidone (VI). Method 1.—To 2-trimethylsilyloxy-6-methyl-4-methylthiopyrimidine (prepared from 5 g of VI) was added 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (prepared from 15 g of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose) in dry acetonitrile (70 ml). After 3 days at room temperature the solution was evaporated to a syrup and treated with sodium bicarbonate, water, and ethanol as in the preparation of II.

The crude syrup was dissolved in a small volume of benzene and applied to a column (5.0 × 35 cm) of alumina prepacked in benzene and the material was washed on with benzene (2 l.). Elution was achieved with benzene–ethyl acetate (19:1) and the fractionation was monitered by tlc with alumina HF 254 with chloroform, as developer. The first three fractions were of 200-ml volume and thereafter of 100-ml volume. Fractions 9–24 were pooled and evaporated to dryness to yield 2.34 g of a yellow syrup. To this syrup was added methanol (100 ml) saturated at 0° with ammonia. The solution was sealed in a steel bomb and heated at 80° overnight. The solution was filtered and evaporated to dryness. Water was added and the mixture was extracted twice with chloroform. The aqueous phase was evaporated to a crystalline solid. This material was dissolved in hot aqueous ethanol, treated with charcoal, and filtered. The filtrate was evaporated and the residue was crystallized three times from water–ethanol–isopropyl alcohol to yield white crystals: 0.66 g (8%); mp 230–232° dec (yellow crystals from *ca.* 208°); $[\alpha]^{30}D$ −41.5° (*c* 1.55, water); $\lambda_{max}^{pH\ 1}$ 278 mμ (ε 14,700), $\lambda_{min}^{pH\ 1}$ 241 (1500), $\lambda_{max}^{pH\ 4}$ 271 (9500), $\lambda_{min}^{pH\ 4}$ 251 (6400), $\lambda_{max}^{pH\ 11}$ 271 (9300), $\lambda_{min}^{pH\ 11}$ 253 (6400), $\lambda_{max}^{pH\ 14}$ 273 (9900), $\lambda_{min}^{pH\ 14}$ 252 (5800); pmr (D_2O), δ 2.37 (s, 3, 6-CH_3), 3.73–4.20 (m, 3, 5′-CH_2OH at 3.88 overlapped by 4′-H), 4.44 (t, 1, width 12.5 $J_{3',2'}$ = 6.0 cps, 3′-H), 4.67 (solvent), 4.85 (q, 1, width 10.5, $J_{2',3'}$ = 6.0, $J_{2',1'}$ = 3.5 cps, 2′-H), 5.73 (d, 1, $J_{1',2'}$ = 3.5 cps, 1′-H), 5.88 ppm (s, 1, 5-H).

Anal. Calcd for $C_{10}H_{15}N_3O_5$: C, 46.68; H, 5.88; N, 16.33. Found: C, 46.78; H, 5.94; N, 16.30.

6-Methylcytidine (VIII) from 6-Methylcytosine (IV). Method 2.—To the crystalline trimethylsilyl derivative prepared from 10 g of 6-methylcytosine, was added 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (from 25 g of the 1-*O*-acetyl derivative) and dry acetonitrile (150 ml). The mixture was sealed and stirred until solution occurred. After 3 days at room temperature the solution was evaporated to a syrup and treated with sodium bicarbonate, water, and ethanol and the mixture was evaporated to dryness. The last traces of moisture were removed by successive evaporations with absolute ethanol. The residue was extracted with dichloromethane and the extract was evaporated to dryness. This residue was again extracted with dichloromethane and the extract evaporated to yield 31.0 g of a syrup.

The bulk of the above syrup (22.43 g) was dissolved in a small volume of benzene and applied to a column (5.0 × 46 cm) of alumina prepacked in benzene. The material was washed on with benzene (1 l.). Elution was carried out with benzene–ethyl acetate (4:1), ethyl acetate, ethyl acetate–methanol (19:1), ethyl acetate–methanol (10:1), and finally with ethyl acetate–methanol (4:1). The fractionation was monitored by tlc on alumina HF 254 with ethyl acetate–methanol (4:1) as solvent and on SilicAR 7GF with ethyl acetate methanol (9:1) as solvent. Two-hundred milliliter fractions were collected up to fraction 32 and 100-ml fractions were collected thereafter. At fraction 10 the solvent was changed to ethyl acetate and at fraction 25 the solvent was changed to ethyl acetate–methanol (19:1). Fractions 32–71 which contained the main nucleoside component were pooled and evaporated to dryness to yield 10.28 g. The material remaining on the column (a mixture of two components) was finally eluted with ethyl acetate–methanol (9:1, 2 l.) and ethyl acetate–methanol (4:1, 3 l.) to yield 6.82 g of crude mixture which proved to be approximately 50% 6-methylcytidine. The contaminating component was not further identified.

The pmr spectrum of the major component in $CDCl_3$ exhibited peaks at δ 2.34 (s, 3, 6-CH_3), 4.50–4.95 (m, 3, 5′-CH_2OH at 4.79 overlapped by a sugar ring H), 5.91 (s, 1, $J_{1',2'}$ < 1 cps, 1′-H), 6.12 (s, 1, 5-H), 6.23–6.63 (m, 2, sugar ring H's), 7.17–7.68, 7.86–8.30 (m, 17, benzoate overlapping 4-NH_2). The signal assigned to the anomeric proton at δ 5.91 ppm had $J_{1',2'}$ < 1 cps and therefore[18] the anomeric assignment made was that of β. The residue, 10.28 g, representing the major component was dissolved in methanol (200 ml) saturated at 0° with ammonia and left at room temperature for 3 days. The solution was filtered and the filtrate was evaporated to a small volume. Crystallization occurred while the solution was being evaporated. Isopropyl alcohol was added and the volume was reduced further. The yield of white crystalline material was 3.70 g (40% from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose), mp 232–236°. The infrared spectrum was identical with that of VIII prepared by method 1. Attachment of the sugar moiety to N_3 was excluded since the ultraviolet spectrum of 3-substituted cytosines exhibit a bathochromic shift in alkali.[28]

6-Methyluridine (IX).—To 6-methylcytidine (VIII) (3.0 g) in 2 *N* acetic acid (600 ml) was added sodium nitrite (12 g). The resulting solution was sealed and left at room temperature for 2 days. The volume of the solution was reduced by evaporation at 35° and the solution was neutralized to pH 7 with dilute sodium hydroxide solution. Acid-washed AU-4 charcoal[29] (45 g) was added and the mixture was stirred for 2 hr. The mixture was filtered on a Celite pad and the charcoal was washed well with water. The charcoal pad was stirred with ethanol (500 ml), which had been saturated with ammonia at 0°, and filtered. This process was repeated three times. The combined filtrates were evaporated to dryness. The residue was dissolved in water (75 ml) and applied to a column (39 × 2.0 cm) of Dowex 50 (H^+, X4, 200-400 mesh). The nucleoside was washed off with water (1,500 ml). The acid (pH 1) eluate was evaporated at 35° to small volume and the solution treated with ethanol and evaporated to dryness. This process was repeated several times until a syrup was obtained. This syrup was crystallized from ethanol–ethyl acetate to yield 1.94 g (65%), mp 174–176°. Recrystallization from methanol–ethyl acetate produced pure material: mp 177–178°; $[\alpha]^{30}D$ −28.6° (*c* 1.52, water); λ_{max}^{KBr} 1660, 1675 cm^{-1} and 1700, 1725 cm^{-1} (carbonyl absorptions of the 6-methyluracil moiety). These strong carbonyl bands at 1660, 1675 cm^{-1} and 1700, 1725 cm^{-1} attest to existence of two carbonyl groups in the nucleoside. The compound also exhibited uv bands at $\lambda_{max}^{pH\ 1\ and\ pH\ 4}$ 261 mμ (ε 11,200), $\lambda_{min}^{pH\ 1\ and\ pH\ 4}$ 232 (1900), $\lambda_{max}^{pH\ 11}$ 262 (9400), $\lambda_{min}^{pH\ 11}$ 239 (4300), $\lambda_{max}^{pH\ 14}$ 264 (7900), $\lambda_{min}^{pH\ 14}$ 244 (4200); pmr (D_2O) signals were at δ 2.42 (s, 3, 6-CH_3), 3.77–4.22 (m, 3, 5′-CH_2OH at 3.91 overlapped by 4′-H), 4.45 (t, 1, width 12.5, $J_{3',2'}$ = 6.2 cps, 3′-H), 4.69 (solvent), 4.76–5.00 (q, 1, width 10.0, $J_{2',3'}$ = 6.2, $J_{2',1'}$ = 3.7 cps, 2′-H), 5.76 (d, 1, $J_{1',2'}$ = 3.7 cps, 1′-H), 5.83 ppm (s, 1, 5-H).

Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.34; H, 5.54; N, 10.72.

6-Methyl-4-thio-2-pyrimidone (V).—To a warm stirred solution of 6-methyluracil (12.6 g) dissolved in reagent grade pyridine (400 ml) was added phosphorus pentasulfide (6.6 g). The stirred solution was heated under reflux overnight. The solution was evaporated to dryness. The residue was boiled with ethanol and the mixture was filtered. The solid was dissolved in warm dilute aqueous ammonia and glacial acetic acid was added to precipitate the crude compound. This precipitate was dissolved in warm dilute ammonia and the solution was treated with charcoal and filtered. The hot filtrate was acidified with glacial acetic acid to give 8.25 g of yellow crystals, mp 337° (darkening at 325°). The reprecipitation process was twice repeated to give pure yellow crystals of V: mp 339–341°; $\lambda_{max}^{pH\ 1}$ 327 mμ (ε 23,400), $\lambda_{max}^{pH\ 11}$ 330 (22,200).

Anal. Calcd for $C_5H_6N_2OS$: C, 42.24; H, 4.25; N, 19.71; S, 22.55. Found: C, 42.33; H, 4.12; N, 19.86; S, 23.04.

Wheeler and McFarland[30] recorded mp >250° for this compound, prepared by another procedure.

Preparation of 6-Methyl-4-methylthio-2-pyrimidone (VI).—To 22.72 g of 6-methyl-4-thio-2-pyrimidone (V) in cold 1 *N* sodium hydroxide (500 ml, cooled in ice) was added methyl iodide (22.72 g) and the mixture was stirred vigorously for several hours during which time the reaction was gradually allowed to come to room temperature. The mixture was acidified with glacial acetic acid and the volume was reduced to one-fourth. The crude methylated product crystallized on cooling. The product was removed by filtration and the mother liquor evaporated to give another crop. The total yield was 20.8 g, mp 150–157°. The product was recrystallized from water to yield 17.7 g (71%),

(28) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 1348 (1962).
(29) Purchased from Barneby-Cheney, Columbus 19, Ohio.
(30) H. L. Wheeler and D. F. McFarland, *Amer. Chem. J.*, **42**, 431 (1909).

mp 163–167°. Two recrystallizations from ethyl acetate afforded pure material: mp 178–180°; $\lambda_{max}^{pH\ 1}$ 265 mμ (ε 3600), 321 (22,000), $\lambda_{max}^{pH\ 11}$ 298 (11,200).

Anal. Calcd for $C_6H_8N_2OS$: C, 46.13; H, 5.19; N, 17.94; S, 20.52. Found: C, 46.16; H, 5.30; N, 17.94; S, 20.59.

Wheeler and McFarland[30] recorded mp 174–175° for this compound prepared by another procedure.

Preparation of 6-Methylcytosine (IV).—6-Methyl-4-methylthio-2-pyrimidone (VI, 7.35 g) was dissolved in methanol, and the solution was filtered into a glass bomb liner. The solution was evaporated to dryness on a steam bath. Methanol (200 ml) saturated at 0° with ammonia was added and the vessel sealed in a bomb. The mixture was heated at 130° overnight. The resulting cooled solution contained large white needles: yield 5.66 g (96%); mp 361–363° dec; $\lambda_{max}^{pH\ 1}$ 276 mμ (ε 13,000), $\lambda_{min}^{pH\ 1}$ 238 (880), $\lambda_{max}^{pH\ 11}$ 267 (8000), $\lambda_{min}^{pH\ 11}$ 246 (3800), $\lambda_{max}^{pH\ 14}$ 280 (8900), $\lambda_{min}^{pH\ 14}$ 249 (1400).

Anal. Calcd for $C_5H_7N_3O$: C, 48.01; H, 5.64; N, 33.59. Found: C, 47.91; H, 5.76; N, 33.54.

Johns[19] reported mp >300° for this compound, prepared by another procedure.

6-Methyl-2′-deoxycytidine (XI).—3,5,-Di-*O*-*p*-toluyl-2-deoxy-D-ribofuranosyl chloride (35 g prepared[21] from 50 g of methyl 2-deoxy-3,5-di-*O*-*p*-toluylribofuranoside) was added to the crystalline trimethylsilyl derivative prepared from 15 g of 6-methylcytosine. Molecular sieves[31] (type 4A, 1/16-in. pellets, 20 g) and dry acetonitrile (450 ml) was added and the sealed mixture stirred at 20° for 4 days. The mixture was diluted with dichloromethane and filtered through Celite. The filtrate was evaporated to dryness. To the residue was added sodium bicarbonate, water, and ethanol and the mixture was finally evaporated to dryness. Evaporation with absolute ethanol removed the last traces of water. The residue was extracted with chloroform and with ethyl acetate. The combined extracts were evaporated to a syrup which was dissolved in benzene and applied to a column (5.1 × 43 cm) of alumina packed in benzene. The material was washed on with benzene (500 ml). Elution was accomplished with benzene–ethyl acetate (4:1), ethyl acetate, ethyl acetate–methanol (49:2), and ethyl acetate–methanol (10:1). Two-hundred milliliter fractions were collected until fraction 43 and from then on 50-ml fractions were collected. Benzene–ethyl acetate (4:1) was the eluting solvent until fraction 5. Ethyl acetate was the eluting solvent from fraction 5 to fraction 35. Ethyl acetate–methanol (49:2) was used from fraction 35 to fraction 40. Ethyl acetate–methanol (10:1) was used from 40 onwards. Fractions 43–63 (fraction A), which contained a single nucleosidic component, were pooled and evaporated to dryness to yield 8.47 g. Fractions 64–92 (fraction B), which contained a mixture, were pooled and evaporated to dryness to yield 8.16 g of isomers which were discarded. Fractions 93–154 (fraction C), which were enriched with a slower moving component, were pooled and evaporated to dryness to yield 4.57 g. The total yield of nucleosidic material was 21.2 g.

Fraction A was dissolved in methanol (300 ml) previously saturated at 0° with ammonia and the vessel was sealed. After 3 days at room temperature the solution was filtered and the filtrate was evaporated to dryness. The residue was partitioned between chloroform and water. The aqueous phase was extracted with three 100-ml portions of chloroform, and the aqueous solution was then evaporated to dryness. Evaporation with absolute ethanol removed the last traces of water. The residual syrup was crystallized from ethanol–isopropyl alcohol to yield 3.04 g of 6-methyl-2′-deoxycytidine (14%), mp 159–162°. This slightly yellow product was dissolved in methanol, decolorized with charcoal, and evaporated to a syrup. The syrup was crystallized from methanol–isopropyl alcohol to yield 2.70 g: mp 164–166° (this process was repeated to raise the melting point to 173–176°); $[\alpha]^{24}D$ +32.2° (c 1, water); $\lambda_{max}^{pH\ 1}$ 278 mμ (ε 14,900), $\lambda_{min}^{pH\ 1}$ 241 (960), $\lambda_{max}^{pH\ 4\ and\ pH\ 11}$ 271 (9500), $\lambda_{min}^{pH\ 4\ and\ pH\ 11}$ 252 (6000), $\lambda_{max}^{pH\ 14}$ 273 (9800), $\lambda_{min}^{pH\ 14}$ 252 (5600); pmr (D_2O), δ 2.40 (s, 3, 6-CH_3), 2.50–2.85 (m, 2, 2′-H's), 3.80 (s, 2, 5′-CH_2OH) 4.21–4.58 (m, 2, 3′-H overlapped by 4′-H), 4.80 (solvent), 5.87 (s, 1, 5-H), 6.20 ppm (t, 1, width 13.5, $J_{1'2'}$ = 6.7 cps).

Anal. Calcd for $C_{10}H_{15}N_3O_4$: C, 49.77; H, 6.27; N, 17.42. Found: C, 49.52; H, 6.49; N, 17.32.

1-(2′-Deoxy-α-D-ribofuranosyl)-6-methylcytosine.—Fraction C from the synthesis of XI was further purified by preparative thin layer chromatography on SilicAR 7GF. The material was applied to the short edge of ten plates (400 × 200 × 2 mm) of SilicAR 7 GF and the plates were developed several times in ethyl acetate–methanol (9:1). The major bands were extracted with methanol and the extract evaporated to dryness. Extraction of the residue with dichloromethane and evaporation of the solvent yielded 3.49 g of purified material.

This material was applied to eight plates (400 × 200 × 2 mm) of alumina HF 254 and the plates were developed several times with ethyl acetate–methanol (4:1). Two bands were observed, a faster band (β anomer) and a broad slower moving band (α anomer). The broad slower band was carefully excised and the absorbent was extracted with methanol. The solvent was evaporated and the residue was extracted with dichloromethane. Evaporation of this extract gave a syrup which was treated with methanol (150 ml) previously saturated with ammonia at 0° for 3 days at room temperature. The solution was filtered and evaporated to dryness. The residue was crystallized from methanol–isopropyl alcohol to yield 0.50 g (melting point, yellows from 197° and gradually decomposes). This material was dissolved in aqueous methanol and decolorized with charcoal. The solution was evaporated to a syrup and recrystallized from ethanol–isopropyl alcohol to yield pure material: mp 197–199° sinters, gradually decomposes, yellows at 192°; $[\alpha]D$ +13.7 (c 1, water); $\lambda_{max}^{pH\ 1}$ 278 mμ (ε 14,900), $\lambda_{min}^{pH\ 1}$ 241 (970), $\lambda_{max}^{pH\ 4\ and\ pH\ 11}$ 271 (9700), $\lambda_{min}^{pH\ 4\ and\ pH\ 11}$ 252 (6400), $\lambda_{max}^{pH\ 14}$ 273 (9900), $\lambda_{min}^{pH\ 14}$ 252 (6200); pmr (D_2O), δ 1.95–2.50 (m, 4, 6-CH_3 (s), at 2.40 overlapped by 2′-H), 2.70–3.25 (m, 1, 2′-H), 3.75–4.22 (m, 3, 5′-CH_2OH at 3.92 overlapped by 4′-H), 4.45–5.00 (m, 3′-H overlapped by solvent at 4.77), 5.89 (s, 1, 5-H), 6.22 ppm (q, 1, width 14.2 cps, "J_H" = 6.2, 8.0 cps, 1′-H).

Anal. Calcd for $C_{10}H_{16}N_3O_4$: C, 49.77; H, 6.27; N, 17.42. Found: C, 49.98; H, 6.39; N, 17.49.

The faster component (β anomer) was isolated and deblocked as described to yield 0.24 g, mp 173–176°.

Registry No.—II, 16710-07-9; IIa, 16710-08-0; IV, 6220-50-4; V, 638-13-1; VI, 16710-11-5; VIII, 16710-12-6; IX, 16710-13-7; XI, 16710-14-8; XII, 16710-15-9; XIII, 16710-16-0.

Acknowledgment.—The authors wish to thank Dr. Mason G. Stout for many helpful suggestions relative to this work.

(31) Purchased from Fisher Scientific Co., Fair Lawn, N. J.

Purine Nucleosides. XXI. The Synthesis of 6-Amino-2-methylthio-7-(β-D-ribofuranosyl)purine, an Anomer of the Nucleoside from Factor F, by Ring Closure of an Imidazole Nucleoside[1]

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Received March 1, 1968

The synthesis of 7-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine-2,6-dithione (**4**) has been accomplished by ring closure of an imidazole nucleoside with carbon disulfide and pyridine. The preparation of a 7-glycosylpurine with an exocyclic group at position 6 susceptible to nucleophilic displacement was achieved for the first time when deacetylation and methylation of **4** furnished 2,6-bismethylthio-7-(β-D-ribofuranosyl)purine (**3**) in 80% yield. Nucleophilic displacement of the 6-methylthio group was achieved to afford 6-amino-2-methylthio-7-(β-D-ribofuranosyl)purine (**5**). A comparison of certain physicochemical data between **5** and the nucleoside isolated from the naturally occurring vitamin B_{12} analog (factor F) has been made and the actual site of ribosyl attachment for the nucleoside from factor F has now been definitely established as N-7. Treatment of **5** with Raney nickel has provided a new route for the preparation of 6-amino-7-(β-D-ribofuranosyl)purine.

A vitamin B_{12} analog (factor F) was isolated[2] and subsequently characterized[2,3] as (α-methylthioaden-7-yl)cobamide cyanide. This was the first time that a sulfur-containing purine had ever been isolated from a naturally occurring source. Five other purines or purine nucleosides isolated from other naturally occurring analogs of vitamin B_{12} were described[3] as either 7-ribosylpurines or purines obtained from the acid hydrolysis of presumed 7-ribosylpurines. The synthesis of several 7-β-D-ribofuranosylpurines has been recently described[4-6] *via* a route which utilizes imidazole nucleosides[7] as precursors. This included the β anomer of all but one[8] of the purine nucleosides or presumed nucleosides which had been isolated from naturally occurring vitamin B_{12} analogs. However, these studies[4-6] provided 7-β-D-ribofuranosylpurines with a single exocyclic group at C-6 or 2,6-disubstituted 7-β-D-ribofuranosylpurines with the 6 substituent generally restricted to a hydroxyl group. This precluded the synthesis of 6-amino-2-methylthio-7-(β-D-ribofuranosyl)-purine utilizing the routes described above. This prompted us to investigate the possibility of using an imidazole nucleoside with a different type of ring-closure procedure to obtain a 2,6-disubstituted 7-(β-D-ribofuranosyl)purine with an exocyclic substituent more amenable toward nucleophilic displacement. We now wish to report the synthesis of 6-amino-2-methylthio-7 (β-D-ribofuranosyl)purine from an imidazole nucleoside prepared *via* the fusion method.[9]

A mixture of 4-amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole[6] (**1**), pyridine and carbon disulfide was heated at reflux temperature for 2 hr to furnish a yellow solid in 76% yield. The structure of this nucleoside was subsequently established as 7-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)pyrine-2,6-dithione (**4**). This ring closure presumably occurs *via* the *m*-thiazine derivative (**2**) analogous to the reported[10,11] ring closures of certain cyclic nonaromatic, aromatic, and heterocyclic *O*-aminonitriles. To our knowledge this is the first use of this ring closure for the synthesis of a nucleoside. Apparently the formation of **2** is followed by a facile ring-opening and ring-closing rearrangement initiated by pyridine to furnish **4** (Scheme I). The assignment of structure **4** to this nucleoside rather than structure **2** was supported by a comparison of the ultraviolet absorption spectra of **4** and 7-methylpurine-2,6-dithione[12] (Table I). The infrared spectrum revealed a strong absorption band at 1580 cm^{-1} which was assigned[13,14] as C=S stretching and part of a —NC=S system. The thiol form was excluded by the absence of any absorption bands at 2550–2600 cm^{-1} usually attributed to —SH[13-15] stretching. The rearrangement of *m*-thiazines to pyrimidine dithiones with cold dilute sodium hydroxide is well documented.[11] However, treatment of the crystalline nucleoside obtained above with warm 10% sodium hydroxide for a prolonged period of time effected no change in the ultraviolet absorption spectra (long-wavelength maxima) which substantiates the above structural assignment. Treatment of **4** with 10% sodium hydroxide has presumably effected a removal of the blocking groups from the carbohydrate moiety of **4**. Isolation of this deacetylated product was not attempted since the addition of methyl iodide to the reaction mixture furnished a white solid (80% over-all yield) which was characterized as 2,6-bismethylthio-7-(β-D-ribofuranosyl)purine (**3**). This structure assignment was established by the disappearance of the absorption bands in the infrared spectrum attributable to —C=S stretching and the appearance of two peaks (singlets) at δ 2.65 (three protons) and δ 2.80 (three protons) in the pmr spectrum (DMSO-d_6) which indicated the presence of two methyl

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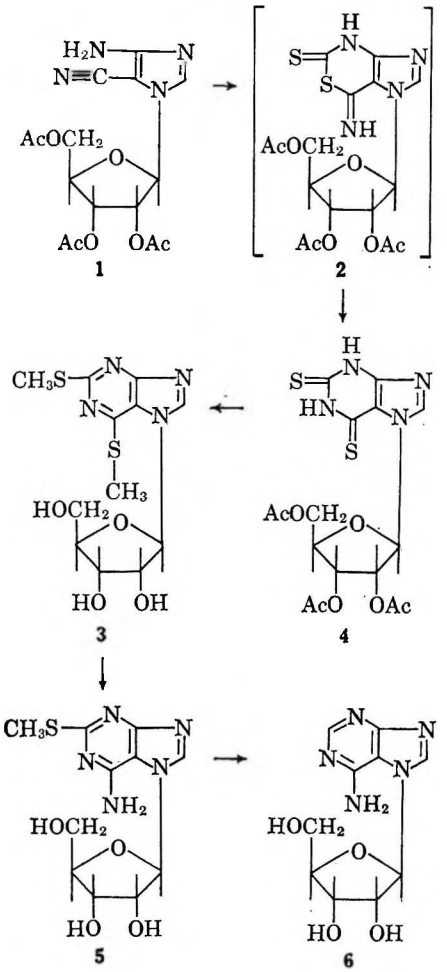
TABLE I
ULTRAVIOLET ABSORPTION SPECTRAL DATA OF CERTAIN 7-SUBSTITUTED PURINES[a]

	pH 1				MeOH				pH 11			
	λmax, nm	ε	λmin, nm	ε	λmax, nm	ε	λmin, nm	ε	λmax, nm	ε	λmin, nm	ε
7-Methylpurine-2,6-dithione[b]	258	13,700	236	4,150	258	17,400	240	12,200	243	15,400	224	14,700
	298	18,400	270	8,400	298	22,600	270	12,100	280	16,700	259.5	10,300
	349	13,500	327	10,300	351	13,100	334	11,900	335	8,100	313	6,400
7-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)purine-2,6-dithione (4)	257.5	16,800	236	9,700	255	13,700	236	9,700	247.5	18,600	223	12,800
	296	17,700	270	11,100	293	16,400	268	10,600	283	14,600	264	9,700
	350	11,100	330	9,700	350	10,000	336	7,500	340	8,000	316	9,700
2,6-Bismethylthio-7-methylpurine[b]	261.5	17,000	240.5	4,750	238.5	15,700			240	15,700	223	6,550
	316	9,500	299	7,450	257.5	17,400	246	13,800	257.5	15,700	247.5	13,300
					316	8,350	287	3,280	315	9,250	288	4,050
2,6-Bismethylthio-7-(β-D-ribofuranosyl)purine (3)	261.5	18,100	245	12,300	240	19,900	248	18,400	240	20,300	223	9,050
	319	9,400	300	7,600	257	19,900	288	3,300	257	18,100	250	17,300
					317	8,300			315	8,700	290	4,300
6-Amino-2-methylthio-7-(β-D-ribofuranosyl)purine (5)	247	22,600	272	8,450	240	21,000	274	5,500	238	22,200	274	6,250
	288	11,600			289	6,600			286.5	6,900		
		0.1 *N* HCl							pH 6–12			
Nucleoside from 2-methylthioadeninecobalamine analog[c]	247	21,100							238	21,400		
	289.5	10,300							287.5	6,100		

[a] Determined on a Beckman DK-2 spectrophotometer. [b] See ref 12. [c] These data obtained from ref 2.

SCHEME I



groups. A comparison of the ultraviolet absorption data of **3** with the ultraviolet absorption data of 2,6-bis-methylthio-7-methylpurine[12] (Table I) lends further support for these structural assignments (*vide supra*).[16] The preparation of 6-amino-2-methylthio-7-(β-D-ribofuranosyl)purine (**5**) was accomplished in an excellent yield from the treatment of **3** with liquid ammonia in a sealed vessel at 100° for 14 hr.[17] The ultraviolet absorption spectral data observed for **5** compares favorably with the ultraviolet absorption spectral data described[2] for the nucleoside isolated from factor F (Table I). It was of considerable interest that the initial assignment[2] of N-7 for the position of ribosidation for the naturally occurring nucleoside was based on the observation that 7-substituted purines generally exhibit, in comparison with 9-substituted purines, a definite bathochromic shift in the long-wavelength maxima. This comparison was made entirely on the basis of a 9-substituted purine since the 7-substituted, 1-substituted, and 3-substituted model compounds were not available for comparison. However, it has been recently reported[18] that several 7-substituted purines (including nucleosides) were in actuality 3-substituted purines and that the actual site of ribosidation could not be made solely on the basis of a bathochromic shift in the long wavelength maxima relative to that observed for a 9-substituted purine. In fact, it has been found that 1-substituted[19] and 3-substituted purines[20] usually exhibit a bathochromic shift for the long wavelength maxima in comparison with 9-substituted purines. This prompted us to investigate the conversion of **5** into a nucleoside of known structure. Removal of the 2-methylthio group from **5** with Raney nickel furnished 6-amino-7-(β-D-ribofuranosyl)purine (**6**). The structure of **6** has been previously established unequivocally by an alternate route[4] and by utilization of the $\Delta\lambda_{min}$ and $\Delta\delta$ rule.[18,21] Therefore, on the basis of these data (*vide infra*) the actual site of ribosyl attachment for the nucleoside from factor F has now been definitely established as N-7. In addition, the actual site of ribosyl attachment and the anomeric configura-

(16) Methylation of a ring nitrogen atom was excluded by the subsequent conversion of **3** into **6**.

(17) That nucleophilic displacement had occurred at position 6 instead of position 2 was subsequently established by the conversion of **5** into **6**.

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tion of all nucleosides prepared in this investigation were predetermined since the imidazole nucleoside used in the initial ring closure possessed a known anomeric configuration and site of ribosyl attachment. The anomeric configuration of the naturally occurring nucleoside could not be established in the present investigation as a comparison with **5** was inconclusive owing to the lack of physicochemical data reported[2] for the nucleoside isolated from factor F. However, the data presented herein have definitely established that the naturally occurring nucleoside isolated from factor F is 6-amino-2-methylthio-7-(D-ribofuranosyl)purine and corroborates the original site[2] of glycosidation assignment.

The preparation of **3** has provided for the first time a 7-glycosylpurine with an exocyclic group (methylthio) at position 6 which is susceptible toward nucleophilic displacement. Therefore, **3** can obviously be utilized for the preparation of numerous 6-substituted and 2,6-disubstituted 7-(β-D-ribofuranosyl)purines dependent only on the nucleophile employed. The preparation of additional 7-glycosylpurines *via* the route described herein utilizing imidazole nucleosides as precursors and the determination of actual anomeric configuration for the nucleoside isolated from factor F are under active investigation in this laboratory.

Experimental Section[22]

7-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)purine-2,6-dithione (4)—4-Amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole[6] (**1**, 8.5 g) was added to a mixture of pyridine (160 ml) and carbon disulfide (80 ml) and the reaction solution heated for 2 hr at reflux temperature. The yellow solution was evaporated to a foam *in vacuo* on a water bath and the residual foam dissolved in toluene (50 ml) and again evaporated to dryness *in vacuo*. The above procedure was repeated two more times to yield a yellow crystalline solid. Recrystallization of this solid from ethanol (2 l.) afforded a yellow powder (5.5 g) which was collected by filtration. Concentration of the filtrate to 500 ml furnished an additional 2.0 g of product. There was obtained a total yield of 7.5 g (76%) of **4**: mp 178–180°; $[\alpha]^{27}D$ +151.4 (*c* 1.0, pyridine).

Anal. Calcd for $C_{18}H_{18}N_4O_7S_2$: C, 43.44; H, 4.12; N, 12.67. Found: C, 43.08; H, 4.00; N, 12.57.

2,6-Bismethylthio-7-(β-D-ribofuranosyl)purine (3).—7-(2′,3′,-5′-Tri-*O*-acetyl-β-D-ribofuranosyl)purine-2,6-dithione (**4**, 3.0 g) was dissolved in 30 ml of 10% sodium hydroxide and stirred for 16 hr at room temperature. To this clear solution was added 30 ml of water and 6 ml of methyl iodide. The reaction mixture was then stirred for 1 additional hr in a loosely stoppered flask. The resulting white solid (2.4 g, 80.5%) was collected by filtration and washed with cold water (50 ml). A small sample was recrystallized from water for analysis to afford long, colorless, transparent needles: mp 195–197°; $[\alpha]^{27}D$ +18.80 (*c* 1.03, pyridine).

Anal. Calcd for $C_{12}H_{16}N_4O_6S_2 \cdot H_2O$: C, 39.78; H, 5.03; N, 15.47. Found: C, 39.49; H, 4.92; N, 15.40.

6-Amino-2-methylthio-7-(β-D-ribofuranosyl)purine (5).—2,6-Bismethylthio-7-(β-D-ribofuranosyl)pyrine (**3**, 1.0 g) and liquid ammonia (50 ml) were placed in a stainless steel reaction vessel and then heated at 100° for 14 hr. The residue remaining after evaporation of the liquid ammonia was dissolved in hot methanol and the solution then evaporated to dryness *in vacuo* on a steam bath to yield 850 mg of a light tan powder. The tan powder was recrystallized from a small amount of methanol (anhydrous) for analysis to give heavy colorless crystals: mp 206–208° with bubbling; $[\alpha]^{26}D$ −106 (*c* 0.785, pyridine).

Anal. Calcd for $C_{11}H_{15}N_5O_4S$: C, 42.18; H, 4.83; N, 22.36. Found: C, 42.27; H, 4.52; N, 22.22.

Treatment of 5 with Raney Nickel.—6-Amino-2-methylthio-7-(β-D-ribofuranosyl)purine (**5**, 50 mg) was heated at reflux temperature for 3 hr in 2 ml of water containing 350 mg of Raney nickel. An ultraviolet absorption spectrum of the reaction mixture indicated that the reaction was not complete and an additional 500 mg of Raney nickel was then added. After the reaction mixture had been heated at reflux for an additional 3 hr, the Raney nickel was removed by filtration and washed with boiling water (10 ml). The combined filtrate and washing exhibited the following ultraviolet absorption spectral data: pH 1, 272 nm; pH 11, 268 nm; and methanol, 268 nm. Paper chromatography of the reaction mixture with solvent system A (butanol saturated with water) and solvent system B [*n*-propanol, ammonium hydroxide, water, (6:3:1 v:v)] using the descending technique and Whatman No 1 chromatography paper gave the following results (Table II): a major spot[23] with an R_f value identical with that observed for 7-(β-D-ribofuranosyl)adenine, a minor spot with the identical mobility as starting material (**5**), and a trace spot which possessed a smaller R_f value than either of the previously mentioned compounds (**5** and **6**). When the ultraviolet absorbing spots with mobilities identical with 7-β-D-ribofuranosyladenine were excised and eluted with boiling water, there was obtained an ultraviolet absorption spectrum identical with that of 7-β-D-ribofuranosyladenine[4,5] (**6**).

TABLE II

CHROMATOGRAPHIC MOBILITIES ARE RECORDED AS R_f VALUES

	Filtrate	7-β-D-Ribofuranosyladenine (6)	6-Amino-2-methylthio-7-(β-D-ribofuranosyl)-purine (5)
Solvent system A	0.37 minor		0.37
	0.18 major	0.18	
	0.01 trace		
Solvent system B	0.75 minor		0.75
	0.59 major	0.59	
	0.13 trace		

Registry No.—**3**, 16797-71-0; **4**, 16797-72-1; **5**, 16797-73-2; **6**, 485-08-5.

Acknowledgment.—The authors wish to thank Professor Roland K. Robins for his interest and encouragement and Mr. A. F. Lewis and his staff and Mr. R. Panzica for large-scale preparation of certain intermediates.

(22) Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. The nuclear magnetic resonance spectra were obtained on a Varian A-60 high resolution spectrometer utilizing tetramethylsilane as an internal standard and the chemical shifts are expressed as δ, parts per million, from tetramethylsilane. The infrared spectra were recorded with a Beckman IR-5A spectrometer. The optical rotations were obtained with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich.

(23) The ultraviolet absorbing spots were detected using short-range (254 nm) ultraviolet light.

Aminocyclitols. XVIII. A Synthesis of *myo*-Inosadiamine-1,3 and Its Derivatives

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Received February 1, 1968

Actinamine has been synthesized as its hexaacetate from a readily available 2,4,5,6-tetra-*O*-acetyl-1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol in a good over-all yield. Hydrazinolysis of this compound, followed by catalytic hydrogenation, afforded *myo*-inosadiamine-1,3 which was a key compound leading to di-*N*-acetyltetra-*O*-acetylactinamine. The configurations of the new compounds obtained were established by nuclear magnetic resonance data and by chemical means. A reaction mechanism is proposed.

Actinamine is a component of the antibiotic actinospectacin,[2] and its structure has been assigned to be *N*,*N*′-dimethyl-*myo*-inosadiamine-1,3.[3] The synthesis has been described by several authors.[4-7]

In the present Article, we wish to report a facile synthesis of *myo*-inosadiamine-1,3 from a readily available 2,4,5,6-tetra-*O*-acetyl-1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**1**),[8a] which was converted into hexaacetylactinamine (**6**) by *N*-methylation and acetylation.

The displacement of two sulfonyloxy groups in **1** by sodium azide had been described in the previous paper of this series, where 1,4-diazido-1,4-dideoxy-*muco*-inositol was obtained as a sole product in 48% yield.[8b]

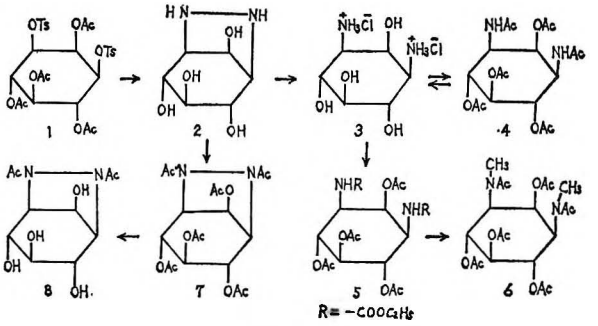
The successful replacement of a sulfonyloxy group in sugar derivatives by hydrazine had been reported by Wolfrom and his coworkers,[9] in cases where this replacement did not occur by an azide ion. Therefore, a diplacement of sulfonyloxy groups in **1** by hydrazine was attempted.

When **1** was heated in a mixture of anhydrous hydrazine and 2-methoxyethanol under reflux for 22 hr, an oily product was obtained by evaporating a reaction mixture. Reduction of the oily product in the presence of a catalyst, followed by acetylation, gave hexaacetyl-*myo*-inosadiamine-1,3 (**4**)[10] in a yield of 45% (Scheme I).

While an analogous reaction was carried out in anhydrous hydrazine without a diluent, **4** was obtained in 35% yield, along with the known hexaacetyl-*muco*-inosadiamine-1,4[5] as a minor product in 2.4% yield.

Several attempts were made to isolate an intermediary compound in the hydrazinolysis of **1**. When an intact hydrazinolysis product in the former reaction was treated with Amberlite IRA-400 to remove acidic

SCHEME I



substances, the crystalline product (**2**) of mp 188–189° dec was obtained in 39% yield.

Hydrogenation of **2** in the presence of a platinum catalyst in an acidic medium afforded *myo*-inosadiamine-1,3 dihydrochloride (**3**) in 92% yield.

3 was treated with ethyl chloroformate in an alkaline solution, followed by acetylation, to give 2,4,5,6-tetra-*O*-acetyl-*N*,*N*′-diethoxycarbonyl-*myo*-inosadiamine-1,3 (**5**) in 87% yield. Reduction of **5** with an excess amount of lithium aluminium hydride, followed by acetylation, gave **6** in 48% yield, which was identified with an authentic sample[11] by a mixture melting point determination, infrared and nuclear magnetic resonance (nmr) spectra. The over-all yield of hexaacetylactinamine from **1** was about 18%.

The structure of the intermediary compound **2** was elucidated on the basis of infrared, nmr spectra, and chemical evidences. Acetylation of **2** gave hexaacetyl derivative (**7**) of mp 186–187°, which showed no amide II band in the infrared spectrum,[12] suggesting a N,N-disubstituted amide structure.

The elementary analysis of **2** showed that one molecule of hydrazine replaced the two sulfonyloxy groups in the same molecule of **1**. Hence a bridged bicyclic structure of 6,7-diazabicyclo[3.2.1]octane system might be a most probable one for the structure of **2**. An analogous bicyclic compound was described by Freudenberg, *et al.*,[13] in the reaction of methyl 2-chloro-2-deoxy-D-glucoside with hydrazine.

Catalytic hydrogenation of **7** did not cleave the N–N bond and **7** was recovered quantitatively. The same inertness of the N–N bond in 2,3-dicarbomethoxy-2,3-diazabicyclo[2.2.1]heptyl derivative has been observed

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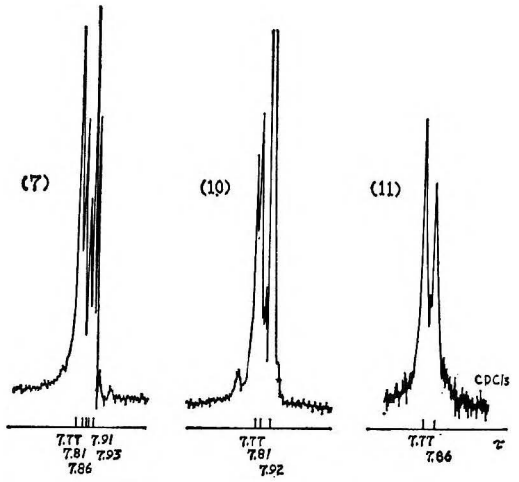


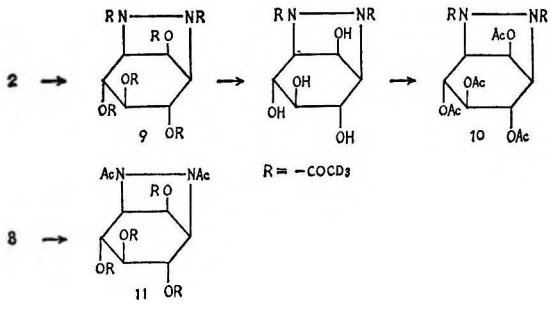
Figure 1.—Nmr spectrum of **7**, **10**, and **11** in $CDCl_3$.

by Allred, *et al.*,[14] and in acyl hydrazine derivatives by Gillis, *et al.*[15]

Nmr spectroscopy has proved to be an extremely useful tool for the conformational studies of sugars[16] and cyclitols.[17] This was true in the present study on the configuration of the bridged bicyclic compound. The nmr spectrum of **7** in $CDCl_3$ revealed five sharp signals at τ 7.77, 7.82, 7.86, 7.91, and 7.93, which were attributed to the four acetoxy and two acetamido groups (Figure 1). To distinguish the signals arising from the two acetamido groups among the five signals, the following method seemed to be feasible. Very recently, in the nmr spectra of acetylated amino sugars, each of the acetyl groups was definitely assigned by a synthesis of their derivatives which had been deuterated in the individual acetyl group.[18]

In the present study, the two hexaacetyl derivatives of **2** (**10** and **11**) which were specifically deuterated in the two *N*-acetyl methyl groups and the four *O*-acetyl methyl groups, respectively, were synthesized, and a direct comparison of the nmr spectra of deuterated and nondeuterated compounds was attempted (Scheme II).

SCHEME II



The nmr spectrum of **10** revealed three signals at τ 7.77, 7.81, and 7.92 (Figure 1). A disappearance of the signal at τ 7.86 and a marked decrease of the intensity of the signal at τ 7.77 suggested that the signals of the acetamido groups were located at τ 7.77 and 7.86. This was further confirmed by the nmr spectrum of **11** which revealed two sharp signals at τ 7.77 and 7.86 (Figure 1). This spectrum could be reasonably explained on the basis of a hindered internal rotation of acetamido groups and the spectrum was a result of a superposition of the signals arising from the rotational conformers caused by the hindrance of the internal rotation. The analogous observations have been described on the restricted rotation around a CO–N bond by several authors.[19-23]

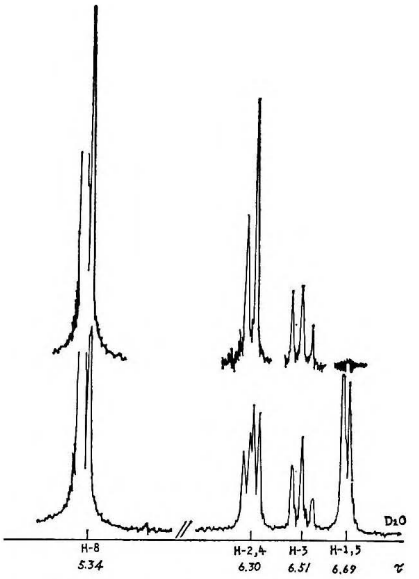


Figure 2.—Nmr spectrum of **2** in D_2O.

The pattern of the signals in the lower field was ascribed to the six ring protons of the cyclohexane ring, which appeared at τ 4.48 (2 H), 4.90 (H), 5.10 (H), and 5.22, 5.37 and 5.48 (2 H). In a bicyclo[3.2.1]octane system, it has been described that the dihedral angle between *syn*-H-8 and a bridgehead proton H-1 (or H-5) is close to 90° (J = 0 cps), and that between *anti*-H-8 and H-1 (or H-5) is approximately 40° (J = 5 cps).[24-26]

Since the catalytic hydrogenation of **2** gave *myo*-inosadiamine-1,3 in an almost quantitative yield, the hydroxyl group on C-8 must be in an *anti* orientation to the three-membered bridge. Hence the sharp singlet with an intensity of one proton at τ 5.10 should be attributed to the *syn*-H-8 proton.[27]

The nmr spectrum of **2** in D_2O gave more informations on the assignment of the configuration (Figure 2). The expected singlet arising from the *syn*-H-8[24-27] appeared at τ 5.34. The doublet centered at τ 6.69 was ascribed to the H-1 and H-5 protons. The observed coupling constant (J = 2.5 cps) was consistant with the

(14) E. L. Allred and C. Anderson, *J. Org. Chem.*, **32**, 1874 (1967).
(15) B. T. Gillis and R. E. Kadunce, *ibid.*, **32**, 91 (1967).
(16) R. U. Lemieux, R. K. Kullnig, and R. Y. Moir, *J. Amer. Chem. Soc.*, **80**, 2237 (1958).
(17) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *ibid.*, **79**, 1005 (1957); F. W. Lichtenthaler, *Chem. Ber.*, **96**, 2047 (1963); T. Suami and S. Ogawa, *Bull. Chem. Soc. Jap.*, **37**, 194 (1964).
(18) D. Horton, J. B. Hughes, J. S. Jewell, K. D. Philips, and W. N. Turner, *J. Org. Chem.*, **32**, 1073 (1967); D. Horton, W. E. Mast, and K. D. Philips, *ibid.*, **32**, 1471 (1967).
(19) W. A. Szarek, Saul Wolfe, and J. K. N. Jones, *Tetrahedron Lett.*, 2743 (1967).
(20) H. Paulsen, *Angew. Chem.*, **78**, 501 (1966).
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(23) H. Paulsen and K. Todt, *Chem. Ber.*, **100**, 3385, 3397 (1967).
(24) A. C. Oehlschlager and L. H. Zalkow, *J. Org. Chem.*, **30**, 4205 (1965).
(25) C. W. Jefford, B. Waegell, and K. Ramey, *J. Amer. Chem. Soc.*, **87**, 2191 (1965).
(26) M. E. Munk, C. S. Sodano, R. L. McLean, and T. H. Haskell, *ibid.*, **89**, 4158 (1967).
(27) The H-8 proton of *p*-nitrobenzoate ester of *N*-acetylactinobolamine methyl ketal appears as a triplet (J = 5.0 cps) at τ 5.10, which has been assigned to an *anti* proton.[26] This might be held in a pyrazolidine ring besides pyrrolidine and cyclopentane ring in a bicyclo[3.2.1]octane system.

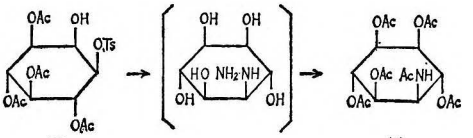
value described by Jefford, *et al.*,[25,28] for the coupling constant between the bridgehead proton (H-5) and the *endo* proton (H-4) in 1-methyl-2,3-benzobicyclo[3.2.1]-octan-4-ol. The triplet at τ 6.51 was assigned to H-3 and the coupling constant (J = 4.2 cps) was close to the value observed in the nmr spectra of bicyclo[3.2.1]-octan-3-ols.[29] The quartet centered at τ 6.30 (J = 4.2 and 2.5 cps) was ascribed to the H-2 and H-4 protons.

A spin-decoupling technique is a valuable aid in an analysis of a complex spectrum, and was used in the present study to confirm the above mentioned assignment of the signals. When H-1 and H-5 (τ 6.69) protons were irradiated, the quartet at τ 6.30 collapsed to a doublet with a coupling constant of 4.2 cps. This irradiation also removed a small splitting from H-8 giving a more sharp signal at τ 5.34, but did not affect the triplet of H-3. Hence the above described assignment of the signals was reasonably accepted.

The cyclohexane ring in 6,7-diazabicyclo[3.2.1]-octane-2,3,4,8-tetrol can theoretically exist in a chair conformation as well as in a boat conformation. Considering the fact that in the nmr spectrum of **2**, none of a large coupling constant (J = *ca.* 10 cps) suggesting a quasi-diaxial relationship between adjacent protons[30-32] was observed, the cyclohexane ring must exist in a chair form. Thus the configuration and structure of **2** was established to be *axial,axial,axial,-anti(equatorial)*-6,7-diazabicyclo[3.2.1]octane-2,3,4,8-tetrol,[33] and the proposed structure was compatible with the chemical and spectral properties.

The reaction mechanism was developed from the structure of **2**. It seemed reliable to assume that a displacement of one of the two sulfonyloxy groups took place with a participation of the vicinal *trans* acetoxy group in **1** to form an intermediary acetoxonium ion, which was then attacked by hydrazine. This occurred in a manner of *trans*-diaxial opening of the cyclic acetoxonium ion, since hydrazinolysis of 3,4,5,6-tetra-*O*-acetyl-1-*O*-*p*-toluenesulfonyl-*myo*-inositol (**12**),[34] followed by hydrogenation and acetylation, yielded hexaacetyl-*muco*-inosamine-1 (**13**)[35] as a sole product in a yield of 66% (Scheme III).

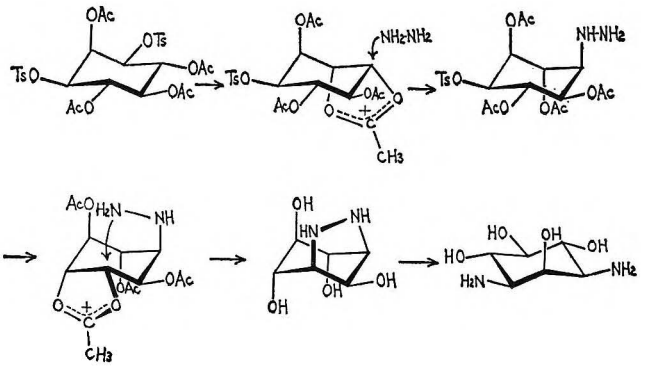
SCHEME III



12 **13**

Then the replacement of another sulfonyloxy group in **1** gave another acetoxonium ion, which was attacked by the hydrazino group, but not by another hydrazine molecule, to give the bridged bicyclic compound, as shown in Scheme IV. At this instance, if hydrazine was used without any diluent, a few acetoxonium ions were attacked by hydrazine in a manner of *trans*-diaxial opening to give a minor product which was corresponding to *muco*-inosadiamine-1,4 derivative.[8] The formation of a bridged bicyclic compound made it possible to obtain *cis*-1,3-diamino derivative selectively.

SCHEME IV



Experimental Section

The melting points were determined on a Mitamura Ricken micro hot stage. The melting points marked with asterisks were measured in a liquid bath and are corrected. The infrared spectra were determined by means of pressed potassium bromide disks. The nmr spectra of the samples were determined at a frequency of 60 and 100 Mc with Japan Electron Optics JNM-C-60 or Varian HA-100 spectrometer in deuteriochloroform, deuterium oxide, or d_6-dimethyl sulfoxide, with tetramethylsilane, sodium trimethylsilylpropanesulfonate, or tetramethylsilane, respectively, used as an internal reference.

Hexaacetyl-*myo*-inosadiamine-1,3 (4). A.—A mixture of 2,4,5,6-tetra-*O*-acetyl-1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**1**) (12.0 g),[7] anhydrous hydrazine (48 ml), and 2-methoxyethanol (240 ml) was heated under reflux for 22 hr. The mixture was evaporated under reduced pressure to give a dark oily residue.[36] The residue was hydrogenated in 50 ml of water with Raney nickel catalyst under an initial hydrogen pressure of 3.4 kg/cm^2 for 22 hr at 50° with a Parr shaker-type hydrogenation apparatus. After the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure to yield an oily residue. The residue was acetylated with acetic anhydride (30 ml) in pyridine (30 ml) overnight at room temperature. Then the mixture was evaporated under reduced pressure to give a crystalline product. Recrystallization from ethanol afforded **4**, yield 3.73 g (45.1%). Recrystallization from ethanol afforded an analytically pure **4** as colorless plates: yield 3.43 g (41.5%); mp *283.5–285° (lit.[3,4] mp 269, 270–271°). A mixture melting point determination with an authentic sample[10] did not show any depression and ir spectrum of **4** was superimposable with that of an authentic sample.[10]

B.—A mixture of **1** (5.0 g) and anhydrous hydrazine (50 ml) was heated under reflux for 48 hr in a nitrogen stream. Then the mixture was treated analogously as described in A. Fractional recrystallization from ethanol yielded 1.03 g (35.2%) of **4**, mp *284–286°. Recrystallization from ethanol afforded pure **4** as colorless plates, mp *285.5–286.5°.

After the mother liquor was evaporated, the residue was recrystallized from ethanol–ether to give 71 mg (2.1%) of hexaacetyl-*muco*-inosadiamine-1,4 (**14**),[8] mp 252.5–253.5°, which was identified with an authentic sample by a mixture melting point determination and comparison of ir spectra (lit.[8] mp 248–250°).

C.—A mixture of 1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (1.5 g)[8] and anhydrous hydrazine (30 ml) was heated under reflux for 48 hr in a nitrogen stream. Then the mixture was treated analogously as described in A. Fractional recrystallization from

(28) C. W. Jefford, S. Mahajan, J. Waslyn, and B. Waegell, *J. Amer. Chem. Soc.*, **87**, 2183 (1965).

(29) W. Kraus, *Chem. Ber.*, **97**, 2719 (1964).

(30) W. R. Vaugham and R. Caple, *J. Amer. Chem. Soc.*, **86**, 4928 (1964).

(31) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(32) K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961).

(33) Nomenclature: *axial* and *equatorial* designate those in a cyclohexane derivative. An analogous nomenclature has been used in bicyclo[3.2.1]-octane-2,8-diol by N. A. LeBel and L. A. Spurlock, *J. Org. Chem.*, **29**, 1337 (1964).

(34) S. J. Angyal, V. Bender, and J. H. Curtin, *J. Chem. Soc.*, 798 (1966).

(35) T. Suami and S. Ogawa, *Bull. Chem. Soc. Jap.*, **37**, 1238 (1964); T. Suami, F. W. Lichtenthaler, and S. Ogawa, *ibid.*, **39**, 170 (1966).

(36) All hydrazine should be removed before heating with Raney nickel as the heating of hydrazine with metals can lead to violent explosions.

ethanol yielded 0.15 g (10.6%) of **14**, mp 252.5–253.5°, and 0.36 g (25.4%) of **4**, mp *285.5–286.5°.

6,7-Diazabicyclo[3.2.1]octane-2,3,4,8-tetrol (2).—A mixture of **1** (5.0 g), anhydrous hydrazine (20 ml), and 2-methoxyethanol (100 ml) was heated for 22 hr as described above. After excess reagent was removed by evaporation, an intact hydrazinolysis product was dissolved in 40 ml of cold water. To the solution was added Amberlite IRA-400 and the mixture was settled overnight at room temperature. After the resin was removed by filtration, the filtrate was evaporated to dryness *in vacuo*. The residue was washed with 20 ml of hot ethanol and dissolved in a small amount of water. To the solution was added ethanol and the solution was kept in a refrigerator to give 545 mg (38.6%) of **2**, mp *188–189° dec.

Anal. Calcd for $C_6H_{12}N_2O_4$ (176.2): C, 40.93; H, 6.87; N, 15.90. Found: C, 40.93; H, 6.88; N, 15.70.

***myo*-Inosadiamine-1,3 Dihydrochloride (3).** A.—A mixture of **2** (182 mg) and 4.13 ml of 1 *N* hydrochloric acid in 15 ml of water was hydrogenated with platinum oxide (28 mg) under 3.4 kg/cm² of hydrogen pressure for 22 hr. After the catalyst was removed by filtration, the filtrate was evaporated *in vacuo*. The residue was crystallized in ethanol–water to give 246 mg (91.5%) of **3**, mp 219–237° dec.

B.—A 479-mg portion of **4** was heated in 25 ml of 6 *N* hydrochloric acid under reflux for 2 hr. The solution was evaporated under reduced pressure, and the residue was crystallized from ethanol–water to give 286 mg (98.7%) of **3**. Recrystallization from ethanol–water yielded an analytically pure sample of **3**, mp 221–241.5° dec.

Anal. Calcd for $C_6H_{16}N_2O_4Cl_2$ (251.1): C, 28.70; H, 6.42; N, 11.15; Cl, 28.24. Found: C, 28.89; H, 6.85; N, 10.84; Cl, 28.36.

Hexaacetyl-6,7-diazabicyclo[3.2.1]octane-2,3,4,8-tetrol (7).—A 144-mg portion of **2** was acetylated with acetic anhydride (3.5 ml) and pyridine (6.0 ml) at room temperature overnight. After the mixture was evaporated *in vacuo*, the residue was crystallized in ethanol to give 211 mg (59.4%) of colorless needles, mp 184–185.5°. Recrystallization from ethanol yielded an analytically pure sample of **7**, mp 186.5–187.5°.

Anal. Calcd for $C_{18}H_{24}N_2O_{10}$ (428.4): C, 50.46; H, 5.65; N, 6.54. Found: C, 50.91; H, 5.92; N, 6.36.

A 100-mg portion of **7** was hydrogenated in 10 ml of ethanol in the presence of platinum oxide. After the reduction product was acetylated in acetic anhydride and pyridine, **7** was recovered quantitatively.

Hexatrideuterioacetyl-6,7-diazabicyclo[3.2.1]octane-2,3,4,8-tetrol (9).—A 224-mg portion of **2** was acetylated with 0.85 ml of d_3-acetyl chloride in 7 ml of pyridine under ice cooling. The solution was settled overnight at room temperature and then poured into ice cold water. After the solution was evaporated under reduced pressure, the residue was dissolved in a small amount of water and extracted by six 5-ml portions of chloroform. The chloroform extracts were evaporated and the residue was crystallized from ethanol to give 165 mg (29.1%) of the product, mp 180–182.5°.

2,3,4,8-Tetra-*O*-acetyl-6,7-*N*,*N*′-trideuterioacetamido-6,7-diazabicyclo[3.2.1]octane-2,3,4,8-tetrol (10).—A 114-mg portion of **9** was dissolved in 16 ml of methanol previously saturated with dry ammonia and settled overnight at room temperature. The solution was evaporated under reduced pressure and the residue was acetylated with acetic anhydride in pyridine to give 89 mg of crystalline product in 80.2% yield, mp 185.5–186.5°.

6,7-Di-*N*,*N*′-acetyl-2,3,4,8-tetra-*O*-trideuterioacetyl-6,7-diazabicyclo[3.2.1]octane-2,3,4,8-tetrol (11).—A 100-mg portion of **8** was O-acetylated with 0.23 ml of d_3-acetyl chloride in 4 ml of pyridine by an application of the procedure described for the preparation of **9**. Crystallization of the product in ethanol–ether gave 29 mg (17.0%) of **11**, mp 184.5–185.5°.

Di-*N*,*N*′-acetyl-6,7-diazabicyclo[3.2.1]octane-2,3,4,8-tetrol (8).—A 448-mg portion of **7** was dissolved in 50 ml of methanol previously saturated with ammonia. The solution was settled at room temperature overnight and evaporated to dryness under reduced pressure. The residue was washed with ten 4-ml portions of ethyl acetate and crystallized in methanol–ether to give 138 mg (51.3%) of the crude product, mp 209.5–211.5°. Recrystallization from methanol–ether afforded colorless needles, mp 222–223°.

Anal. Calcd for $C_{10}H_{16}N_2O_6$ (260.2): C, 46.15; H, 6.20; N, 10.77. Found: C, 46.39; H, 6.33; N, 11.13.

Hexaacetyl-*muco*-inosamine-1 (13).—1,4,5,6-Tetra-*O*-acetyl-3-*O*-*p*-toluenesulfonyl-*myo*-inositol (**12**)[34] (1.70 g) was heated in 20 ml of anhydrous hydrazine under reflux for 50 hr in a nitrogen stream. The solution was evaporated under reduced pressure and the residual oil was hydrogenated in 12 ml of water with Raney nickel catalyst for 21 hr under 3.4 kg/cm² of an initial hydrogen pressure. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was acetylated with acetic anhydride (8 ml) and pyridine (8 ml). An excess acetylating reagent was removed by evaporation and the residue was crystallized in ethanol to give 377 mg (43.9%) of **13**, mp 203–205°, which was identified with an authentic sample[35] by a mixture melting point determination and a comparison of ir spectra (lit.[35] mp 205–205.5°). When the same hydrazinolysis was carried out in 2-methoxyethanol, **13** was obtained in 37.7% yield.

2,4,5,6-Tetra-*O*-acetyl-*N*,*N*′-diethoxycarbonyl-*myo*-inosadiamine-1,3 (5).—**3** was converted into **5** by the procedure described in a previous paper[6] in 86.8% yield.

Hexaacetylactinamine (6).—Reduction of **5** by lithium aluminium hydride gave **6** in the procedure described in the previous paper[6] in 47.6% yield.

Registry No.—**2**, 16703-84-7; **3**, 16656-63-6; **7**, 16703-87-0; **8**, 16656-64-7; **9**, 16703-85-8; **10**, 16703-86-9; **11**, 16656-65-8.

Acknowledgment.—The authors are grateful to Professor Sumio Umezawa for his helpful advice and to Mr. Saburo Nakada for his elementary analysis. Also the authors are indebted to Dr. Keiji Kotera and Dr. M. C. Woods for the measurements of the nmr spectra. This research has been financially supported by a grant of the Japanese Ministry of Education.

Alicyclic Carbohydrates. XXXII. Synthesis of Pseudo-β-DL-gulopyranose from a Diacetoxybutadiene. Proton Magnetic Resonance Studies[1,2]

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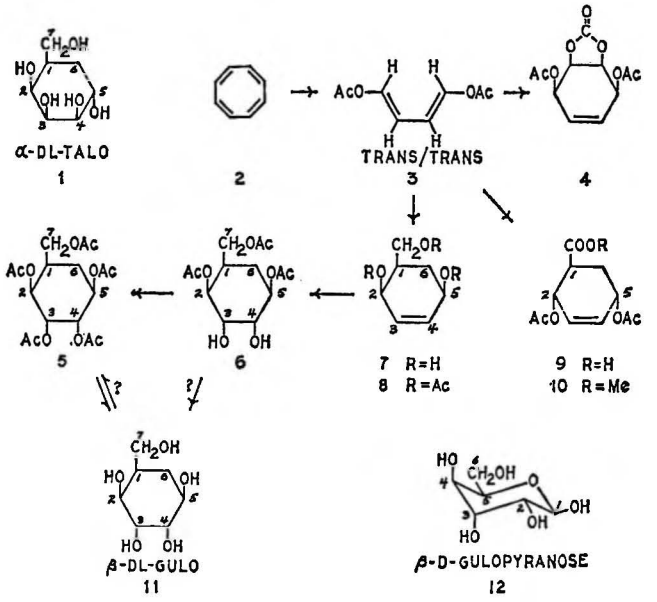
Received January 9, 1968

Configurations of the three diastereomeric 1,4-diacetoxy-1,3-butadienes were confirmed by nmr spectroscopy. The assignments were based on coupling constants calculated from measured frequency differences in the AA'XX' (or AA'BB') patterns present in the spectra of the *cis, cis* and *trans, trans* diastereomers. The *trans,trans* diene was used for synthesis of a pseudo-sugar (here defined as a cyclic monosaccharide whose ring-oxygen atom has been replaced by methylene). Diels–Alder reaction of the *trans,trans* diene with allyl acetate gave the all-*cis* diastereomer of 2,5-dihydroxy-3-cyclohexene-1-methanol triacetate. The carbon–carbon double bond in this adduct was remarkably inert, but did react with *t*-butyl hydroperoxide–osmium tetroxide to give 2,3,4,5-tetrahydroxy-1-cyclohexanemethanol triacetate, shown by proton magnetic double resonance to have the β-DL-gulopyranose configuration. This pentol triacetate on reaction with acetic anhydride gave the pentol pentaacetate, which on hydrolysis gave the desired free pentol, pseudo-β-DL-gulopyranose.

We recently reported the synthesis of a hydroxymethylcyclohexanetetrol which was shown by proton magnetic resonance (pmr) to have the configuration (see formula 1, Scheme I) of α-DL-talopyranose.[4a] This pseudo-talopyranose belongs to a class of compounds which have been designated *pseudo-sugars* (alicyclic analogs of cyclic monosaccharides); it appears to be the first known pseudo-hexose.[4]

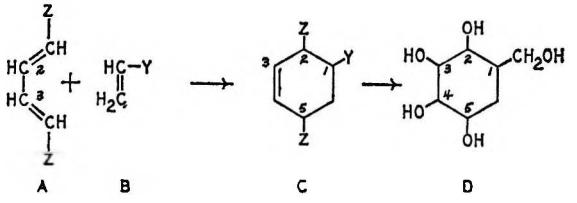
SCHEME I



We now report the synthesis of a second pseudohexose (**11**), which has been shown by pmr and spin-decoupling studies to have the configuration of β-DL-gulopyranose (**12**). It is hoped that in some cases pseudo-sugars will be accepted by enzymes or biological systems in place of corresponding true sugars, and thus may serve to inhibit the growth of malignant or pathogenic cells.[5,6]

The most general and convenient route (Scheme II) to pseudo-hexopyranoses (D) appears to be the Diels–Alder reaction of a 1,4-disubstituted 1,3-butadiene (A) with a dienophile (B) to give a 1,2,5-trisubstituted 3-cyclohexene (C), convertible into a hydroxymethylcyclohexanetetrol (D). Here Z would be a univalent group (*e.g.*, acetoxyl) readily convertible into hydroxyl, and Y would be either hydroxymethyl or some group (*e.g.*, carbomethoxyl or acetoxymethyl) readily convertible into hydroxymethyl.

SCHEME II



For our present synthesis, it appeared that a suitable diene would be 1,4-diacetoxy-1,3-butadiene,[7–9] and in particular its *trans, trans* diastereomer, whose position 2–3 single bond can readily assume the cisoid conformation (A) needed for the Diels–Alder reaction. In the course of this work, we have used pmr spectroscopy (see below) to confirm the configurations of the three diastereomers of 1,4-diacetoxy-1,3-butadiene, which previously were based on infrared spectroscopy.[10]

(1) Presented in part by G. E. M. at the Winter Meeting of the American Chemical Society, Division of Carbohydrate Chemistry, Phoenix, Ariz., Jan 1966.

(2) For preceding paper, see G. E. McCasland, M. O. Naumann, and Lois J. Durham, *Carbohyd. Res.*, **4**, 516 (1967).

(3) To whom any correspondence should be addressed: University of San Francisco.

(4) G. E. McCasland, S. Furuta, and Lois J. Durham, *J. Org. Chem.*, **31**, 1516 (1966).

(4a) NOTE ADDED IN PROOF.—H. J. Schaeffer and R. Vince have prepared nucleoside analogs in which, for example, a purine residue is attached to position 5 of *trans*-2-hydroxy-1-cyclohexanemethanol: see *J. Med. Chem.*, **11**, 15 (1968), and earlier publications there cited.

(5) With the experience gained on pseudo-talose and pseudo-gulose, efforts to synthesize pseudo-sugar analogs of the biologically more important (and optically active) natural sugars, such as D-glucose, are in progress; these isomers in all probability will be more active biologically. (Note: Preliminary results on the compound here described as pseudo-β-DL-gulopyranose appeared to indicate an α-DL-mannopyranose configuration; actually, the pseudo-mannopyranoses are still unknown.)

(6) The synthesis of pseudo-α-DL-galactopyranose has recently been completed: G. E. McCasland, S. Furuta, and Lois J. Durham, *ibid.*, **33**, 2841 (1968).

(7) W. Reppe, O. Schlicting, K. Klager, and T. Toepel, *Ann.*, **560**, 1 (1948). A product reported by these authors as 1,2-diacetoxy-3-cyclobutene was later shown by Criegee and coworkers[8] to be 1,4-diacetoxy-1,3-butadiene.

(8) (a) R. Criegee and P. Becher, *Chem. Ber.*, **90**, 2516 (1957); (b) R. Criegee, W. Hörauf, and W. D. Schellenberg, *ibid.*, **86**, 126 (1953).

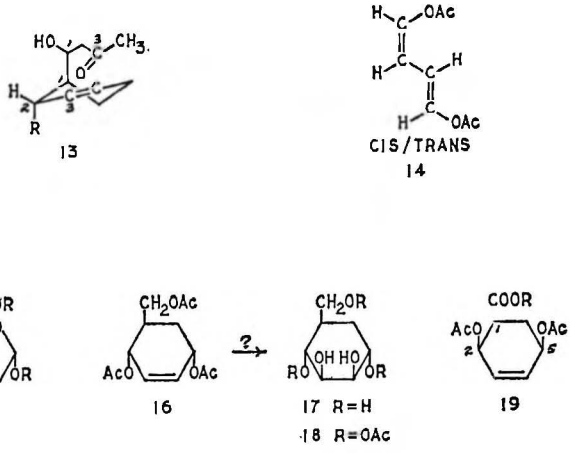
(9) A. C. Cope, N. Nelson, and D. Smith, *J. Amer. Chem. Soc.*, **76**, 1100 (1954).

(10) H. H. Inhoffen, J. Heimann-Trosien, H. Muxfeldt, and H. Krämer, *Chem. Ber.*, **90**, 187 (1957).

Although acrylic acid and methyl acrylate had previously been used as dienophiles with this same diene[11,12] we chose instead to use allyl acetate, in order to avoid possible difficulties in reduction of the carboxy or carbomethoxy group to hydroxymethyl at a later stage in the synthesis. (Such difficulties had previously been encountered in the synthesis[4] of pseudo-talopyranose.) Although allyl acetate is much less reactive than methyl acrylate, a good yield of the desired enetriol triacetate (**8**) was obtained after 2 days of reaction at 200°.

The enetriol triacetate, so far obtained only as a syrup, gave a correct microanalysis and appropriate infrared and pmr spectra. On hydrolysis it gave the free enetriol, also obtained as a syrup, which is an alicyclic analog of the true sugar derivative (see Scheme III) known as "pseudo-glucal" (**15**), although differing in configuration.[13] The configurations **7** and **8** of the enetriol and its triacetate are based primarily on chemical correlation with the pentol triacetate (see below).

Scheme III



Efforts to convert the enetriol triacetate **8** into the pentol 2,5,7-triacetate **6** by hydroxylation of the double bond were at first unsuccessful.[14] This double bond is extraordinarily inert to nearly all additive reagents which normally react readily with cyclohexenes, including bromine, hypobromous acid, performic acid, the Prévost reagent, and hydrogen with a catalyst (at least under low pressure). The carbon–carbon double bond was not detected by infrared spectroscopy (apparently because of near-symmetry); however its presence was readily and definitely demonstrated by pmr spectroscopy. Reaction of the enetriol triacetate with osmium tetroxide in pyridine finally did give the desired pentol triacetate **6**, but only in 11% yield. In later preparations the yield of product, isolated as pentol pentaacetate **5**, was increased to nearly 40% by use of *t*-butyl hydroperoxide catalyzed with osmium tetroxide.[15]

The striking inertness of the double bond in the enetriol triacetate **8** is perhaps due to deactivation through π-complex interaction with the carbonyl group of the acetoxymethyl side chain. It appears that the side chain can assume an *"endo"* conformation which would be sterically favorable for such interaction. A similar interaction has been postulated by Kugatova-Shemyakina and Ovchinnikov[16] to account for the unique behavior of certain side-chain carbonyl derivatives of the 3-cyclohexene series, such as the 2-substituted derivatives of 1-(1-hydroxy-3-oxobutyl)-3-cyclohexene (**13**).

Our enetriol triacetate adduct was at first assigned the *endo* or DL(1/25) configuration **16** by analogy with the adduct from acrylic acid or methyl acrylate, **9** or **10**, claimed by Smissman and coworkers[12] to have this configuration, although McCrindle and coworkers[11] had favored the DL(125/0) or *exo* configuration **19**. Also, our own pmr studies at first seemed to support the DL-(1/25) configuration. However, more complete pmr studies on the enetriol triacetate, and especially on the pentol triacetate **6** derived from it (see below), now definitely have established the enetriol triacetate configuration as *exo* or DL(125/0), **8**.[5] Certain other Diels–Alder adducts also are known to have the *exo* or all-*cis* configuration, for example, the adduct **4** from vinylene carbonate, reported by Criegee and Becher.[8] It is noteworthy that vinylene carbonate (or allyl acetate) requires 2 days at about 200° for reaction, while acrylic acid or ester reacts with the diacetoxy diene under much milder conditions. The varying steric results possibly could be explained in terms of the relative rates of formation and thermodynamic equilibration of the adducts from the various pairs of reactants.

The pentol triacetate **6** was a sharp-melting, crystalline compound with appropriate microanalysis and infrared spectrum. The possibility was considered that one of the acetyl groups had migrated from position 2, 5, or 7 to position 3 or 4 to give a structurally isomeric product. However, it was demonstrated by pmr (see below) that no acetyl migration[17] takes place under the conditions of preparation used for this compound.

It would be expected, from many similar examples, that the two hydroxyl groups would add to positions 3 and 4 of the enetriol triacetate **8** in a manner *trans* to the acetoxy groups at positions 2 and 5. The resulting pentol triacetate was at first thought to have the α-DL-mannopyranose configuration **18**, because of preliminary pmr results and the assumed configuration **16** of the enetriol triacetate. However, the pentol triacetate is now known to have the β-DL-gulopyranose configuration **6**.[6]

The pentol triacetate **6**, mp 105°, on acetylation in the usual manner gave the pentol pentaacetate **5**, mp 133°, whose characterization is described below. Hydrolysis of the pentol pentaacetate finally gave the desired free pentol, pseudo-β-DL-gulopyranose **11** as a colorless syrup with appropriate infrared and pmr spectra. The configuration is based primarily on chemical correlation with the pentol triacetate and pentaacetate. The free pentol presumably could also be prepared by hydrolysis of the pentol triacetate.

(11) R. McCrindle, K. H. Overton, and R. A. Raphael, *J. Chem. Soc.*, 1560 (1960).

(12) E. E. Smissman, J. T. Suh, M. Oxman, and R. Daniels, *J. Amer. Chem. Soc.*, **84**, 1040 (1962).

(13) The pseudo-glucal 4,6-diacetate (anomeric configuration unknown?) was obtained by heating tri-*O*-acetyl D-glucal with water. On acetylation of pseudo-glucal diacetate, the triacetate was obtained. See B. Helferich, *Advan. Carbohyd. Chem.*, **7**, 210 (1952).

(14) Note that the cyclohexane ring-numbering used here for pseudohexopyranoses is different from the accepted numbering of true hexopyranoses.

(15) R. Daniels and J. L. Fischer, *J. Org. Chem.*, **28**, 320 (1963).

(16) G. P. Kugatova-Shemyakina and Y. A. Ovchinnikov, *Tetrahedron*, **18**, 697 (1962).

(17) Recent work by S. J. Angyal, P. T. Gilham, and G. J. H. Melrose [*J. Chem. Soc.*, 5252 (1965)] indicates that such acetyl migrations are more common than formerly supposed.

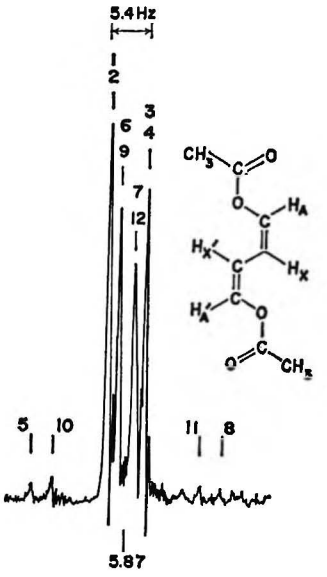


Figure 1.—Proton magnetic resonance spectrum at 60 MHz of the *cis,cis* diastereomer (mp 101–102°) of 1,4-diacetoxy-1,3-butadiene in chloroform-*d*.

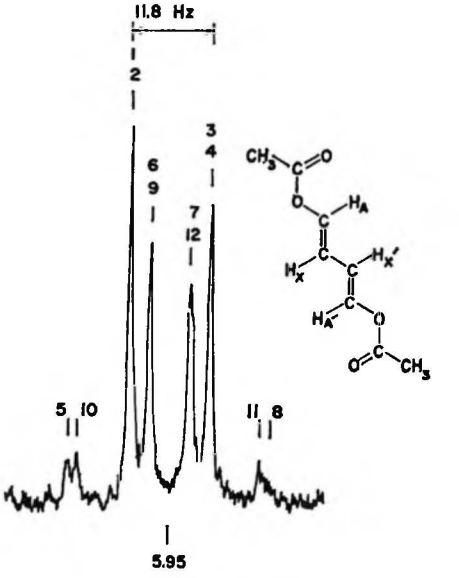


Figure 2.—Proton magnetic resonance spectrum at 60 MHz of the *trans,trans* diastereomer (mp 103–104°) of 1,4-diacetoxy-1,3-butadiene in chloroform-*d*.

Proton Magnetic Resonance Studies on the Diacetoxybutadienes.—The pmr spectrum (Figure 1) of *cis,cis*-1,4-diacetoxy-1,3-butadiene in chloroform-*d* contained only three sets of signals, with relative areas of six, two, and two protons. The two acetate methyl groups produced a sharp singlet at 2.18 ppm. The four olefinic protons produced a symmetrical pattern consisting of one two-proton component at 5.87 and another at 7.10 ppm. Such a pattern is characteristic of a set of two pairs of equivalent nuclei with unequal coupling constants, often described as an AA′XX′ (or AA′BB′) case.[18,19]

For our present analysis, the AA′XX′ approximation has been used.[20,21] Coupling constants for the *cis,cis* diene were calculated from measurements of the observed line spacings in either the AA′ or XX′ component: $J_{AX} = 6.7$, $J_{AX'} = -1.3$, $J_{XX'} = 11.0$ and $J_{AA'} = 1.6$ Hz.

The spectrum of the *trans,trans* diene (Figure 2) was very similar, with the three sets of signals located at 2.13, 5.95, and 7.35 ppm. The calculated coupling constants for this isomer were $J_{AX} = 12.5$, $J_{AX'} = -0.7$, $J_{XX'} = 11.5$, and $J_{AA'} = 0.8$ Hz. Each set of coupling constants was calculated from measurements of the observed line spacings, which correspond to energy levels given by Pople, Schneider, and Bernstein[18,19] (see Table I). Although these calculations do not in themselves permit one to distinguish J_{AX} from $J_{AX'}$ or $J_{AA'}$ from $J_{XX'}$, or to choose the relative signs, the values given are believed correct by analogy to known *cis*, *trans*, single-bond vicinal, and long-range coupling constants for other 1,4-disubstituted 1,3-dienes.[22–24] Nevertheless, the numerical values of Table I are dependent on correct assignment of the lines, and any error in these assignments might cause reversal of the relative magnitudes or signs of the coupling constants.

TABLE I

PARAMETERS USED FOR CALCULATING COUPLING CONSTANTS OF THE 1,4-DIACETOXY-1,3-BUTADIENES

Parameter	Frequency difference measured between lines[a]	Assignment	Observed values from the spectra (Hz)[b] *cis,cis*	*trans,trans*
N	1–3; 2–4	$J_{AX} + J_{AX'}$	5.4	11.8
K	5–6; 7–8	$J_{AA'} + J_{XX'}$	12.6	12.2
M	9–10; 11–12	$J_{AA'} - J_{XX'}$	−9.5	−10.7
$(K^2 + L^2)^{1/2}$	5–7; 6–8	...	±15.2	±18.3
$(M^2 + L^2)^{1/2}$	9–11; 10–12	...	±12.0	±16.7
L	(Calcd)	$J_{AX} - J_{AX'}$	(7.9)	(13.2)

[a] Designations of Pople, *et al.*[18,19] [b] Average of data taken from the AA′ and XX′ components, using two tracings of each expanded 60-MHz spectrum.

The 1,4-diacetoxy-1,3-butadiene isomers of mp 101–102° and 103–104° may thus be assigned the configurations *cis,cis* and *trans,trans*, respectively.[25] The one remaining isomer then necessarily has the one remaining, *cis,trans* configuration, **14**. Our assignments to the three diastereomers confirm those of

(18) (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp 138–140; (b) see also Table 6–18, p 141.

(19) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1965, Vol. 1, pp 392–99.

(20) An AA′XX′ spectrum theoretically consists of 12 "A" transitions and 12 "X" transitions. Since the A transitions 1 and 2 are both equal to $N/2$, and 3 and 4 to $-N/2$, a maximum of 10 A lines is actually found. These ten lines theoretically consist of a high intensity doublet (lines 1,2,3,4) and two symmetrical quartets (lines 5,6,7,8 and 9,10,11, and 12), all centered on the frequency ν_A. (The predicted X spectrum, centered on ν_X, is identical with the A spectrum.) Although the inner lines of each quartet are always more intense, the numbering of the lines depends on the signs of K and M, so that in our present example the two quartets are numbered from left to right 5, 6, 7, 8 and 10, 9, 12, 11, respectively. The line 9 is coincident with line 6, and 12 with 7.

(21) For similar analysis of an AA′XX′ pattern in the spectrum of a dimercaptocyclohexanetetrol, see G. E. McCasland, S. Furuta, A. Furst, L. F. Johnson, and J. N. Shoolery, *J. Org. Chem.*, **28**, 456 (1963).

(22) R. T. Hobgood, Jr., and G. H. Goldenstein, *J. Mol. Spectrosc.*, **12**, 76 (1964).

(23) For example, the coupling constants J_{AX}, $J_{XX'}$, $J_{AX'}$, and $J_{AA'}$ for certain 1,3-butadienes having the substituents indicated are, respectively, as follows (see ref 24): 1,4-dicarbomethoxy, *cis,cis*, 11.8, 11.3, −1.3 and ±1.3; 1,4-dicarbomethoxy, *trans,trans*, 16.5, 11.2, −0.7, and ±0.6; 1,4-dicarboxy, *trans,trans*, 15.8, 11.7, −0.71, and 0.5; 1,4-diphenyl, *trans,trans*, 15.6, 10.8, −0.94, 0.90; 1,4-dichloro, *cis,cis*, 7.3, 10.4, −1.2, 1.7; 1,4-dichloro, *trans,trans*, 13.1, 11.2, −0.69, 0.83.

(24) (a) A. A. Bothner-By and R. K. Harris, *J. Amer. Chem. Soc.*, **87**, 3445 (1965); (b) *ibid.*, **37**, 3451 (1965).

(25) Although the *cis,cis* and *trans,trans* isomers have nearly the same melting point, they are prepared from different starting materials, and are readily distinguished spectroscopically.

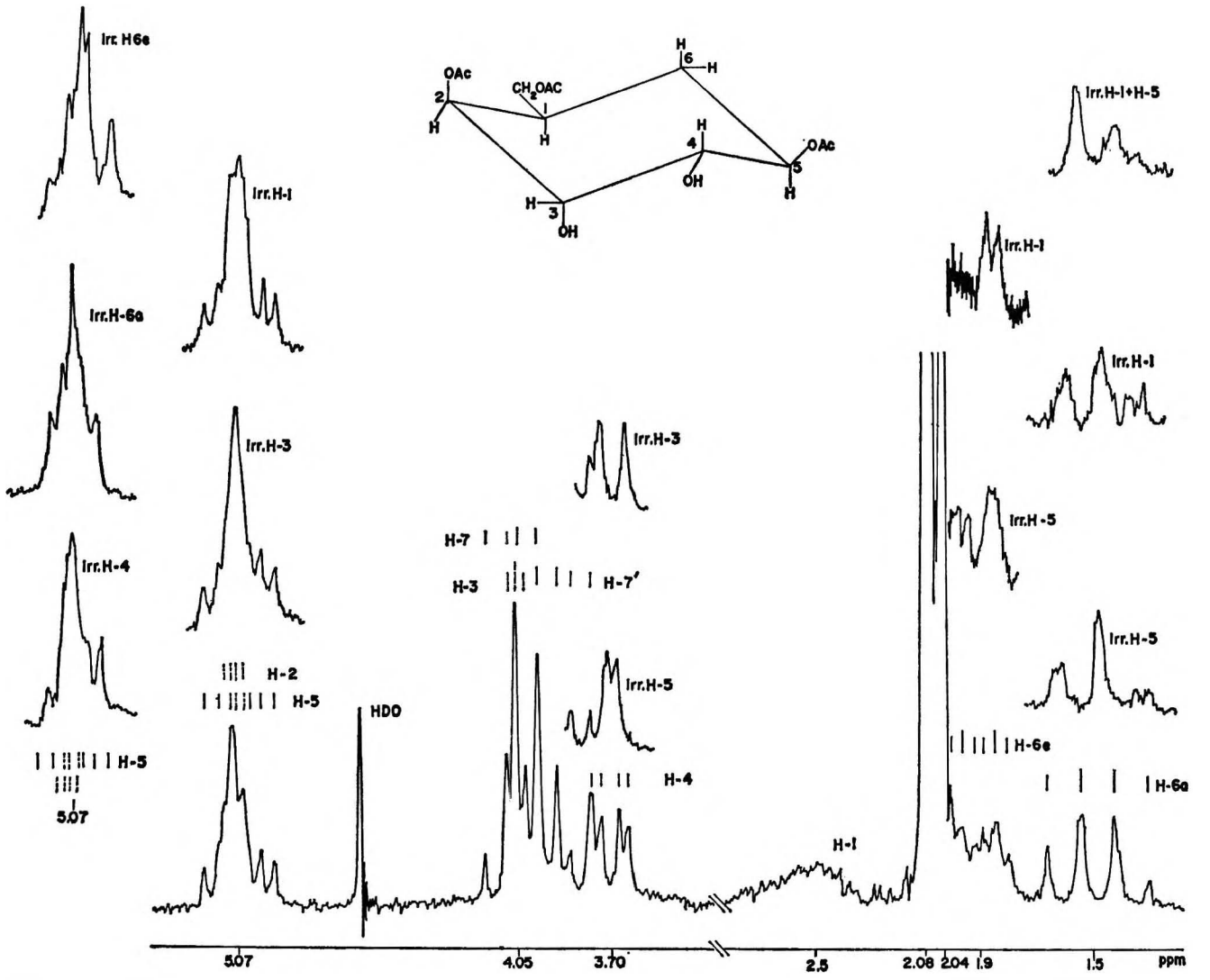


Figure 3.—Proton magnetic resonance and double resonance spectra at 100 MHz of pseudo-β-DL-gulopyranose 2,5,7-triacetate in chloroform-*d* (containing deuterium oxide).

Inhoffen and coworkers, which were based on infrared spectroscopy.[10] The *cis* and *trans* double bonds were reported by these authors to have characteristic C–H deformation frequencies of 760 and 940 cm^{-1}, respectively.

If one desired merely to distinguish the *cis,cis* and *trans,trans* isomers, it would be sufficient to measure the spacing of the intense doublet (lines 1 and 3, Figure 1 or Figure 2) which gives $J_{AX} + J_{AX'}$, since in such isomers $J_{AX'}$ is negligible compared to J_{AX}.

The pmr results suggest that the *cis,cis* and *trans,trans* isomers have *trans*-coplanar favored conformations with respect to the C_2–C_3 single bond and both C=C double bonds. Apparently no evidence is yet available to indicate the favored conformations of the C_1—O or C_4—O single bonds, or of the acetoxy group C—C or C—O single bonds, in these molecules. The *cis,cis* and *trans,trans* isomers in the *trans*-coplanar conformations both belong to the symmetry point-group C_{iv}, due to possession in each case of a twofold proper rotation axis and a vertical plane (each also has an inversion center). These symmetry characteristics[26] are reflected in the spectra.

(26) (a) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, N. Y., 1966, pp 23–33; (b) M. Zeldin, *J. Chem. Educ.*, **43**, 17 (1966).

No satisfactory pmr spectrum of the *cis,trans* isomer **14** has yet been obtained, because of inadequate sample purity, resulting apparently from instability. However, since this compound in its most symmetrical conformation **14**, belongs to the less symmetrical point-group C_S, one would expect its spectrum to be quite different in certain respects. The suggested conformation has no proper rotation axis (or inversion center), but does have a plane of symmetry.

Pmr Studies on Pseudo-Gulose Derivatives.—The spectrum (not shown) of the **enetriol triacetate** (8) was recorded at 60 MHz only. Presence of the chemically inert carbon–carbon double bond was confirmed by a two-proton signal centered at 5.93 ppm (W_h = 7–8 Hz).

Integration revealed twelve protons in the region 1.5–2.5 ppm, nine of which belong to the three acetate methyl groups. However, only two sharp methyl singlets (2.03, 2.06 ppm) of about equal intensity, emerging from a broader signal, were actually observed. The spectral region 1.5–2.5 ppm must also contain signals for the one tertiary proton and two methylene protons of the ring.

The two side-chain methylene protons appeared at 4.07 ppm (complex multiplet) and the two AcO-CH ring protons at 5.25 ppm (overlapping multiplets).

Configurational interpretation was not attempted; however, it is known from chemical correlations that this enetriol triacetate has the all-*cis* configuration (8).

The spectrum (Figure 3) of the **pentol triacetate 6** was recorded at 100 MHz in chloroform-*d* (containing a little deuterium oxide). Deuterium exchange simplified this spectrum by eliminating both the hydroxyl proton signals, one a doublet (J = 7 Hz) at 3.40 ppm and the other somewhere in the region 3.7–4.2 ppm, masked by signals of H-3, 4, 7, and 7′.

Although comparisons with the 60-MHz spectrum were helpful, detailed analysis was achieved only with the aid of field-swept double resonance.[27] The assignments from left to right (Figure 3) were as follows.

At 5.07 ppm there is a presumably eight-line pattern (sum of J = 26 Hz, central four lines masked by H-2) of the axial proton H-5, due to coupling with axial H-4 and H-6_a, and equatorial H-6_e. This H-5 pattern was superimposed on that of equatorial H-2, which was a pair of doublets, with 2 and 3 Hz spacings arising from EA and EE couplings. Observation of this region while sequentially irradiating H-1, H-3, H-4, H-6_a and H-6_e (see upper traces, left side, Figure 3) revealed the expected simplifications in the H-5 and H-2 patterns.

The signal of H-3 at 4.05 ppm was nearly masked by the eight line pattern of H-7 and H-7′ centered at 3.97 ppm. However, the H-3 signal was located by irradiating H-3 while observing H-2 and H-4, and H-3 was shown to have two small couplings, about 3 Hz. This proves H-3 is equatorial, since H-4 is known to be axial.

At 3.70 ppm the axial proton H-4 appeared as a pair of doublets, due to couplings with axial H-5 and equatorial H-3 (9.5 and 3 Hz, respectively). This was shown by irradiating H-5 and H-3 while observing H-4 (upper traces, center of Figure 3).

The broad poorly resolved multiplet at about 2.5 ppm must be due to axial H-1, which is coupled to no less than five other protons.

At about 1.9 ppm, the equatorial H-6_e signal was partially masked by the three acetate methyl singlets (2.04, 2.07, and 2.08 ppm), but was still easily located by irradiation of H-1 or H-5 (upper traces, Figure 3).

At 1.5 ppm, axial H-6_a appeared as a quartet (spacing of 11–12 Hz), due to near-equal coupling with one geminal and two vicinal axial protons. Upon irradiation of H-6_e, H-1, H-5, or both H-1 and H-5 (nuclear magnetic triple resonance), the appropriate spectral changes were noted (upper traces, right side, Figure 3).

The double resonance results thus establish the DL (125/34) configuration, and the side-chain equatorial-favored conformation, for the pentol triacetate (see formula, Figure 3). Furthermore, the observed chemical shifts for H-2 and H-5 confirm the acetyl group positions 2 and 5 (no acetyl migration). It is interesting that equatorial H-2 and axial H-5 have nearly the same chemical shift, presumably due to 1,3-diaxial deshielding of H-5 by the 3-OH group. Lemieux and Stevens have discussed such effects.[28]

From chemical correlation, the **pentol pentaacetate 5** must have the same configuration (and conformation) as the triacetate; the spectrum in chloroform-*d* (not shown) was consistent with such an assignment. At

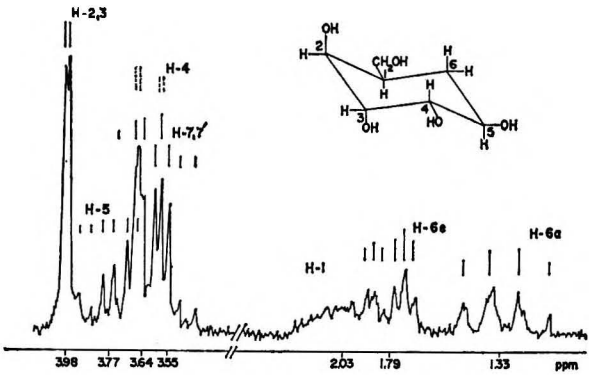


Figure 4.—Proton magnetic resonance spectrum at 100 MHz of pseudo-β-DL-gulopyranose in deuterium oxide.

5.0–5.3 ppm, three of the four AcO-CH ring protons appeared as superposed multiplets; the fourth proton produced a separate multiplet at 5.38 ppm. The latter signal probably is that of H-3, formula **5**, since in the spectrum of the true sugar, β-D-gulopyranose pentaacetate, the signal of H-3, formula **12**, also appears at this location.[28] However, we do not yet have completely reliable assignments for the four pseudo-sugar protons H-2, H-3, H-4, and H-5 of **5**.

Signals of the sidechain methylene protons (H-7, H-7′) appeared as the AB part of an ABX pattern (X part is H-1), with AB centered at 4.97 ppm and having spacings of 11 (J_{AB}), 8, and 6 Hz in the 60-MHz spectrum.

The five acetate methyls (15 protons) produced the usual singlets, at 2.13 (axial, six protons), 2.04 (equatorial, six protons), and 1.98 ppm (side chain, three protons). In the same region (1.4–2.8 ppm) were seen broad poorly resolved multiplets, which must be due to H-1, H-6_a and H-6_e.

In the spectrum of the *true* sugar, β-D-gulopyranose pentaacetate, the signal of the anomeric proton and the tertiary proton (H-1 and H-5) of **12** are each shifted about 2 ppm downfield as compared with the pseudo-sugar pentaacetate, due to presence of the ring-oxygen.[28]

The spectrum (Figure 4) of the *free pentol*, pseudo-β-DL-gulopyranose, was consistent with the configuration **11** deduced by chemical correlations. Double resonance techniques were used in making the configurational assignment.[27] At 3.98 ppm the equatorial protons H-2 and H-3 appeared as a doublet. The chemical shift between H-2 and H-3 was too small, even at 100 MHz, to permit observation of J_{23}. However, irradiation of either H-1 or H-4 filled in or collapsed part of the H-2 plus H-3 "doublet," confirming its identity.

The axial H-5 pattern (3.77 ppm) presumably is a doubled triplet, resulting from couplings with axial H-4 and the two ring-methylene protons. Double resonance was used to confirm the large and small couplings with H-6_a and H-6_e, respectively.

The signals at 3.64 and 3.55 ppm are produced by H-7 and H-7′ (side-chain methylene); presumably each is a pair of doublets. These signals totally mask the signal (presumable a pair of doublets) of axial H-4 at about 3.64 ppm. The location of H-4 was shown by irradiating H-4 while observing H-2 and H-3 (see above). Since J_{45} would be large, and J_{34} and J_{23} small, the lines should be in the positions indicated in Figure 4 (compare pentol triacetate).

(27) D. W. Whiffen and R. Freeman, *Mol. Phys.*, **4**, 321 (1961).

(28) (a) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **43**, 2059 (1965); (b) *ibid.*, **44**, 249 (1966).

At 2.03 ppm there was a broad, unresolved multiplet, arising from axial H-1. This was confirmed by irradiation of H-1 while observing H-2 and H-3.

The signal for H-6_e, presumably a pair of triplets, appeared at 1.79 ppm, and of H-6_a (quartet) appeared at 1.33 ppm.

The free pentol is thus shown to have the DL (125/34) or β-DL- gulopyranose configuration, and the side chain-equatorial conformation (formula, Figure 4).

Experimental Section

All melting points (corrected) were measured on a Nalge-Axelrod micro hot-stage, Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Darco G-60 decolorizing charcoal[29] and Woelm alumina[30] were used. All evaporations were performed under reduced pressure. Light petroleum of bp 60–110° was used.

Infrared spectra were recorded with Perkin-Elmer Model 427 and Model 137 (Infracord) spectrometers.

Except where otherwise noted, the nmr spectra of free polyols were recorded in deuterium oxide solution, using sodium 2,2-dimethyl-2-silapentanesulfonate (SDSS) as internal reference; spectra of other compounds were recorded in chloroform-*d*, using tetramethylsilane (TMS) as internal reference; and spectra were run at *both* 60 and 100 MHz, using Varian A-60 and HR-100 spectrometers. Chemical shifts are reported in parts per million (ppm) (δ) from the SDSS or TMS reference taken as zero. Field-swept double resonance experiments were conducted with the HR-100 spectrometer according to the method of Johnson.[31] Modulation was provided by the fixed oscillator of the Varian V-3521-A nmr integrator (operated on its lower side-band), and a Hewlett-Packard hp-200-J audio oscillator (monitored by a hp Hewlett-Packard 521-C frequency counter), for fixed and variable modulation, respectively. Triple resonance experiments were conducted with additional modulation from a Hewlett-Packard 200-CD oscillator.

cis,cis-1,4-Diacetoxy-1,3-butadiene.—A 1.30-g portion of 4-acetoxycrotonaldehyde (prepared from commercial 1,1-diacetoxy-2-butene *via* the 4-bromo derivative by the procedures of Schmidt and Grob[32]) was treated by the procedure of Inhoffen and coworkers[10] to give a 0.11-g (11%) yield of the pure product, mp 102–103° (lit.[10] 13% yield, mp 101–102°).

The nmr spectrum was recorded (see above).

cis,trans-1,4-Diacetoxy-1,3-butadiene (14).—A 8.0-g portion of 4-acetoxycrotonaldehyde diacetate[32] treated by the procedure of Inhoffen and coworkers[10] gave 1.9 g of the crude product as a colorless oil, bp 92–95° (1 mm). On standing in the refrigerator the product solidified (lit.[10] mp 34–36°) but it appeared to be unstable and no satisfactory melting point or nmr spectrum could be obtained.

trans,trans-1,4-Diacetoxy-1,3-butadiene.—A 25.0-g portion of commercial cyclooctatetraene treated by the improved three-step synthesis of Hill and Carlson[33] gave a 56% over-all yield o the diacetoxydiene, mp 100–102° (lit.[10] mp 103–104°).

The infrared spectrum contained peaks at 3150, 1750, 1620, 1350, 1220, 1130, 950, and 910 cm^{-1}, and was essentially identical with that reported by Inhoffen and coworkers.[10] The peak at about 950 cm^{-1} reportedly is characteristic of the *trans*-substituted C=C double bond in such compounds.

The nmr spectrum was recorded (see above).

A 3.87-g portion of the diacetoxydiene treated with methyl acrylate by the procedure of Smissman and coworkers[12] gave a 5.12-g (88%) yield of methyl 2,5-diacetoxy-3-cyclohexene-1-carboxylate, as a colorless oil, bp 139–142° (1.5 mm) (lit.[12] 152–155° (3 mm)).

A 2.5-g portion of the diacetoxydiene treated with acrylic acid by the method of McCrindle and coworkers[11] gave a 1.14-g (32%) yield of 2,5-diacetoxy-3-cyclohexene-1-carboxylic acid, mp 142–145° (lit. mp[11] 142–143°).

A portion of the diacetoxydiene failed to react with allyl alcohol (1 mol) when the mixture was boiled under reflux for 24 hr. When another portion of the mixture was heated at 185° for 3 days, no pure product could be isolated.

When a portion of the diacetoxydiene was heated with *cis*-1,2-dichloroethylene (1 mol) at 190–200° for 2 days, only starting material could be isolated.

DL(125/0) Diastereomer of 2,5-Dihydroxy-3-cyclohexene-1-methanol Triacetate (8).—A mixture of 1.5 g of allyl acetate and 1.7 g of *trans,trans*-1,4-diacetoxy-1,3-butadiene[33] in a sealed Pyrex bomb tube (13 × 180 mm) was heated in an electric bomb furnace at 205–210° for 48 hr. After cooling, the tube was opened (no pressure) and the contents were evaporated, giving a brown oil. This oil was transferred to a column of neutral aluminum oxide (250 × 20 mm), and the column was eluted with 200 ml of benzene. (An ultraviolet lamp is helpful for locating the product, which is fluorescent.) Evaporation of the eluate gave a yellow oil, which was distilled under vacuum, giving 2.35 g of material, bp 142–145° (1 mm). Redistillation gave 1.9 g (70%) of the desired product in the form of a colorless syrup, bp 143–145° (1 mm).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.63; H, 6.73.

The infrared spectrum contained peaks at 1725 and 1230 cm^{-1}. The nmr spectrum was recorded (see above).

A portion of this triacetate was hydrolyzed by dissolving it in a 1 *N* solution of hydrogen chloride in ethanol–water (1:1). The resulting solution was boiled under reflux for 6 hr, then evaporated. A colorless syrup, presumably the desired triol, was obtained, but has not been further characterized.

Reactions which were attempted with the enetriol triacetate included: (a) *trans*-hydroxylation of the double bond with performic acid under various conditions; (b) reaction with hypobromous acid or N-bromosuccinimide under various conditions; (c) reaction with 30% aqueous hydrogen peroxide in trifluoroacetic acid; (d) reaction with potassium permanganate and magnesium sulfate. In each case, only starting material was obtained.

A 2.7-g portion of the enetriol triacetate was saponified with hot aqueous–ethanolic sodium hydroxide. The reaction mixture was neutralized, deionized, and evaporated in the usual manner, giving 1.04 g of the free enetriol as a colorless oil. The double bond in the free enetriol failed to react with (a) silver chlorate–osmium tetroxide; (b) performic acid; (c) bromine–carbon tetrachloride; (d) silver acetate and iodine (Prévost reagent); or (e) hydrogen and platinum (or nickel) catalyst. In each reaction, starting material was recovered.

DL(125/34) Diastereomer of 2,3,4,5-Tetrahydroxycyclohexanemethanol 2,5,7-Triacetate (Pseudo-β-DL-Gulopyranose Triacetate) (6).—The procedure was similar to one described by McCrindle, Overton, and Raphael.[11] A solution of 0.54 g of the enetriol triacetate in 25 ml of anhydrous ether was slowly added with stirring to a solution of 0.5 g of osmium tetroxide in 3.0 ml of anhydrous pyridine and 5.0 ml of anhydrous ether. The mixture was stirred for 5 days in the dark at 25°. The brown residue obtained upon evaporation was taken up in 25 ml of absolute methanol and the solution was saturated with hydrogen sulfide. After 30 min the mixture was filtered, and the filtrate was evaporated. The dark residue was extracted with boiling benzene (3 × 7 ml), and to the combined extract was added 15 ml of light petroleum. After 1 hr the supernatant liquid was decanted from the dark oily sediment, concentrated to about one-third volume, and kept at 25° for 3 days. The colorless needles which had separated were collected and dried: weight 65 mg (11%), mp 103–104°. The product was recrystallized, giving 40 mg of the pure pentol triacetate, mp 104–105°.

Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.62. Found: C, 51.27, 51.19; H, 6.74, 6.50.

The nmr spectrum was recorded (see above).

DL(125/34) Diastereomer of 2,3,4,5-Tetrahydroxy-1-Cyclohexanemethanol Pentaacetate (Pseudo-β-DL-gulopyranose Pentaacetate) (5). A. From the Enetriol Triacetate.—A stock solution of 0.5 g of osmium tetroxide in 100 ml of *t*-butyl alcohol was prepared. To a stirred solution of 4.0 ml of 30% aqueous hydrogen peroxide in 6.0 ml of the catalyst solution was added dropwise a solution of 2.16 g of the enetriol triacetate in 8 ml of *t*-butyl

(29) A product of the Darco Division, Atlas Powder Co., Wilmington, Del.

(30) A product of Alupharm Chemicals, New Orleans, La.

(31) L. F. Johnson, Varian Associates Technical Information Bulletin, Vol. III, No. 3, 1962, p 5.

(32) H. Schmidt and E. Grob, *Helv. Chim. Acta*, **32**, 77 (1949).

(33) R. K. Hill and R. M. Carlson [*J. Org. Chem.*, **30**, 2414 (1965)] report that many Diels–Alder adducts from 1,4-diacetoxy-1,3-butadiene undergo spontaneous aromatization. (It appears that little, if any, aromatic product is formed when the less reactive dienophiles, such as allyl acetate or vinylene carbonate, are used.)

alcohol. Stirring was continued at 25° for 5 days. On evaporation, a colorless syrup was obtained, and to it was added 6.0 ml of anhydrous pyridine and 6.0 ml of acetic anhydride. The mixture was kept at 25° for 1 day, then evaporated. The residual brown syrup was taken up in 15 ml of chloroform, and the chloroform solution processed in the usual manner, giving a pale yellow syrup. This syrup was crystallized from 2-propanol, giving 1.62 g of colorless crystals, mp 126–131°. This product was recrystallized, giving 1.19 g (38%) of the pure pentaacetate, mp 132–133°.

Anal. Calcd for $C_{17}H_{24}O_{10}$: C, 52.60; H, 6.23. Found: C, 52.45; H, 6.35.

The infrared spectrum (KBr) contained peaks at 3000, 1750, 1350, 1220, 1050, 900, and 820 cm^{-1}.

The nmr spectrum was recorded (see above).

B. From the Pentol Triacetate.—Acetylation of a 12-mg portion of the pentol triacetate with acetic anhydride and pyridine in the usual manner gave a 9-mg (58%) yield of the pentaacetate, mp 131–132°. A mixture melting point with a sample prepared by procedure A was not depressed, and the infrared spectra were identical.

DL(125/34) Diastereomer of 2,3,4,5-Tetrahydroxy-1-cyclohexanemethanol (Pseudo-β-DL-gulopyranose) (11).—To 175 mg of the pentaacetate was added 4.0 ml of a *M* solution of hydrogen chloride in ethanol–water (1:1). The resulting solution was boiled for 6 hr under reflux. The solution was then treated with decolorizing charcoal, and evaporated. The syrupy residue was repeatedly evaporated after additions of small volumes of absolute ethanol. The product (70 mg, 88%) was obtained as a colorless syrup; a correct microanalysis was obtained on the crystalline pentaacetate derivative (see above).

The same product was obtained by hydrolysis with hot sodium hydroxide (1 *M*) in ethanol–water (1:1), in somewhat lower yield.

The nmr spectrum was recorded (see above).

Registry No.—*cis,cis*-1,4-diacetoxy-1,3-butadiene, 10489-24-4; *trans,trans*-1,4-diacetoxy-1,3-butadiene, 15910-11-9; **5**, 16656-57-8; **6**, 16656-59-0; **8**, 16703-82-5; **11**, 16656-62-5.

Acknowledgment.—This research was made possible by a generous grant (CA-07250) to the Institute of Chemical Biology, University of San Francisco, from the National Cancer Institute, U. S. Public Health Service. We wish to thank Professor Edward E. Smissman, University of Kansas, and Professor Henry Z. Sable, Western Reserve University, for helpful discussions, and Dr. Yoko Kanazawa for some of the double resonance experiments.

Alicyclic Carbohydrates. XXXIII. Epimerization of Pseudo-α-DL-talopyranose to Pseudo-α-DL-galactopyranose. Proton Magnetic Resonance Studies[1]

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Received January 8, 1968

The expression pseudo-sugar is used to denote an alicyclic analog of a cyclic monosaccharide. For example, a hydroxymethylcyclohexanetetrol (formula 1) may be described as a "pseudo-hexose," or more explicitly, as a "pseudo-hexopyranose." When pseudo-α-DL-talopyranose (2) was heated with 95% acetic acid containing sulfuric acid, it underwent the expected epimerization at position 4 (position 2 by usual hexopyranose numbering). The crude product was treated with acetic anhydride. The yield of pure crystalline pentol pentaacetate (8, mp 147–148°) was less than 15%. This pentaacetate was readily converted in high yield by acidic hydrolysis into the desired free pentol, pseudo-α-DL-galactopyranose (7), mp 173–174°. The DL(123/45) or α-DL-galactopyranose configuration, 7, which should exist in the (EAEEA) or side chain–equatorial favored conformation, 13, was assigned for mechanistic reasons. Proton magnetic resonance studies on the pentol and its pentaacetate were consistent with this configuration and conformation. An improved preparation of pseudo-α-DL-talopyranose is described.

Recently we reported[3,4] the synthesis of pseudo-α-DL-talopyranose (1 or 2) (Scheme I). This was the first member of a new series of compounds which we propose to designate pseudo-sugars, *i.e.*, cyclic forms of monosaccharides in which the usual ring-oxygen atom is replaced by methylene.[3,4] It is hoped that pseudo-sugars will be found acceptable to some although not all enzymes or biological systems, and thus may have useful biological properties.

More recently, we reported the synthesis of a second pseudohexose, which had the β-DL-gulopyranose configuration.[1b]

We now wish to report synthesis and pmr characterization of a third diastereomer in the pseudo-hexopyranose (formula 1) series, namely pseudo-α-DL-galactopyranose (7). In order to prepare this isomer, we utilized the valuable epimerization method recently developed by Angyal, Gorin, and Pitman.[5–7] Our starting material was the already available talopyranose isomer (2). This was heated for a prolonged period with the Angyal reagent,[5] 95% acetic acid (containing a little sulfuric acid). According to Angyal,[5] epimerization takes place most readily at a hydroxy or acetoxy group which has one *cis* and one *trans* neighboring functional group. Thus we predicted epimerization would take place at position 4 of formula **3** to give the acetylated α-DL-galactopyranose diastereomer **8**, and, in fact, the only new product isolated did have this configuration, as shown by pmr studies. The epimerization is believed to take place through the anchimeric effect of the neighboring *trans*-acetoxy group at position 5 of formula **3**, *via* the bicyclic acetoxonium intermediate **4**, which has not been isolated.

The yield of the α-DL-*galacto* pentaacetate product

(1) For the two preceding papers, see (a) G. E. McCasland, M. O. Naumann and L. J. Durham, *Carbohyd. Res.*, **4**, 516 (1967); (b) G. E. McCasland, S. Furuta, and L. J. Durham, *J. Org. Chem.*, **33**, 2835 (1968).

(2) To whom any correspondence should be addressed at the University of San Francisco.

(3) G. E. McCasland, S. Furuta, and L. J. Durham, *ibid.*, **31**, 1516 (1966).

(4) See also G. E. McCasland, *Advan. Carbohyd. Chem.*, **20**, 41 (1965).

(5) S. J. Angyal, P. A. J. Gorin, and M. E. Pitman, (a) *J. Chem. Soc.*, 1807 (1965); (b) *Proc. Chem. Soc.*, 337 (1962).

(6) P. A. J. Gorin, K. Horitsu, and J. F. T. Spencer, *Can. J. Chem.*, **43**, 2259 (1965).

(7) P. A. J. Gorin, *ibid.*, **41**, 2417 (1963).

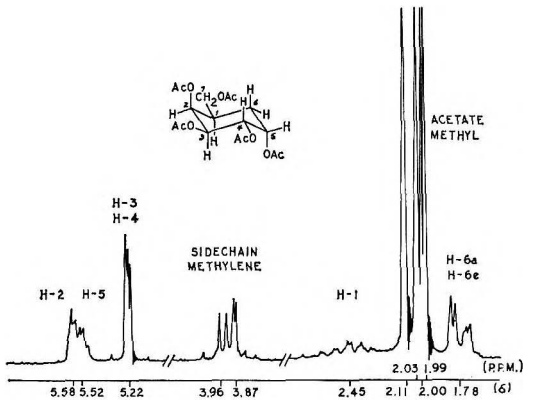
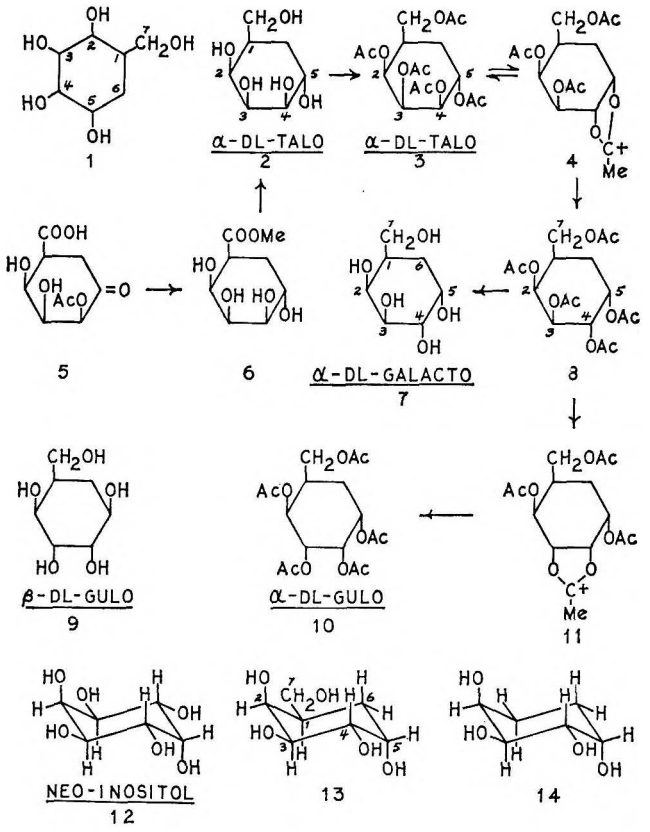


Figure 1.—Proton magnetic resonance spectrum of pseudo-α-DL-galactopyranose pentaacetate in chloroform-*d* at 100 MHz.

Scheme I



was poor, only about 14%; nevertheless, the synthesis by epimerization is much more convenient (if one has the starting material) than a total synthesis of the pseudo-hexopyranose structure would be, and probably the over-all yield of any total synthesis would be less than 14%. Since the starting material was recovered from the mother liquors (as pentaacetate) in about 20% yield, the yield of *galacto* product could perhaps be increased by use of a longer reaction time (or higher temperature); however, some decomposition was noted after the reaction time of 90 hr actually used.

We anticipated that the α-DL-*galacto* product might itself undergo further epimerization. Such epimerization might be expected at position 4 (formula **8**), causing reversion to the starting material configuration. The recovery of starting material pentaacetate in 20% yield (see above) may well be due,[8] in part, to the reverse epimerization mentioned. Epimerization also might be expected at position 3 (formula **8**), since the group at position 3 also has one *cis* and one *trans* neighboring group. The product from this epimerization would be pseudo-α-DL-gulopyranose pentaacetate (**10**), formed *via* the acetoxonium intermediate (**11**). As yet we have no evidence for the formation of the α-DL-*gulo* product (**10**); however, no systematic effort to isolate this (unknown) isomer from the mother liquors has yet been made. The anomer, pseudo-β-DL-gulopyranose (**9**) recently has been prepared by us but will not epimerize to the α form in solution in the typical manner of *true* hexopyranose sugars.[9]

After the 90-hr heating period used in our epimerization reaction, we added acetic anhydride to ensure complete acetylation of the products (which might have one or more free hydroxyl groups), and isolated pseudo-α-DL-galactopyranose in the form of its pentaacetate **8**. This pentaacetate was readily converted by acidic aqueous hydrolysis into the desired free pentol (**7**) in high yield. The pentol and pentaacetate were both colorless, crystalline, sharp-melting substances with appropriate microanalyses and infrared and pmr spectra.

We previously[4] prepared pseudo-α-DL-talopyranose (**2**) by *lithium aluminum hydride* reduction of the tetrol methyl ester **6**, obtained by sodium borohydride reduction, and methylation, of the keto acid monoacetate[10] (**5**); the over-all yield was 23%. We now find it more convenient to carry out a second *borohydride* reduction on the crude tetrol methyl ester; the over-all yield is increased to 53%.

Pmr Evidence for the Configurations.—The spectrum (Figure 1) of the pentol pentaacetate (**8**) was recorded at 60 and 100 MHz using a chloroform-*d* solution. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane (TMS) used as an internal reference. The number of protons in each signal was confirmed by integration of the spectrum.

The one sidechain acetate methyl and two equatorial acetate methyl groups produced sharp singlets at 1.99, 2.00, and 2.03 ppm (three protons each). The two axial groups produced a sharp singlet at 2.11 ppm (six protons).

The side-chain methylene protons H-7 and H-7′ produced an eight-line pattern, each proton a perturbed pair of doublets, located at 3.87 and 3.96 ppm, with spacings indicative of a geminal coupling of about 11 Hz, and vicinal couplings of about 6 and 9 Hz. The ring-methylene protons H-6_a and H-6_e produced overlapping multiplets centered at about 1.78 ppm. The methine proton H-1 gave a complex, poorly resolved multiplet at about 2.45 ppm.

The remaining four (AcO–CH) ring protons produced two groups of signals. The first group, due to the two axial protons H-3 and H-4, consisted of a relatively sharp multiplet centered at 5.22 ppm. The second group, due to the two equatorial protons H-2 and H-5, was not completely separated but could be identified as a narrow tripletlike signal for H-2 at 5.58 ppm and a quartetlike signal for H-5 at 5.52 ppm. The

(8) It would be of interest to try the same epimerization procedure on pure pseudo-α-DL-galactopyranose to find out what products are actually formed from it. As yet we do not have a large enough quantity of the pseudo-galactose for such studies.

(9) We have recently completed the synthesis of pseudo-β-DL-gulopyranose and established its configuration by use of proton magnetic resonance and spin decoupling.[1b]

(10) M. M. Doshi, *Dissertation Abstr.*, **24**, 3998 (1964).

spacings of both these patterns were indicative of small coupling interactions, consistent with the equatorial orientations.[11,12]

The similarity of chemical shifts for H-2 and H-5, and especially for H-3 and H-4, results from the relatively high symmetry of the molecule in its favored chair conformation (**13**). Although the molecule (**13**) does not actually contain any symmetry element, its symmetry[13] approaches that of the tetrol (**14**), which has a twofold simple axis (symmetry point-group C_2), and the hexol (**12**), which has a center of symmetry (point-group C_{1h}).

The pmr results are consistent with the DL (123/45) or α-DL-*galacto* configuration (**7**), and the (EAEEA) or side-chain-equatorial favored conformation (**13**).

The spectrum (Figure 2) of the free pentol (**7** or **13**) was recorded at 60 and 100 MHz in deuterium oxide. Chemical shifts (δ) are recorded in parts per million downfield from the sodium 2,2-dimethyl-2-silapentane sulfonate (SDSS) internal reference. A large HDO peak (not shown in Figure 2) was observed at 4.70 ppm.

The side-chain methylene protons H-7 and H-7′ again showed up as an eight-line pattern, with components located this time at 3.50 and 3.64 ppm, and spacings indicative of a geminal coupling of 11 Hz and vicinal couplings of 6 and 7 Hz. The ring methylene protons H-6a and H-6e produced overlapping signals at about 1.6 ppm. The complex, poorly resolved multiplet of the methine proton H-1 this time was located at 2.0 ppm.

The remaining four (HO–CH) ring protons produced signals at 3.72 (axial, H-3 and H-4), and at 4.10 ppm (equatorial, H-2 and H-5). The outer lines of the presumed axial–axial coupling pattern of H-3 and H-4 were not visible because of the nearly equal chemical shifts of these two protons.

As with the pentaacetate, the relatively high symmetry of the pentol molecule (**13**) is reflected in its spectrum. The spectrum is consistent with the DL(123/45) or α-DL-*galacto* configuration (**7**), and the (EAEEA) or side-chain equatorial conformation (**13**).

Experimental Section

All melting points are corrected, and were measured on a Nalge-Axelrod micro hot-stage. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. Darco G-60 decolorizing charcoal[14] was used. All evaporations were performed under reduced pressure. Light petroleum of bp 60–100° was used. Infrared spectra were recorded on each intermediate and product with a Perkin-Elmer Model 421 or Model 137 (Infracord) spectrometer. Nuclear magnetic resonance spectra were recorded with Varian A-60 and HR-100 spectrometers.

DL(1234/5) Diastereomer of 2,3,4,5-Tetrahydroxy-1-cyclohexanemethanol (Pseudo-α-DL-Talopyranose) (2) (Improved Procedure Using Sodium Borohydride).—To a well-stirred solution of 2.32 g of the keto acid monoacetate[4,10] (**5**), mp 146–147°, in 20 ml of water was added dropwise a solution of 0.70 g of sodium borohydride in 20 ml of water. The resulting solution was stirred for 12 to 24 hr at 25°, then acidified with 12 *M* hydrochloric acid, and the solution was evaporated. To the residue portions of anhydrous methanol were repeatedly added and evaporated to dryness.

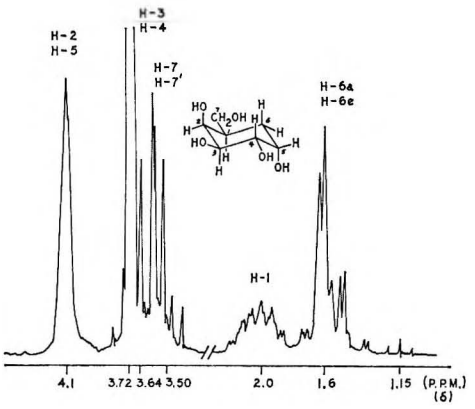


Figure 2.—Proton magnetic resonance spectrum of pseudo-α-DL-galactopyranose in deuterium oxide at 100 MHz.

To the residue was added 40 ml of a 2% solution of hydrogen chloride in anhydrous methanol, and the resulting mixture was boiled under reflux for 2 hr. After cooling, the mixture was filtered, and the filtrate was evaporated.

The residual crude methyl ester (a syrup) was dissolved in 15 ml of water, and the solution was added dropwise with stirring to a solution of 1.9 g of sodium borohydride in 20 ml of water. Stirring was continued for 12 to 24 hr at 25°. The mixture was then acidified with 12 *M* hydrochloric acid, and the solution was evaporated. To the residue portions of anhydrous methanol were repeatedly added and evaporated. Finally a 25-ml portion of methanol was added, the mixture was filtered, and the filtrate was evaporated.

The syrupy residue was dissolved in 15 ml of water, and the solution was decolorized with charcoal and passed through a 15-ml column of moist Amberlite MB-1 resin.[15] The column was eluted with 75 ml of water, and the eluate evaporated, giving 1.5 g of a colorless syrup. This syrup was crystallized from 2-propanol, giving 1.1 g of product, mp 159–161°. Recrystallization gave 0.93 g (52%) of pure pseudo-α-DL-talopyranose, mp 161–162° (lit.[4] mp 160–162°). We previously[4] obtained this pseudo-talose free pentol by the less convenient lithium aluminum hydride reduction of the tetrol methyl ester.

DL(123/45) Diastereomer of 2,3,4,5-Tetraacetoxy-1-cyclohexanemethanol Acetate (Pseudo-α-DL-galactopyranose pentaacetate) (8).—A solution of 0.534 g of pseudo-α-DL-talopyranose (free pentol, mp 161–162°) in 50 ml of 95% acetic acid (containing 1.5% by volume of 18 *M* sulfuric acid) was boiled under reflux for 90 hr (general procedure of Angyal[5]). The resulting brownish mixture, containing some charred particles, was treated with charcoal, and concentrated to about one-third volume.

Acetic anhydride (15 ml) was added, and the solution was kept at 25° for 2 days. Anhydrous sodium acetate (1.3 g) was added to neutralize the sulfuric acid, and the mixture was concentrated to one-third volume, and poured slowly into 50 ml of ice-cold water. The mixture was stirred for 30 min, then extracted repeatedly with chloroform. The chloroform extract was processed in the usual manner to give 0.87 g of a light orange syrup.

The syrup was dissolved in 3.0 ml of benzene, and the solution was transferred to a 150 × 10 mm column of basic Woelm aluminum oxide (Activity Grade I).[16] The column was eluted with 80 ml of benzene. The eluate on evaporation gave 0.63 g of a colorless syrup. This syrup was crystallized from a mixture of 2-propanol and light petroleum, giving 165 mg (14%) of colorless product, mp 145–148°. A sample was recrystallized for analysis from 2-propanol, mp 147–148°.

Anal. Calcd for $C_{17}H_{24}O_{10}$: C, 52.57; H, 6.23. Found: C, 52.69; H, 6.12.

The infrared spectrum (Nujol) contained absorption maxima at 1545, 1235, and 1050 cm^{-1}.

The proton magnetic resonance spectrum was recorded as noted in the beginning of the article.

When the original mother liquor was concentrated and then diluted with petroleum ether, a 225 mg (20%) yield of the starting material pentaacetate was obtained in the form of colorless

(11) (a) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **43**, 2059 (1966); (b) *ibid.*, **44**, 249 (1966).

(12) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 8.

(13) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, N. Y., 1966, pp 23–32.

(14) A product of the Darco Division, Atlas Powder Co., Wilmington, Del.

(15) A product of the Resinous Products Division, Rohm and Haas Co., Philadelphia, Pa.

(16) A product of Alupharm Chemicals, New Orleans, La.

crystals, mp 113–115° (lit.[4] mp 111–112°). A mixture melting point was only slightly depressed, and the infrared spectrum was identical with that of an authentic sample.

DL(123/45) **Diastereomer of 2,3,4,5-Tetrahydroxy-1-cyclohexanemethanol (Pseudo-α-DL-galactopyranose) (7).**—A 186-mg portion of the pentaacetate was dissolved in 5.0 ml of a 1 *M* solution of hydrochloric acid in 50% (by volume) aqueous ethanol, and the resulting solution was boiled under reflux for 6 hr, then evaporated. To the residual syrup 10-ml portions of 2-propanol were repeatedly added and evaporated. The crystalline residue was recrystallized from 3.0 ml of 2-propanol, giving 60 mg (71%) of the free pentol as colorless crystals, mp 173–174°. The melting point was not raised upon further recrystallization.

Anal. Calcd for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 46.97; H, 8.07.

The infrared spectrum (Nujol) contained absorption maxima at 3360, 3280, 1140, 1060, 1050, and 1030 cm^{-1}.

The proton magnetic resonance spectrum was recorded as noted previously in this article.

Registry No.—**2**, 10226-73-0; **7**, 16802-98-5; **8**, 16802-99-6.

Acknowledgment.—This research was made possible by a generous grant (CA-07250) to the Institute of Chemical Biology, University of San Francisco, from the National Cancer Institute, U. S. Public Health Service.

Synthesis of 3-*O*-(*p*-Tolylsulfonyl)-β-D-*altro*-heptulopyranose and Its Conversion into 2,7:3,4-Dianhydro-β-D-*allo*-heptulopyranose

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The oxidation of 2,7-anhydro-4,5-*O*-isopropylidene-β-D-*altro*-heptulopyranose (**1**) with methyl sulfoxide and acetic anhydride followed by reduction with sodium borohydride and subsequent hydrolysis with an acidic ion-exchange resin yielded two 2,7-anhydroheptuloses, namely, 2,7-anhydro-β-D-*altro*-heptulopyranose (sedoheptulosan, **2**) and the new anhydride, 2,7-anhydro-β-D-*allo*-heptulopyranose (**3**), isolated as its crystalline tetraacetate (**4**). These results confirmed the position of the isopropylidene group in compound **1** and, incidentally, demonstrated a simple method for the preparation of **3**. The 3-*O*-tosyl derivative of sedoheptulosan (**7**) was prepared by the selective tritylation of the primary hydroxyl group of **1**, tosylation of the remaining unsubstituted hydroxyl group at C-3, and removal of the isopropylidene and trityl groups. The only product of interest in the reaction of the monotosylate (**7**) with a slight excess of sodium methoxide in boiling methanol was a small amount of 2,7:3,4-dianhydro-β-D-*allo*-heptulopyranose (**9**) obtained as a crystalline diacetate (**10**). The structural assignment of compound **10** is based on its nmr spectrum and also the scission of its epoxide ring to give the expected 2,7-anhydro-β-D-*gluco*-heptulopyranose (**13**). 4,5-Di-*O*-acetyl-2,7-anhydro-1,3-di-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulopyranose (**12**) was also prepared and, although found to be much more resistant than the 3-tosylate under the same conditions, presumably gave the same results when a large excess of sodium methoxide was employed. In conclusion the nmr spectrum of **10** is discussed briefly.

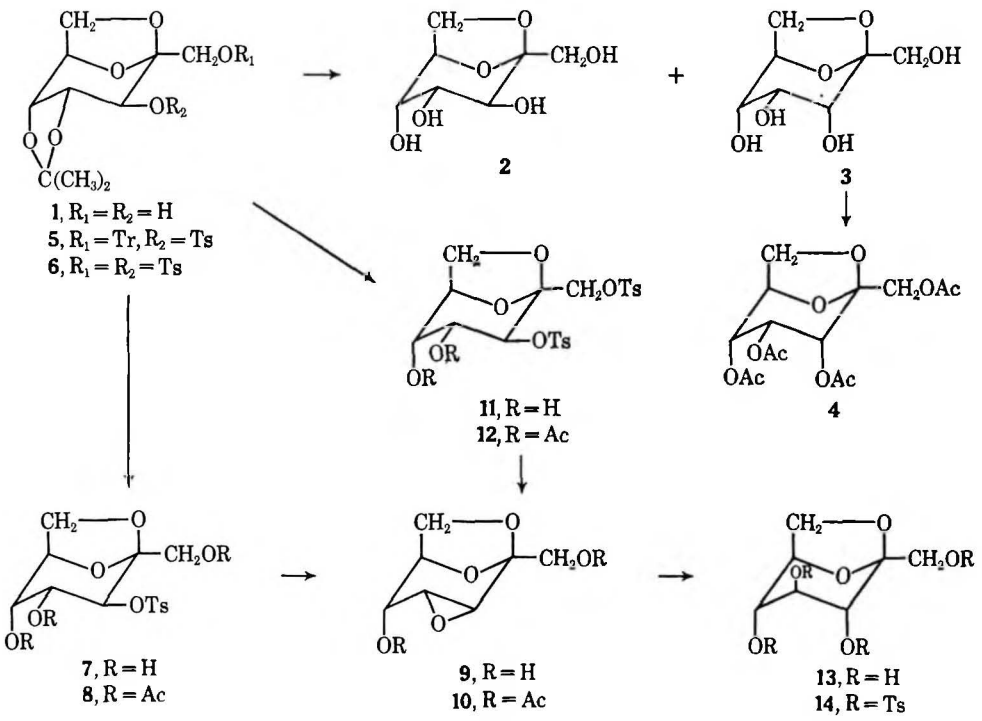
In 1967 the first epoxide in the 2,7-anhydroheptulose series, 2,7:3,4-dianhydro-β-D-*manno*-heptulopyranose,[1] anhydro-4-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulopyranose. The case of reactivity of this monotosylate pyranose. The case of reactivity of this monotosylate was in contrast to the behavior of the tosyl derivatives of the analogous 1,6-anhydro-β-D-altrose which were highly resistant to sodium methoxide.[2] The synthesis of 2,7-anhydro-3-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulopyranose (**7**) seemed not only desirable for further study of these discrepant behaviors but also as a source for the preparation of another epoxide. 2,7-Anhydro-4,5-*O*-isopropylidene-β-D-*altro*-heptulopyranose (**1**) appeared to be a suitable intermediate for the synthesis of **7** (Scheme I).

Originally prepared in 1952[3] the structure of **1** has more recently[4] been confirmed through nmr studies. Further and unequivocal chemical confirmation has now been obtained in the course of the present research. The use of methyl sulfoxide–acetic anhydride[5] as a oxidizing agent for secondary hydroxyl groups is well known. Recently in this laboratory the structure of 1,3,5-tri-*O*-acetyl-β-D-*altro*-heptulopyranose was determined[1] by the oxidation of the unprotected hydroxyl group at C-4 with methyl sulfoxide–acetic anhydride. Reduction of the resulting keto derivative and removal of the acetyl groups yielded 2,7-anhydro-β-D-*altro*-heptulopyranose and 2,7-anhydro-β-D-*manno*-heptulopyranose. Horton and Jewell applied this method in obtaining 1,6-anhydro-β-D-talopyranose from 1,6-anhydro-2,3-*O*-isopropylidene-β-D-mannopyranose[6] or from 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose.[7] The confirmation of the structure of **1** by this method seemed questionable owing to the unprotected hydroxyl group at C-1 which might result in other products. Nevertheless, oxidation of **1** by methyl sulfoxide–acetic anhydride, followed by reduction with sodium borohydride and then removal of the acetal group, yielded only two products, namely, 2,7-anhydro-β-D-*altro*-heptulopyranose (**2**) and 2,7-anhydro-β-D-*allo*-heptulopyranose (**3**). The former was isolated crystalline and the latter was shown to be the enantiomorph of the known 2,7-anhydro-β-L-*allo*-heptulopyranose[8] through a direct comparison of their crystalline tetraacetates.

The tritylation of **1** yielded a syrupy product which was subsequently tosylated to give crystalline 4,5-

(1) E. Zissis, *J. Org. Chem.*, **32**, 660 (1967).
(2) F. H. Newth, *J. Chem. Soc.*, 441 (1956).
(3) W. T. Haskins, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, **74**, 2198 (1952).
(4) E. Zissis and N. K. Richtmyer, *J. Org. Chem.*, **30**, 462 (1965).
(5) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **87**, 4214 (1965).
(6) D. Horton and J. S. Jewell, *Carbohyd. Res.*, **2**, 251 (1966).
(7) D. Horton and J. S. Jewell, *ibid.*, **5**, 149 (1967).
(8) J. W. Pratt and N. K. Richtmyer, Abstracts, the 126th National Meeting of the American Chemical Society, New York, N. Y., Sept 1954, p 22D.

SCHEME I



O-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-1-*O*-(triphenylmethyl)-β-D-*altro*-heptulopyranose (**5**). Hydrolysis of **5** with hot 80% acetic acid gave the desired 2,7-anhydro-3-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulopyranose (**7**).

In the preparation of 2,7:3,4-dianhydro-β-D-*manno*-heptulopyranose,[1] which was isolated as the crystalline diacetate in 43% yield, the 4-*O*-tosyl derivative of sedoheptulosan was allowed to react with excess sodium methoxide at room temperature for several days. The reaction of 3-*O*-tosylsedoheptulosan (**7**) under similar conditions was found to proceed with much degradation and to give a small amount of material which on a thin-layer plate sprayed with sodium iodide and methyl red in butyl alcohol solution developed as a yellow spot, characteristic of epoxides.[9] After variations of temperature and amount of reagent showed no improvement in the yield of the epoxide, the 3-monotosylate was refluxed with a slight excess of sodium methoxide in methanol for 1 hr; tlc then showed no evidence of any starting material. Acetylation of the isolated dianhydride yielded 6% of crystalline 1,5-di-*O*-acetyl-2,7:3,4-dianhydro-β-D-*allo*-heptulopyranose (**10**).

The only structural difference between the reactive 3- and 4-*O*-tosyl derivatives of sedoheptulosan and the resistant 2- and 3-*O*-tosyl derivatives of 1,6-anhydro-β-D-altropyranose is that the former compounds have a hydroxymethyl group at the anomeric carbon in place of a hydrogen atom. In view of this, it was decided to prepare 2,7-anhydro-1,3-di-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulopyranose (**11**) and test its reactivity with alkoxide ion. Hydrolysis of the known[4] 2,7-anhydro-4,5-*O*-isopropylidene-1,3-di-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulopyranose (**6**), prepared from **1**, afforded, however, a syrupy product and consequently was acetylated to give crystalline 4,5-di-*O*-acetyl-2,7-anhydro-1,3-di-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulopyranose (**12**). Compound **12** heated overnight with about an equivalent amount of methoxide was not affected to any great extent. When a large excess of reagent was used it reacted quite readily with a high degree of degradation similar to that noted with 3-*O*-tosylsedoheptulosan (**7**). Investigation of the resulting syrup by tlc showed that the main product was again the dianhydride (**9**) and not the expected 1-*O*-tosyldianhydride.

The implications of these findings are not clear. The fact that the reaction is retarded until the tosyl group at C-1 is eliminated favors the possibility that the hydroxyl group at C-1 plays a direct role in the reaction. On the other hand, the isolation of dianhydride (**9**) does not support this theory since one would expect a different product. A simpler explanation for the slow reaction rate of **12** with methoxide might therefore be steric hindrance due to the presence of the tosyl group at C-1.

The structure of 1,5-di-*O*-acetyl-2,7:3,4-dianhydro-β-D-*allo*-heptulopyranose (**10**) was established by chemical means and substantiated by its nmr spectrum. According to the Fürst–Plattner rule,[10] scission of an epoxide ring in a rigid, six-membered ring should yield predominantly a *trans*-diaxial derivative; thus the anticipated product from **10** should be 2,7-anhydro-β-D-*gluco*-heptulopyranose ("D-*gluco*-heptulosan," **13**). An examination of the reaction of the dianhydride **10** with hot alkali by paper chromatography showed only one product, namely, "D-*gluco*-heptulosan" which was eventually isolated and identified through its crystalline tetratosylate (**14**). There was also evidence of **13** on acid treatment of the dianhydride **10**, although in this case, a second, more intense spot was observed and had a mobility similar to that of D-*gluco*-heptulose.

The structural assignment of **10**, based on the aforementioned results, was also in accordance with its nmr spectrum (Figure 1). The two hydrogen atoms at C-1 appeared as one sharp peak at δ 4.41 ppm. Furthest

(9) J. G. Buchanan and J. C. P. Schwarz, *J. Chem. Soc.*, 4770 (1962).

(10) A. Fürst and P. A. Plattner, *Intern. Congr. Pure Appl. Chem.*, 405 (1951).

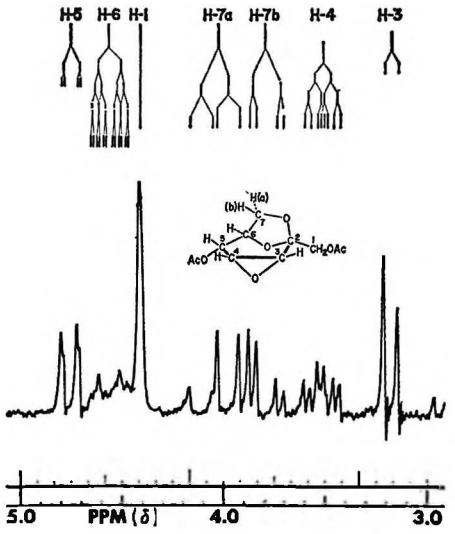


Figure 1.—The nmr spectrum of 1,5-di-*O*-acetyl-2,7:3,4-dianhydro-β-D-*allo*-heptulopyranose (10) at 60 MHz in deuteriochloroform.

downfield (δ 4.77 ppm) was H-5, a doublet ($J_{4,5}$ = 4.4 Hz) whose peaks were slightly split by a weak coupling between H-5 and H-6 ($J_{5,6}$ = 0.7 Hz). The geminal hydrogens at C-7 gave a well-resolved octet due to the A and B protons of an ABX system in the area of δ 3.70–4.18 ppm. The most complex pattern at δ 4.46–4.67 ppm was assigned to H-6. Signals for the protons of the epoxide ring were observed furthest upfield: H-3, δ 3.20; H-4, δ 3.52 ppm ($J_{3,4}$ = 3.8 Hz). These findings are in good agreement with other carbohydrate epoxides, episulfides, and epimines, studied by Buss, *et al.*,[11] in which case the δ values ranged from 2.3 to 3.6 ppm. In reference to a more specific example, H-3 and H-4 of 1,5-di-*O*-acetyl-2,7:3,4-dianhydro-β-D-*manno*-heptulopyranose[1] appeared as an AB quartet (δ 3.02 and 3.22 ppm, respectively ($J_{3,4}$ = 3.9 Hz)) where the two peaks assigned to H-4 were slightly broadened by coupling to H-5.

Although the sharp doublet (δ 3.20 ppm) was suitably assignable to H-3 in formula **10**, the unique features of the system for H-4 (δ 3.52 ppm) required a closer, more subtle evaluation of the structure and the necessity for several decoupling experiments. Since the hydrogen atoms at C-3 and C-5 have similar dihedral angles in relationship to the hydrogen atom at C-4 (about 0 and 10°, respectively), it is possible that the expected quartet for H-4 merges into a triplet. Its subsequent division ($J_{4,6}$ = 1.8 Hz) into a six-line pattern can then be accounted for by long-range coupling to H-6.

Various spin-decoupling experiments supported this theory. Irradiation of the regions assigned to H-3 and H-5 in either case collapsed the sextet of H-4 to a quartet which, without long range coupling, should otherwise have been a doublet. Several meaningful changes in the spectrum were also noted on irradiation of H-6. In this instance, the significant shoulders of the H-5 doublet disappeared, the octet of the geminal hydrogens at C-7 showed signs of converging into an AB quartet, and most importantly the sextet of H-4 had collapsed into a triplet.

(11) D. H. Buss, L. Hough, L. D. Hall, and J. F. Manville, *Tetrahedron*, **21**, 69 (1965).

Experimental Section

Confirmation of the Structure of 2,7-Anhydro-4,5-*O*-isopropylidene-β-D-*altro*-heptulopyranose (1).—Compound **1** (0.5 g) was oxidized overnight at room temperature with 6 ml of methyl sulfoxide and 4 ml of acetic anhydride. The reaction solution was then diluted with ice and concentrated *in vacuo* to a mobile syrup which was repeatedly taken up in toluene and concentrated *in vacuo* until a constant weight was obtained. The oxidation product was dissolved in 25 ml of aqueous ethyl alcohol and added dropwise to a stirred solution of 0.5 g of sodium borohydride in 20 ml of water. The solution was stirred an additional hr and then the excess of reagent was destroyed by the addition of 10 ml of acetone. The solution was then mixed with some Amberlite IR-120 ion-exchange resin, filtered, and concentrated *in vacuo* to a syrup. The syrup was taken up in methanol and concentrated on a steam bath by the passage of a stream of air across its surface. This procedure was repeated several times until boric acid could no longer be detected. An aqueous solution (20 ml) of the dionized product containing 2 g of Amberlite IR-120 ion-exchange resin was refluxed for 2 hr, the resin was removed by filtration, and the filtrate was concentrated *in vacuo* to a syrup (0.25 g). A paper chromatogram of the reaction mixture run in ethyl acetate–acetic acid–formic acid–water (18:3:1:4) and developed with orcinol–hydrochloric acid showed two blue spots. The lower one corresponded to sedoheptulosan (**2**) and the higher one corresponded to 2,7-anhydro-β-D-*manno*-heptulopyranose which has a mobility similar to that of 2,7-anhydro-β-D-*allo*-heptulopyranose (**3**) in the solvent system employed.[12] The two anhydrides were separated on several sheets of Whatman 3MM paper in the same system described above. Sedoheptulosan (**2**) was isolated in crystalline form but the other anhydride (**3**) was a syrup which was acetylated to give crystalline 1,3,4,5-tetra-*O*-acetyl-2,7-anhydro-β-D-*allo*-heptulopyranose (**4**). After one recrystallization from ethyl alcohol–pentane the prisms melted at 112–113° and showed $[\alpha]^{20}D$ −44.9° (c 0.25, chloroform). The ir spectra of **4** and of known 1,3,4,5-tetra-*O*-acetyl-2,7-anhydro-β-L-*allo*-heptulopyranose[8] (mp 116°, $[\alpha]^{20}D$ +46°) were compared and found to be identical.

Anal. Calcd for $C_{15}H_{20}O_{10}$: C, 50.00; H, 5.60. Found: C, 49.77; H, 5.44.

2,7-Anhydro-4,5-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-1-*O*-(triphenylmethyl)-β-D-*altro*-heptulopyranose (5).—The optimum conditions for the tritylation of compound **1** were determined in a series of preliminary experiments. In each instance the progress of the reaction was followed by tlc as the temperature, concentration, and ratio of reagent were systematically varied. A small amount of the 1-*O*-trityl derivative of **1** was separated from the reaction mixture on a preparative tlc plate (Brinkman's silica gel F_{254}) run in benzene–ether (3:2). The desired product could not be crystallized and was finally tosylated to give crystalline 2,7-anhydro-4,5-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-1-*O*-(triphenylmethyl)-β-D-*altro*-heptulopyranose (**5**).

After these preliminary experiments compound **5** was prepared on a large scale by the following method. Compound **1** (30 g) was partially dissolved in 150 ml of hot pyridine (60–70°). On the addition of 54 g of chlorotriphenylmethane and continued heating the remainder of **1** went into solution within 30 min. In the later stages of an additional hour of heating the pyridine hydrochloride began to crystallize out of the hot solution. When the reaction reached completion after 4 days at room temperature 60 g of tosyl chloride was added. Following another 4 days the reaction solution was filtered free of the pyridine hydrochloride and poured onto crushed ice. The resulting mixture of product and triphenylmethanol, filtered and washed with water and then ethyl alcohol, weighed 93 g. Recrystallization from six parts ethyl acetate afforded 55 g (68%) of product which was only slightly contaminated with triphenylmethanol. After a second recrystallization the prisms melted with decomposition at 177–179°, $[\alpha]^{20}D$ −7.3° (c 1, chloroform).

Anal. Calcd for $C_{36}H_{36}O_8S$: C, 68.77; H, 5.77; S, 5.10. Found: C, 68.97; H, 5.73; S, 5.10.

2,7-Anhydro-3-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulopyranose (7).—A 30-g sample of **5** was dissolved in 240 ml of glacial

(12) According to Dr. R. Begbie of the Rowett Research Institute, Aberdeen, Scotland (personal communication, 1966), D-*allo*-heptulopyranose on acid treatment was partly converted into one product, presumably **3**. The mobility of this product on a paper chromatogram run in ethyl acetate–formic acid–water (18:3:1:4) was similar to that of 2,7-andro-β-D-*manno*-heptulopyranose.

acetic acid at 75–85°. The hot solution was then diluted slowly with 60 ml of water and held at the same temperature for 1 hr. After cooling overnight, the precipitated triphenylmethanol was removed by filtration and washed with 100 ml of 80% acetic acid. The combined filtrate and washing were concentrated *in vacuo* to a crystalline mass which was mixed with some chloroform, filtered, and washed with chloroform. The monotosylate (16 g, 97%) was successively recrystallized from acetone, ethyl alcohol, and ethyl acetate as prismatic needles: mp 163–164.5° dec; $[\alpha]^{20}D$ −115° (*c* 1.1, pyridine).

Anal. Calcd for $C_{14}H_{18}O_8S$: C, 48.55; H, 5.24; S, 9.26. Found: C, 48.41; H, 5.20; S, 9.32.

1,4,5-Tri-*O*-acetyl-2,7-anhydro-3-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulopyranose (8).—Acetylation of 0.4 g of **7** yielded a syrup which crystallized during several months in the refrigerator (0.4 g, 73%). After two recrystallizations from ethyl alcohol–water the large prisms melted at 88–92° and showed $[\alpha]^{20}D$ −106° (*c* 0.9, chloroform).

Anal. Calcd for $C_{20}H_{24}O_{11}S$: C, 50.84; H, 5.12; S, 6.79. Found: C, 50.54; H, 5.41; S, 6.91.

1,5-Di-*O*-acetyl-2,7:3,4-dianhydro-β-D-*allo*-heptulopyranose (10).—The course of the reaction of 1 g of **7** in 20 ml of methanol and 12 ml of 2 *N* methanolic sodium methoxide was monitored by tlc using ethyl acetate–acetic acid–formic acid–water (18:3:1:4); after 17 days at room temperature there was no evidence of any remaining starting material. The dark reaction solution which had deposited a large amount of sediment was filtered, neutralized with some Amberlite IR-120 and Duolite A-4 ion-exchange resins, and refiltered, and the resins were washed thoroughly with methanol. The filtrate and washings were combined and concentrated *in vacuo* to a colored syrup (0.1 g). Examination (tlc) of the syrup showed only two well-defined spots, the faster, more predominant spot being the epoxide **9**. They were also observed as blue spots on Whatman No. 1 paper sprayed with orcinol–hydrochloric acid. The two products which were extracted from the syrup with chloroform were resolved on Whatman 3MM paper developed with butyl alcohol–ethyl alcohol–water (3:1:1). Acetylation of the amorphous epoxide (20 mg) yielded 17 mg of the crystalline diacetyl epoxide **10**.

In a final experiment a solution of 10 g of **7** in 60 ml of methanol and 25 ml of 2 *N* methanolic sodium methoxide was refluxed for 90 min resulting in a black solution containing sediment and practically no monotosylate. Following the same procedure described above, the final dark, viscous residue was shaken with 200 ml of chloroform for 2–3 hr and allowed to settle overnight, and the chloroform was decanted. This process was repeated several times until most of the epoxide had been extracted. The concentrated extracts weighed 0.9 g and were reextracted with chloroform which on concentration yielded 0.6 g of syrup highly enriched with epoxide. Acetylation of this final syrup produced 455 mg of **10** representing a 6% yield. Recrystallization from ethyl alcohol–pentane and finally from ethyl alcohol afforded stout prisms: mp 75–77°; $[\alpha]^{20}D$ +35.4° (*c* 1.1, chloroform).

Anal. Calcd for $C_{11}H_{14}O_7$: C, 51.16; H, 5.43. Found: C, 51.05; H, 5.42.

2,7-Anhydro-4,5-*O*-isopropylidene-1,3-di-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulopyranose (6).—The ditosylate **6**, originally obtained as a by-product,[4] was prepared in high yield by the following procedure. An 8-g sample of **1** was almost completely dissolved in 75 ml of hot pyridine and following the introduction of 20 g of tosyl chloride the heating was continued for a short period of time until a clear reaction solution was obtained. It was then allowed to reach room temperature and after 3 days the pyridine solution was decanted from the pyridine hydrochloride which was washed with a small quantity of pyridine. The decantate and washing on being mixed with ice deposited 18 g (97%) of product. The ditosylate, recrystallized from 50 ml of ethyl alcohol, melted at 128–131°; the reported melting point is 131–132°.[4]

4,5-Di-*O*-acetyl-2,7-anhydro-1,3-di-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulopyranose (12).—Hydrolysis of 8 g of **6** with 80 ml of 80% glacial acetic acid at 80–90° for 3 hr yielded 1,3-di-*O*-tosylsedoheptulosan (**11**) which could not be crystallized and consequently was acetylated. The crystalline diacetyl derivative (**12**) weighed 8.5 g (98%) and was recrystallized from ten parts ethyl alcohol and finally from chloroform–pentane. The physical constants of the prismatic needles were mp 137.5–138° and $[\alpha]^{20}D$ −71.3° (*c* 1, chloroform).

Anal. Calcd for $C_{25}H_{28}O_{12}S_2$: C, 51.36; H, 4.83; S, 10.97; CH_3CO, 14.38. Found: C, 51.10; H, 4.69; S, 11.08; CH_3CO, 14.25.

Reaction of 4,5-Di-*O*-acetyl-2,7-anhydro-1,3-di-*O*-(*p*-tolylsulfonyl)-β-D-*altro*-heptulopyranose (12) with Sodium Methoxide.—A solution of 1.1 g of **12** in 6 ml of methanol and 1.5 ml of 2 *N* methanolic sodium methoxide was refluxed overnight. A comparative examination (tlc) of the dark reaction solution with an aliquot which had been removed after the first 3 hr of refluxing showed no appreciable change. The only significant product was deacetylated starting material. An additional 6 ml of reagent was added to the reaction solution which was again heated overnight. During this time the deacetylated starting material had reacted yielding in small quantities two products which were isolated by tlc on a preparative plate (Brinkman's silica gel F_{254}) using butyl alcohol–ethyl alcohol–water (3:1:1). The faster moving fraction (15 mg) cochromatographed in two different systems with the dianhydride **9** produced from **7** and also developed as a yellow spot when sprayed with sodium iodide and methyl red in butyl alcohol.[9] This fraction was then acetylated and the resulting product found to have a mobility (tlc) similar to that of the diacetate **10**.

The other isolated fraction (10 mg) had the same mobility (tlc) in two different solvent systems as the secondary product observed in the reaction of 3-*O*-tosylsedoheptulosan (**7**) with sodium methoxide. Although this minor product was not definitely identified, it should be mentioned that it had a mobility similar to that of sedoheptulosan when cochromatographed on Whatman No. 1 paper in ethyl acetate–acetic acid–formic acid–water (18:3:1:4).

Alkaline and Acid Hydrolysis of 1,5-Di-*O*-acetyl-2,7:3,4-dianhydro-β-D-*allo*-heptulopyranose (10).—Investigation by tlc (ethyl acetate–acetic acid–formic acid–water, 18:3:1:4) of the reaction of **10** (62 mg) refluxed overnight (17 hr) in 6 ml of 3% potassium hydroxide solution showed only one significant spot with mobility similar to that of 2,7-anhydro-β-D-*gluco*-heptulopyranose ("D-*gluco*-heptulosan," **13**). After neutralization of the dark reaction solution with Amberlite IR-120 ion-exchange resin, it was filtered free of resin and concentrated *in vacuo* to a residue which was extracted with water. When the concentrated extract (5 mg) did not readily crystallize, it was tosylated to the crystalline tetratosylate of "D-*gluco*-heptulosan." After one recrystallization the tosyl derivative (**14**) melted at 130–136° and a mixture melting point with an authentic sample[13] (mp 138–139°) was not depressed.

A 10-mg sample of **10** in 1 ml of 0.1 *N* sulfuric acid was heated on a steam bath for 3 hr. A paper chromatogram of the neutralized solution run in ethyl acetate–acetic acid–formic acid–water (18:3:1:4) and sprayed with orcinol–hydrochloric acid developed three blue spots in addition to deacetylated **10**. Two of the spots had mobilities similar to those of "D-*gluco*-heptulosan" and D-*gluco*-heptulose; the third one was not identified.

Registry No.—**4**, 16526-57-1; **5**, 16526-58-2; **7**, 16526-59-3; **8**, 16526-60-6; **10**, 16526-61-7; **12**, 16526-62-8.

Acknowledgment.—The author wishes to thank Dr. W. C. Alford and his associates of the Section on Microanalytical Services and Instrumentation of this laboratory for the microanalyses, infrared spectra, and nmr spectra. The author would also like to thank Dr. E. D. Becker of this institute for the nmr decoupling experiments and his valuable assistance in the interpretation of the spectrum of **10**.

(13) L. C. Stewart, E. Zissis, and N. K. Richtmyer, *Ber.*, **89**, 535 (1956).

Reaction of Nitrosobenzene with Tetramethylallene

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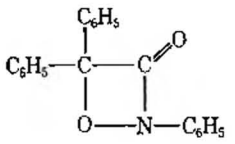
Received March 1, 1968

Reaction of nitrosobenzene with tetramethylallene in chloroform produces *anti*-α-isopropenyl-α-[1-methyl-1-(N-phenylhydroxylamino)ethyl]-N-phenylnitrone, **3**. Reduction of **3** with lithium aluminum hydride yields N-(2-anilino-1,1,3-trimethyl-3-butenyl)-N-phenylhydroxylamine, **4**. Reduction of **4** with zinc in acetic acid gives 2,4-dimethyl-N,N′-diphenyl-4-pentene-2,3-diamine. Pyrolysis of **3** produces *syn*-α-(1-hydroxy-1-methylethyl)-α-isopropenyl-N-phenylnitrone, **6**, and azoxybenzene. Nmr deuteriochloroform–benzene solvent shifts were employed to help establish the nitrone configuration in **3** and **6**; protons of groups *anti* to the nitrone oxygen atom undergo greater shifts than protons of *syn* groups. Observation of coupling of the CH–NH protons of **4** in dimethyl sulfoxide solution allowed exclusion of an alternative structure, N-(2-anilino-1-isopropenyl-2-methylpropyl)-N-phenylhydroxylamine, for the reduction product of **3**.

An interest in small-ring heterocycles as biologically active agents and the knowledge that 1,2-oxazetidin-3-ones[1] such as **1** are reasonably stable materials led us to attempt preparation of **2** by reaction of nitrosobenzene with tetramethylallene. This report deals with the isolation, characterization, and subsequent transformations of a reaction product other than **2** from reaction of nitrosobenzene and tetramethylallene.



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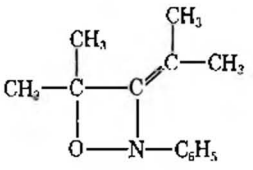
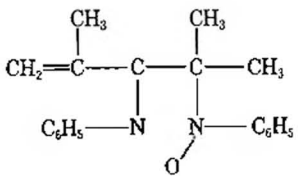


2

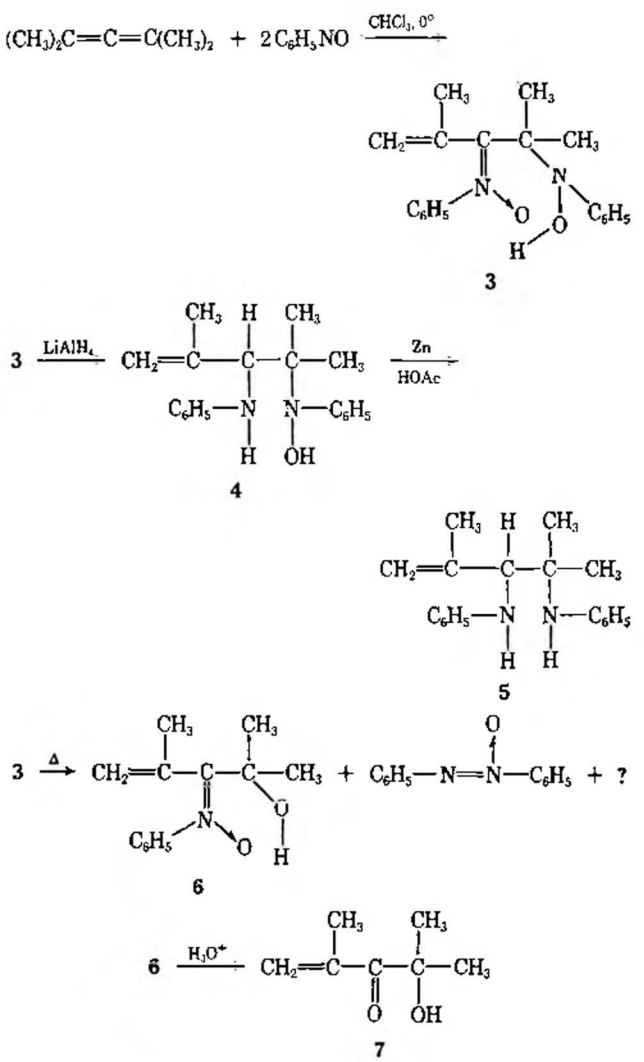
Results and Discussion

Production of 3.—Nitrosobenzene and tetramethylallene react at 0° in chloroform to produce a single product, *anti*-α-isopropenyl-α-[1-methyl-1-(N-phenylhydroxylamino)ethyl]-N-phenylnitrone, **3** (Scheme I). The structures of **5** and **7**, which are derived from **3**, allow the carbon atom backbone of **3** to be deduced independent of the spectral data for **3**. The structure of **5** establishes the sites of attachment of the two C_6H_5N groups to the carbon atom backbone. Compound **4** indicates that to the partial structure **A** must be added one oxygen atom and one hydrogen atom. Of the possible structures, only **3** satisfies the spectral data that includes equivalence of the geminal dimethyl nmr resonances in three different solvents, the benzene-induced solvent shifts, and the quite strong intramolecular hydrogen bonding (*vide infra*).



A

SCHEME I



Positive tests of **3** with Tollen's reagent and with alkaline triphenyltetrazolium chloride[2] demonstrate the presence of the hydroxylamine group. Strong intramolecular hydrogen bonding of the hydroxyl proton to the nitrone group is revealed by the infrared spectra of **3** (chloroform solvent). The hydroxyl absorption begins at 3.0 μ and increases in intensity up to 3.3 μ and exhibits no dilution shifts. This, with the nmr data discussed later, establishes the configuration of the nitrone group as having the oxygen atom *syn* to the hydroxylamino function. The infrared spectrum further reveals a weak absorption at 6.13 μ due to the terminal methylene group and strong and medium absorptions at 6.27 and 6.51 μ, respectively, due to the

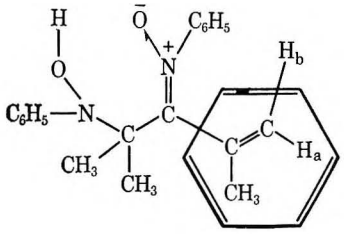
(1) (a) H. Staudinger and S. Jelagin, *Chem. Ber.*, **44**, 365 (1911); (b) G. Kresze and A. Trede, *Tetrahedron*, **19**, 133 (1963).

(2) (a) G. A. Snow, *J. Chem. Soc.*, 2588 (1954); (b) M. A. T. Rogers, *ibid.*, 769 (1955).

aromatic double bonds and possibly also the nitrone[3] group.

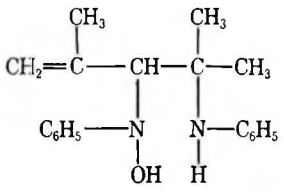
The hydroxyl proton nmr resonance of **3** in deuteriochloroform solution is at quite low field (τ −0.73) due to the strong intramolecular hydrogen bond to the nitrone oxygen atom. In the conformer of intramolecularly hydrogen bonded **3** that has minimal steric interactions, the isopropenyl protons lie in the shielding region of the hydroxylamino phenyl ring and thus appear at higher fields (vinyl protons at τ 5.13 and 5.81 and methyl protons at τ 8.65) than usual. Rapid inversion of the hydroxyl-bearing nitrogen atom results in equivalence of the geminal dimethyl groups, τ 8.20. The magnetic equivalence of the geminal dimethyl groups in three quite different solvents, deuteriochloroform, benzene, and pyridine, establishes with a high degree of certainty that these methyl groups are truly chemically equivalent. The chemical equivalence rules out unsymmetrical structures for **3**.

That the nitrone oxygen atom is *syn* to the hydroxylamino group is established further by the deuteriochloroform–benzene solvent shifts. Benzene induces upfield shifts of 0.39 and 0.07 ppm for the isopropenyl olefinic protons and 0.28 ppm for the isopropenyl methyl protons, while the geminal dimethyl protons are shifted only 0.02 ppm upfield. The greater solvent shifts of the isopropenyl proton resonances than for the geminal dimethyl proton resonances results from a benzene–**3** complex in which the electron-rich benzene ring avoids the negatively charged nitrone oxygen atom and associates with the positively charged nitrone nitrogen and carbon atoms. Similar complexes have been



proposed to explain the benzene-induced shifts of the nmr resonances of N-nitrosamines,[4,5] oximes,[5] amides,[6] and ketones[7] (among others).

Reduction of 3 and of 4.—Treatment of **3** with lithium aluminum hydride produced N-(2-anilino-1,1,3-trimethyl-3-butenyl)-N-phenylhydroxylamine, **4**, in 76% yield. The presence of the hydroxylamine group is indicated by positive tests of **4** with Tollen's reagent and with triphenyltetrazolium chloride. The infrared spectrum of **4** reveals both OH absorption at 2.81 μ and NH absorption at 2.99 μ. Exclusion of the alternative structure, N-(2-anilino-1-isopropenyl-2-methylpropyl)-N-phenylhydroxylamine, **8**, was made possible by observation of coupling, J = 5 Hz, between the CH–NH protons of **4** in dimethyl sulfoxide solution. Similarly, the nmr spectrum of N-(1-isopropyl-2-methylpropyl)aniline, **9**, reveals 10 Hz coupling between the CH–NH protons.[8]



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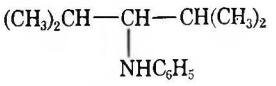


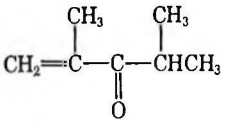
9

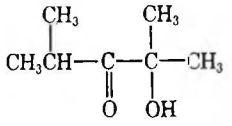
Reduction of **4** with zinc in acetic acid produces 2,4-dimethyl-N,N′-diphenyl-4-pentene-2,3-diamine, **5**, in 69% yield. The nmr and infrared spectral data (see Experimental Section) clearly establish the structure of **5**. The coupling of the CH–NH protons of **5** in dimethyl sulfoxide is 7 Hz.[8]

Pyrolysis of 3.—At its melting point **3** produces azoxybenzene (47% isolated yield), *syn*-α-(1-hydroxy-1-methylethyl)-α-isopropenyl-N-phenylnitrone (63% isolated yield), **6**, and unidentified products. The presence of a nitrone group in **6** is demonstrated by (1) a negative test of **6** with Tollen's reagent and (2) a positive test with Tollen's reagent of a solution resulting from treatment of **6** in water with dilute nitric acid followed by neutralization of the acid with ammonium hydroxide. Apparently, the nitrone group in **6** hydrolyzes rapidly in dilute acid to produce phenylhydroxylamine, which gives a positive test with Tollen's reagent.

That the nitrone group bears the oxygen atom *syn* to the hydroxyl group is revealed by the infrared and nmr spectra of **6**. The infrared spectrum reveals that the hydroxyl proton is strongly intramolecularly hydrogen bonded to the nitrone oxygen atom; the hydroxyl absorption occurs at 3.12 μ, and no shift of this absorption and no additional hydroxyl absorption occurs upon dilution of the sample. The deuteriochloroform–benzene nmr solvent shifts of 0.50 and 0.30 ppm upfield for the isopropenyl vinyl protons, 0.36 ppm upfield for the isopropenyl methyl group, and 0.00 ppm for the geminal dimethyl groups confirm the *syn* relationship of the hydroxyl group and the nitrone oxygen atom.

Hydrolysis of **6** in dilute acid leads to 4-hydroxy-2,4-dimethyl-1-penten-3-one, **7**, in addition to phenylhydroxylamine. The nmr proton resonances of the isopropenyl group of **7** compare quite well with those of the isopropenyl group of 2,4-dimethyl-1-penten-3-one,[9] and the singlet resonance of the geminal dimethyl group of **7** and that of the corresponding geminal dimethyl group of 2-hydroxy-2,4-dimethyl-3-pentanone[9] appear at nearly the same field.





(3) P. A. S. Smith and J. E. Robertson, *J. Amer. Chem. Soc.*, **84**, 1197 (1962).

(4) G. J. Karabatsos and R. A. Taller, *ibid.*, **86**, 4373 (1964).

(5) G. J. Karabatsos, R. A. Taller, and F. M. Vane, *ibid.*, **85**, 2326 (1963).

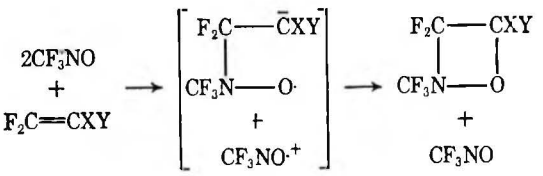
(6) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **3**, 253 (1960); **5**, 139 (1962).

(7) (a) N. S. Bhacca and D. H. Williams, *Tetrahedron Lett.*, 3127 (1964); (b) D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 2021 (1965).

(8) Generally, primary and secondary alcohols in dimethyl sulfoxide exhibit CH–OH coupling due to slow hydroxyl proton exchange in this strongly hydrogen bonding solvent: O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964); W. B. Moniz, C. F. Poranski, Jr., and T. N. Hall, *ibid.*, **88**, 190 (1966). However, NH exchange of amines in dimethyl sulfoxide generally is still too rapid for CH–NH coupling to be observed. The extreme steric hindrance about the nitrogen atoms of **4**, **5**, and **9** decreases the proton exchange rates sufficiently that the CH–NH couplings of **4**, **5**, and **9** in dimethyl sulfoxide can be observed.

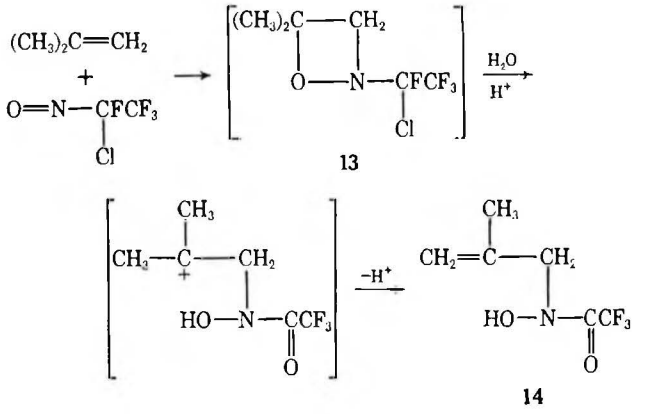
(9) H. O. House and G. A. Frank, *J. Org. Chem.*, **30**, 2948 (1965).

Discussion.—Ginsburg and coworkers[10] have advanced evidence based on esr studies that addition of trifluoronitrosomethane to olefins involves radical ion intermediates, which can lead to oxazetidines.



Knunyants, Dyatkin, and Gevorkyan[11] have reported that reaction of 1-chlorotetrafluoro-1-nitrosoethane with isobutylene proceeds *via* an oxazetidine intermediate **13** (not isolable from solution) to produce, after hydrolysis, **14** (Scheme II). Many other

SCHEME II

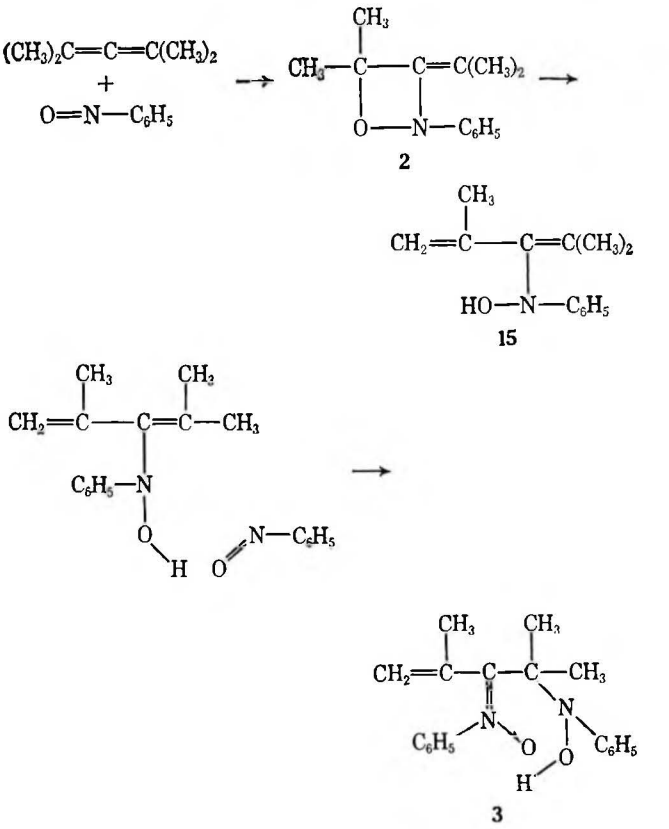


cases of formation of unsaturated hydroxylamines from reaction of C-nitroso compounds with olefins containing γ protons have been reported.[12]

In light of this literature,[10-12] the reaction pathway depicted in Scheme III seems likely for reaction of nitrosobenzene with tetramethylallene. Formation of **2**,[13] the originally desired compound, could occur *via* radical ions, similar to those[10] from trifluoronitrosomethane and olefins. Conversion of **2** to **15** could proceed by way of an allylic carbonium ion, which would make this conversion quite facile. Rapid addition[14] of another molecule of nitrosobenzene to **15** produces **3**.

Reaction of nitrosobenzene with nonfluorinated olefins that have no γ protons, such as styrene, usually leads to cleavage of the double bond with production of

SCHEME III



nitrones and azoxybenzene.[15,16] The reaction conditions can be quite critical, however; 2:1 adducts, the isomeric 2,3,5-triphenyltetrahydro-1,2,5-oxadiazole N-oxides, were isolated from reaction of nitrosobenzene and styrene at low temperature.[17] Reactive C-nitroso compounds and olefins with γ protons often react to produce unsaturated hydroxylamines;[11,12] again, the reaction conditions and the olefin structure are critical in determining the final outcome of such reactions. The present work provides another clear illustration of this.

Experimental Section

Melting points were determined in open capillary tubes with a Mel-Temp apparatus and are corrected. Nmr spectra were determined on a Varian A-60 spectrometer with internal TMS standard. Infrared spectra were determined with a Beckman IR-5 spectrometer.

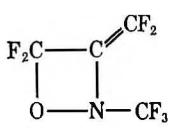
***anti*-α-Isopropenyl-α-[1-methyl-1-(N-phenylhydroxylamino)-ethyl]-N-phenylnitrone, 3.**—To 20 g (0.187 mol) of nitrosobenzene in 120 ml of chloroform (purified by passage through neutral alumina) stirred and cooled in an ice bath was added during 15 min 9.0 g (0.0938 mol) of tetramethylallene in 20 ml of purified chloroform. The reaction mixture was stirred another 1.25 hr at 0° and then was poured into 1400 ml of pentane. The resultant white solid was collected and washed with pentane to give 29 g of solid, mp 91–95°. This solid was dissolved in the minimum amount of tetrahydrofuran at room temperature, and the solution was diluted to four times the volume with pentane. There resulted 15.5 g (53.5%) of white solid: mp 100–100.5°; nmr ($CDCl_3$) spectrum taken within 1 min of preparation of solution because of acid-catalyzed decomposition of **3** in $CDCl_3$, which usually contains traces of acid, τ −0.73

(10) V. A. Ginsburg, A. N. Medvedev, L. L. Martynova, M. N. Vasil'eva, M. F. Lebedeva, S. S. Dubov, and A. Ya. Yakubovich, *J. Gen. Chem. USSR*, **35**, 1917 (1965).

(11) I. L. Knunyants, B. L. Dyatkin, and A. A. Gevorkyan, *Bull. Acad. Sci. USSR*, 1322 (1966).

(12) For example: (a) R. E. Banks, M. G. Barlow, and R. N. Hazeldine, *J. Chem. Soc.*, 4714 (1965); (b) A. B. Sullivan, *J. Org. Chem.*, **31**, 2811 (1966); (c) C. E. Griffin, N. F. Hepfinger, and B. L. Shapiro, *Tetrahedron*, **21**, 2735 (1965); (d) V. A. Ginsburg, L. L. Martynova, S. S. Dubov, B. I. Tetel'baum, and A. Ya. Yakubovich, *J. Gen. Chem. USSR*, **35**, 855 (1965).

(13) In regards to the intermediacy of **2**, it is interesting to note that reaction of perfluoroallene with trifluoronitrosomethane can be controlled to produce an oxazetidine: R. E. Banks, R. N. Haszeldine, and D. R. Taylor, *J. Chem. Soc.*, 5602 (1965).



(14) Production of **3** results even from slow addition of 1 mol of nitrosobenzene to 1 mol of tetramethylallene in chloroform.

(15) A. Alessandri, *Gazz. Chim. Ital.*, **54**, 426 (1924), and earlier references.

(16) Reaction of substituted nitrosobenzenes with several alkenes and with allene has been reported to occur, but no identification of products other than the azoxybenzenes was given: J. Hamer and A. Macaluso, *Tetrahedron Lett.*, 381 (1963).

(17) N. F. Hepfinger and C. E. Griffin, *ibid.*, 1361 (1963).

(bs, 1 H, OH), 2.76 (bm, 10, C_6H_5), 5.13 (s, 1, W = 4.5 Hz, H_aH_bC=C), 5.81 (s, 1, W = 3 Hz, H_aH_bC=C), 8.20 [s, 6, $C(CH_3)_2$], 8.65 (s, 3, W = 3 Hz, CH_3C=C); nmr (C_6H_6), τ 5.52 (s, 1 H, W = 4.5 Hz, H_aH_bC=C), 5.88 (s, 1, W = 3 Hz, H_aH_bC=C), 8.22 [s, 6, $C(CH_3)_2$], 8.93 (s, 3, W = 3 Hz, CH_3—C=C). *Anal.* Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.15; N, 9.03. Found: C, 73.33; H, 7.27; N, 9.02.

N-(2-Anilino-1,1,3-trimethyl-3-butenyl)-N-phenylhydroxylamine, 4.—To 1.00 g of lithium aluminum hydride in 40 ml of tetrahydrofuran cooled in an ice bath was slowly added 2.0 g of **3**. An exothermic reaction occurred. The reaction mixture was allowed to stand 2 hr at room temperature. Water was cautiously added with ice bath cooling to decompose excess hydride. Sodium sulfate was added, followed by ether. The ether was decanted, and the precipitate was washed several times with ether. The ether layers were combined, redried (Na_2SO_4), and concentrated to give 2.0 g of solid, which yielded 1.46 g (76.5%) of white solid, mp 122–126°, upon recrystallization from hexane. Several recrystallizations of the solid produced 0.95 g (50%) of solid: mp 124–126°; ir ($CHCl_3$) 2.81 μ (OH), 2.98 (NH), 6.10 (weak; aliphatic C=C), 6.24 (strong; aromatic C=C); nmr ($CDCl_3$), τ 2.6–3.5 (bm, 10 H, C_6H_5), 4.90 (bs, 2 H, OH + NH, disappears upon addition of D_2O), 4.90 (s, 2, W = 3 Hz, H_aH_bC=C), 6.05 (s, 1, CH–N), 8.21 (s, 3, CH_3C=C), 8.88 (s, 3, CH_3–C), 8.98 (s, 3, CH_3–C); nmr (DMSO), τ 1.67 (s, 1 H, OH, disappears upon addition of D_2O), 4.35 (d, 1, J = 5 Hz, NHCH, disappears upon addition of D_2O), 4.92 (s, 2 H, W = 4 Hz, H_aH_bC=C), 6.00 (d, 1, J = 5 Hz, NHCH, collapses to singlet upon addition of D_2O), 8.18 (s, 3, CH_3C=C), 8.95 [s, 6, $C(CH_3)_2$]. *Anal.* Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.72, 76.92; H, 8.06, 8.21; N, 9.40, 9.60.

N-(1-Isopropyl-2-methylpropylidene)aniline.—A solution of 114 g (1.0 mol) of diisopropyl ketone, 100 g (1.07 mol) of aniline, 0.5 g of *p*-toluenesulfonic acid monohydrate, and 400 ml of xylene was held 21 hr at reflux with a Dean–Stark trap employed to collect the water. An infrared spectrum of the reaction mixture at this point indicated *ca.* 50% conversion to the imine. The mixture was distilled. The product, 71.6 g (38%), was collected at 105° (10 mm): $n^{23}D$ 1.5052; ir (CCl_4) 6.05 μ (C=N). *Anal.* Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.64; H, 10.30; N, 7.60.

N-(1-Isopropyl-2-methylpropyl)aniline, 9.—A mixture of 27.8 g of the above imine and 7.0 g of lithium aluminum hydride in 300 ml of tetrahydrofuran was held 25 hr at reflux. After this time the reaction mixture exhibited no imine ir absorption. Ice was cautiously added to the reaction mixture with cooling, followed by ether and sodium sulfate. The ether solution was filtered through fresh sodium sulfate and was distilled. The product, 19.5 g (69%), was collected at 121–121.5° (10 mm): $n^{25}D$ 1.5202; ir (CCl_4) 2.92 μ (NH); nmr (DMSO), τ 2.8–3.7 (bm, 5 H, C_6H_5), 5.07 (d, 1, J = 10 Hz, NHCH, disappears upon addition of D_2O), 7.08 (six-component signal resulting from each component of a doublet, J = 10 Hz, further split into triplets, $J \simeq$ 6.1 Hz; collapses to triplet, $J \simeq$ 6.0 Hz, upon addition of D_2O; 1 H, NHCH), 8.12 [octet, 2, $J \simeq$ 6.5 Hz, $(CH_3)_2CH$], 9.08 [d, 6, $J \simeq$ 6.6 Hz, $CH_3(CH_3)CH$–C–(CH_3)-CH_3] 9.11 [d, d, $J \simeq$ 6.6 Hz, $CH_3(CH_3)CH$–C–$CH(CH_3)CH_3$]. *Anal.* Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.07; N, 7.32. Found: C, 81.46; H, 11.02; N, 7.20.

2,4-Dimethyl-N,N′-diphenyl-4-pentene-2,3-diamine, 5.—Zinc dust, 12 g, was slowly added to a cooled solution of 4.0 g of **4** in 50 ml of glacial acetic acid. The mixture was stirred 1.5 hr at room temperature and filtered. The solid was washed with 10 ml of acetic acid. The filtrate and washing were combined and slowly poured into a cold solution of 1.25 mol of NaOH in 300 ml of water with cooling. The mixture was extracted with five 50-ml portions of benzene. The benzene extracts were combined, dried (Na_2SO_4), and distilled. There was obtained 2.6 g (69%) of liquid, bp 130–134° (0.05 mm), that crystallized to a solid of mp 51–60°. Two crystallizations of the solid from pentane resulted in 1.78 g (47%) of white needles: mp 64–66°; ir (CCl_4) 3.01 μ (NH), 6.13 (weak; aliphatic C=C), 6.29 (strong; aromatic C=C); nmr (DMSO), τ 2.7–3.7 (bm, 10 H, C_6H_5), 4.52 (d, 1, J = 7 Hz, NHCH, disappears upon addition of D_2O), 4.98 (s, 2, W = 3.5, H_2C=C), 5.12 [s, 1, $NHC(CH_3)_2$, disappears upon addition of D_2O], 5.97 (d, 1, J = 7 Hz, NHCH, collapses to singlet upon addition of D_2O), 8.28 (s, 3, CH_3C=C), 8.67 [s, 6, $C(CH_3)_2$]. *Anal.* Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.62; N, 9.99. Found: C, 81.16; H, 8.73; N, 10.05.

syn-α-(1-Hydroxy-1-methylethyl)-α-isopropenyl-N-phenylnitrone, 6.—A sample of **3** was heated gently until it had all melted. A 23.2-g (0.0750 mol based on starting nitrone) portion of the melt was chromatographed on 350 g of Florisil, 60–100 mesh. With 2 l. of 5% ether in benzene 7.00 g (0.0354 mol, 47%) of orange crystals, mp 26–29°, identified (ir) as azoxybenzene, was eluted off the column. A mixture of materials (nmr analysis), 1.73 g, was eluted with 6 l. of 25% ether in benzene. With 2 l. of 100% ether there was eluted 3.16 g (0.0144 mol, 19.2%) of nitrone contaminated with impurities (nmr analysis). The next 10 l. of ether eluted 7.14 g (0.0326 mol, 43.4%) of relatively pure nitrone (nmr analysis); two crystallizations of this solid from hexane (charcoal) gave 3.6 g of solid, mp 76–83°. Recrystallization of this from hexane gave material of mp 77–80°, and a further crystallization of this from hexane with decantation of the hexane solution away from a small amount of colored oil gave 0.95 g of white crystals: mp 77–79°; ir (CCl_4) 3.12 μ (OH), 6.13 and 6.28 (C=C); nmr ($CDCl_3$), τ 2.47 (s, 1, H, OH), 2.59 (s, 5, C_6H_5), 4.83 (s, 1, W = 4 Hz, H_aH_bC=C), 5.03 (s, 1, W = 2.5 Hz, H_a-H_bC=C), 8.26 (unresolved m, W = 2.5 Hz, CH_3–C=C), 8.41 [s, 6, $C(CH_3)_2$]; nmr (C_6H_6), τ 5.33 (m, 2, W = 4 Hz, H_aH_bC=C), 8.41 [s, 6, $C(CH_3)_2$], 8.62 (unresolved m, 3, W = 2.5, CH_3–C=C). (Another 1.80 g of light brown solid, mp 73–77°, was recovered from the mother liquors.) *Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39; mol wt, 219.28. Found: C, 71.40, 71.47; H, 7.87, 7.89; N, 6.24, 6.27; mol wt, 231, 224.

4-Hydroxy-2,4-dimethyl-1-penten-3-one, 7.—A sample of **3** was heated gently until it had all melted. A 10.3-g sample of the melt was added to 60 ml of 6% HCl and 50 ml of ether. The layers were stirred together 1 hr. The ether layer was dried first with K_2CO_3, then with Na_2SO_4. Distillation of the solution gave 1.56 g of colorless liquid ketone: bp 69° (22 mm); ir (CCl_4) 2.90 μ (OH), 3.24 (weak; vinyl H), 6.00 (C=O), 6.15 (weak; C=C); nmr ($CDCl_3$), τ 4.02 (unresolved m, 1 H, W = 2 Hz, HHC=C), 4.18 (unresolved m, 1, W = 4 Hz, HHC=C), 6.09 (bs, 1, OH), 8.04 (unresolved m, 3, W = 3 Hz, CH_3C=C), 8.49 [s, 6, $C(CH_3)_2$]. *Anal.* Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.28; H, 9.48. The pot residue, 3.22 g, appeared to be azoxybenzene with impurities (nmr analysis).

Registry No.—Nitrosobenzene, 586-96-9; tetramethylallene, 1000-87-9; **3**, 16723-43-6; **4**, 16723-44-7; **5**, 16723-45-8; **6**, 16723-46-9; **7**, 16185-08-7; **9**, 16723-48-1; *N*-(1-isopropyl-2-methylpropylidene)-aniline, 16723-49-2.

The Chemistry of N-Nitrosoketimines[1]

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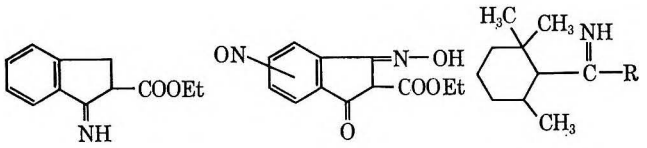
Received January 4, 1968

The reaction of nine ketimines with nitrosyl chloride in cold carbon tetrachloride produced brightly colored N-nitrosoketimines of varying stability, which decomposed *via* a first-order mechanism to the corresponding ketones and nitrogen. Stability toward such decomposition is enhanced by the presence of bulky substituents on the ketimine carbon atom, and, in the case of the N-nitrosobenzophenonimines, by the presence of electron-withdrawing substituents on the benzene rings. The reaction of four N-nitrosoketimines with triethyloxonium fluoroborate produced the corresponding 1,1-disubstituted propylene oxides, whose structure was proved by chemical and spectral evidence. A notable contribution of a 1,4-dipolar structure to the ground state of the N-nitrosoketimines is consistent with observed chemical and spectral properties.

N-Nitrosoketimines (**1**) were desired as starting materials for a projected synthesis of certain sydnones. The present work was initiated by preparing nine ketimines (**2a–i**) from the appropriate nitriles (**3**) and Grignard reagents (**4**).[2] Of these, seven (**2c–i**) were 2,4′- or 4,4′-disubstituted benzophenonimines and two (**2a**, b) were alkyl *o*-tolyl ketimines. The three 2,4′-disubstituted benzophenonimines (**2g–i**) were notably more stable toward hydrolysis than their respective 4,4′ isomers (**2c**, **d**, **f**) or benzophenonimine itself (**2e**). Our observations substantiate earlier work by Pickard,[3,4] who showed that, though electronic factors may exert some influence, stability toward hydrolysis increases with increasing bulk of the groups attached to the ketimine carbon atom.

Until recently, the rather extensive literature on ketimines contained only two references[5] to their nitrosation, and our work casts doubt on the authenticity of the products reported. Though Mitchell and Thorpe[5a] proposed structure **6** for the product of the attempted nitrosation of 1-imino-2-carboethoxyhydrindene (**5**),



5 **6** **7a**, R = C_6H_5; **b**, R = CH_3

Beilstein[6] reports it only as a "compound derived from 1-iminohydrindene-2-carboethoxy." Lochte, *et al.*,[5b] attempted the nitrosation of two ketimines (**7a**, **b**), but the products obtained gave combustion analyses which offered questionable support for the proposed N-nitroso structure.

When 4,4′-dimethoxybenzophenonimine (**2c**) and the 4,4′-dimethyl analog (**2d**) were treated with nitrous fumes[5b] at room temperature, we obtained products which gave positive Liebermann tests; however, their combustion analyses indicated the presence of two more atoms of oxygen per molecule than expected for the N-nitrosoketimines. Isolation of 4,4′-dimethoxy- and 4,4′-dimethylbenzophenone in excellent yields on acid hydrolysis of these products proved that ring nitrosation had not occurred. The virtual identity of the nmr spectra of these two products with those of the hydrochloride salts of **2c** and **2d** showed them to be the nitrate salts of **2c** and **2d**.

It was interesting to note that Thorpe's analysis of **6** also indicated the presence of two more atoms of oxygen per molecule than was expected.[5a] This leads us to suggest that Mitchell and Thorpe[5a] and also Lochte, *et al.*,[5b] probably had obtained nitrate salts of the respective ketimines rather than N-nitroso derivatives. Their own combustion analyses support this suggestion.

Our ketimines (**2**) were successfully nitrosated by treatment with nitrosyl chloride in cold carbon tetrachloride. Initially, the presence of **1h** in the cold solution was surmised by the appearance of an intense blue color on mixing the reagents; both the color and the product were lost during attempts at isolation at room temperature, and an excellent yield of 2,4′-dimethylbenzophenone resulted.[7] The isolation of the N-nitrosoketimines finally was accomplished by the method of Paskovich,[8] who with Zimmerman[9] had independently synthesized three very stable, highly hindered N-nitrosoketimines by the action of dinitrogen tetroxide on the ketimines. These were neither purified nor characterized, but were immediately reduced to the corresponding diazoalkanes.

The seven diaryl N-nitrosoketimines (**1c–i**) are deep blue or purple in color and differ widely in stability. Though the color was produced on addition of nitrosyl chloride to the ketimine in each case, some products (**1c**, **d**, **g**) were so unstable that they decomposed during attempted isolation. Those which could be isolated (**1e**, **f**, **h**, **i**) decomposed more or less slowly at room temperature. The two highly hindered alkyl aryl N-nitrosoketimines (**1a**, **b**) are raspberry-red oils which took 6 to 8 weeks to decompose at room temperature. One

(1) From the Ph.D. Dissertation of C. J. Thoman, University of Massachusetts, 1966. Partial support of this work by a research grant (CA-05478) from the National Cancer Institute of the National Institutes of Health, and by a University of Massachusetts Research Grant (FR-J11-65) is gratefully acknowledged.

(2) P. L. Pickard and T. L. Tolbert, *J. Org. Chem.*, **26**, 4886 (1961).

(3) P. L. Pickard and D. J. Vaughan, *J. Amer. Chem. Soc.*, **72**, 876 (1950).

(4) (a) P. L. Pickard and D. J. Vaughan, *ibid.*, **72**, 5017 (1950); (b) P. L. Pickard and C. W. Young, *ibid.*, **73**, 42 (1951); (c) P. L. Pickard and E. F. Engles, *ibid.*, **74**, 4607 (1952); (d) P. L. Pickard and E. F. Engles, *ibid.*, **75**, 2148 (1953); (e) P. L. Pickard and S. H. Jenkins, Jr., *ibid.*, **75**, 5899 (1953).

(5) (a) A. D. Mitchell and J. F. Thorpe, *J. Chem. Soc.*, **97**, 2261 (1910); (b) H. L. Lochte, J. Horeczy, P. L. Pickard and, A. D. Barton, *J. Amer. Chem. Soc.*, **70**, 2012 (1948); (c) Nitrososydnonimines [H. Kato, M. Hashimoto, and M. Ohta, *Nippon Kagaku Zasshi*, **78**, 707 (1957); P. Brookes and J. Walker, *J. Chem. Soc.*, 4409 (1957)] and nitrosoiminothiazolinones [H. Beyer and H. Drews, *Chem. Ber.*, **87**, 1500 (1954)] are not "true" nitrosoketimines.

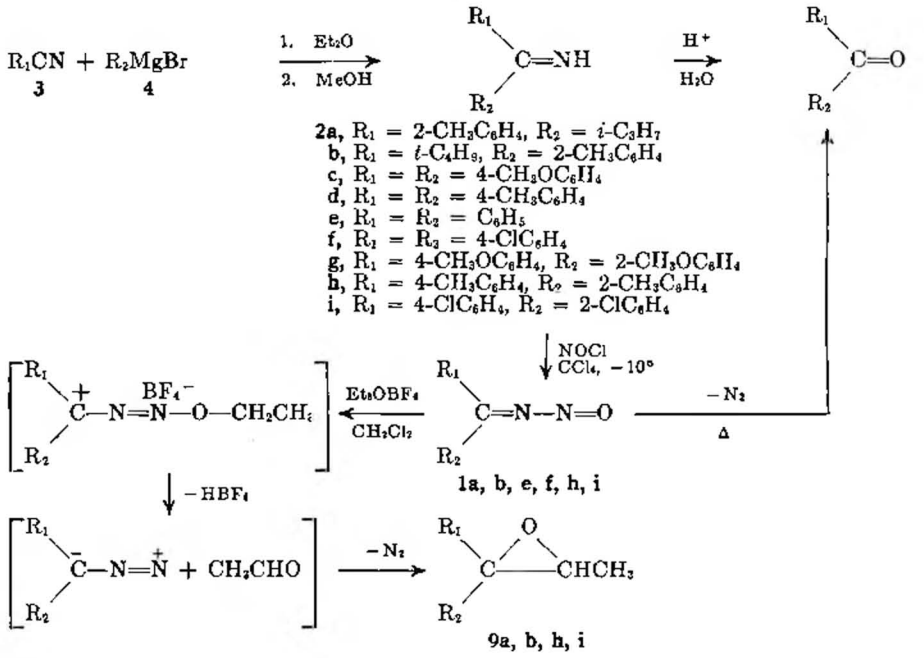
(6) F. K. Beilstein, "Handbuch der organischen Chemie," IVth ed, under $C_{12}H_{10}N_2O_5$ in the General Formelregister, **29** II, p 1237; *cf.* **10** I, pp 345, 346.

(7) E. Robson and J. M. Tedder, *Proc. Chem. Soc.* (London), 13 and 344 (1963), reported similar behavior when diacetylenic mercury compounds were nitrosated with nitrosyl chloride at −78°.

(8) D. H. Paskovich, University of Ottawa, private communication, 1963.

(9) H. Zimmerman and D. H. Paskovich, *J. Amer. Chem. Soc.*, **86**, 2149 (1964).

SCHEME I

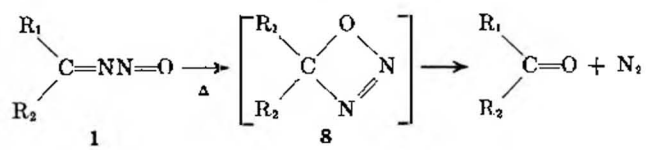


of the products of these decompositions was always the ketone.

This tendency of the N-nitrosoketimines to decompose to the corresponding ketones parallels the propensity of the parent ketimines toward hydrolysis, which in some cases is effected merely by atmospheric moisture. In each case, resistance to decomposition is enhanced by the presence of bulky R groups. It was surprising, then, to discover that a given N-nitrosoketimine is transformed to the corresponding ketone as readily in the absence of, as in the presence of, moisture (*e.g.*, under nitrogen, both in the solid state and in a dry solvent; at reduced pressure; and on a column of silica gel during attempted chromatography). Furthermore, when highly stable **1b** was allowed to stand at room temperature in water for several days, it was recovered virtually unchanged (nmr spectrum), while heating a carbon tetrachloride solution of the same compound on a steam bath caused total decomposition to the ketone within 30 min. This is not to deny that hydrolysis may be a competing reaction, especially for the less stable **1**.

That the above decomposition is not hydrolysis was further indicated by a kinetic study; appropriate plots of nitrogene volution *vs.* time indicated that the reaction is first order.

That nitrogen gas is the other product of this decomposition was proved by infrared and mass spectrometry. In view of the first-order kinetics, the thermally initiated decomposition of the N-nitrosoketimines would seem to involve an intra- rather than an intermolecular transition state (**8**).



If the nitroso oxygen atom is nucleophilic, an N-nitrosoketimine might be expected—by analogy with sulfoxides[10] and amine oxides[11]—to oxidize appropriate halides to aldehydes or ketones with the simultaneous formation of the corresponding disubstituted diazomethane. Numerous attempts to react N-nitrosoketimines with a variety of halides produced either unchanged starting materials or the ketone, the latter being formed by loss of nitrogen from the nitroso compound. However, reaction of **1b** with triethyloxonium fluoroborate produced an epoxide (**9b**), presumably by combination of the intermediate diazomethane (or the carbene derived from it) with transiently formed acetaldehyde[12] (see Scheme I).

The reaction was repeated with the other five N-nitrosoketimines (**1a, e, f, h, i**) that had been isolated. The two least stable of them (**1e, f**) yielded the corresponding benzophenones, owing to decomposition of the starting material. That the products (**9a, h, i**) obtained from the others were the corresponding epoxides was indicated by their combustion analyses, spectral properties, and chemical behavior, and was substantiated for one of them (**9i**) by the independent synthesis shown in Scheme II. Surprisingly, the final product of this synthesis was not the epoxide but one of the ketones (**10** or **11**). This ketone, a pale yellow oil, formed a 2,4-dinitrophenylhydrazone but did not give a positive iodoform reaction. The same yellow 2,4-dinitrophenylhydrazone slowly deposited when epoxide **9i** was allowed to stand for several days at room temperature in an acidic aqueous ethanolic solution of 2,4-dinitrophenylhydrazine.

The infrared spectrum of the above pale yellow oil had a strong carbonyl band at 1721 cm^{-1}; slow vacuum distillation of epoxide **9i** caused the appearance of this same band at 1719 cm^{-1}. The nmr spectrum showed

(10) N. Kornblum, *et al.*, *ibid.*, **79**, 6562 (1957); H. R. Nace and J. J. Monagle, *J. Org. Chem.*, **24**, 1792 (1959); I. M. Hunsberger and J. M. Tien, *Chem. Ind.* (London), 88 (1959).

(11) L. J. Fliedner, M.S. Thesis, Fordham University, New York, N. Y., 1960; A. Javellana, M.S. Thesis, Fordham University, New York, N. Y., 1959.

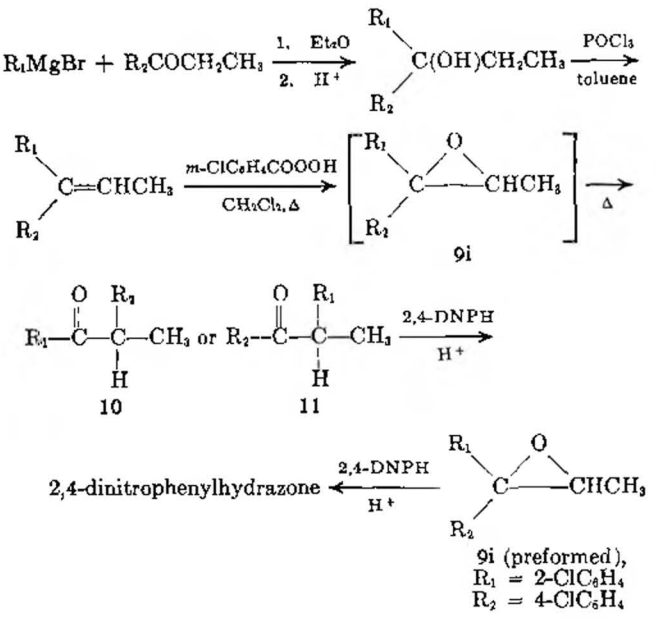
(12) Attempts to identify acetaldehyde in the reaction mixture proved fruitless.

TABLE I
KETIMINES

Compd	Bp (mm) or mp, °C	Lit. bp (mm) or mp, °C	Yield, %	Nmr[a] (δ) N–H	ArH[b]	ArCH₃
2a	59–63 (0.4)	86–87 (5)[3]	6.2	...	7.23 (4.0)	2.30 (2.4)[c]
2b[d]	234–235 (755)	235 (740)[3]	77	8.80 (?)	6.73 (4.0)	1.98 (3.0)[e]
2c[f,g]	131–132	129–130[14]	54	...	7.27 (8.0)[h]	
2d[i]	65–67	67–69,[j] 81[4a]	50	9.20 (0.5)	7.44 (8.0)	2.38 (6.0)
2e	135–138 (4)	127 (3.5)[2]	68	...	7.32	
2f[k]	55–57	59.5–60.5[l]	80	9.52 (0.7)	7.21 (8.0)	
2g[l,m]	64–67		87	8.95 (0.6)	7.19 (8.0)[n]	
2h	134–137 (2.5)	138–140 (2)[4a]	54	8.92 (0.8)	7.01 (8.0)	1.95 (3.0) 1.78 (3.0)
2i[o]	163–164 (0.8)		57	9.52 (0.7)	7.25 (8.0)	

[a] Nmr values were measured in parts per million (ppm) downfield from TMS as an internal standard; intensities (in parentheses) relative to phenyl H; CCl_4 solvent. [b] The approximate center of complex absorption for the diaryl compounds is listed. [c] Alkyl CH_3 absorption is at 1.43 (5.7); the isopropyl methyne absorption is at 2.31 (0.8). [d] Prepared from *t*-BuCl (rather than *t*-BuBr). [e] Alkyl CH_3 absorption is at 1.02 (9.0). [f] Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.06, 74.24; H, 6.05, 5.94; N, 5.27, 5.35. [g] Reaction with NOCl (green color on mixing) gave 4,4′-dimethoxybenzophenone (89% yield). [h] Aromatic OCH_3 absorption is at 3.85 (3.0), 3.82 (3.0). [i] Reaction with NOCl (blue color on mixing) gave 4,4′-dimethylbenzophenone (62% yield). [j] E. J. Grubbs, J. D. McCullough, B. H. Weber, and J. R. Maley, *J. Org. Chem.*, 31, 1098 (1966). [k] Calcd for $C_{13}H_9NCl_2$: C, 62.42; H, 3.63; N, 5.60; Cl, 28.35. Found: C, 62.61; H, 3.60; N, 5.51; Cl, 28.50. [l] Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found. C, 74.20; H, 6.36; N, 5.68. [m] Reaction with NOCl (blue color on mixing) gave 2,4′-dimethoxybenzophenone (59% yield). [n] Aromatic OCH_3 absorption is at 3.72 (3.0), 3.62 (3.0). [o] Calcd for $C_{13}H_9NCl_2$: C, 62.42; H, 3.63; N, 5.60; Cl, 28.35. Found: C, 62.61; H, 3.60; N, 5.51; Cl, 28.50.

SCHEME II



no indication of an aldehydic hydrogen, but it did contain a quartet–doublet pairing at 3.42 and 1.12 ppm, indicating the presence of a >CH–CH_3 group in the molecule.

Apparently, the conditions of the epoxidation were severe enough to open the transiently formed epoxide (**9i**), the resulting intermediate then stabilizing itself by migration of one of the aryl groups (probably 4-ClC_6H_4) to form **10** or **11**. No attempt was made to further identify this product.

Pertinent data on the infrared and nmr spectra of the ketimines, N-nitrosoketimines, and 1,1-disubstituted propylene oxides are collected in Tables I, II, and III, respectively. Pickard and Polly[13] studied the infrared spectra of 15 dialkyl, alkyl aryl, and diaryl ketimines and reported the presence of N–H stretching absorption between 3247 and 3205 cm^{-1}, and of C=N stretching absorption between 1653 and 1603 cm^{-1}. They compared the latter to the stretching absorption of the corresponding ketones, which lies between 1718 and 1661 cm^{-1}. For 2c, Williams and his coworkers[14] found these two absorptions at 3257 and 1646 cm^{-1}, respectively.

Our ketimines showed N–H stretching absorption between 3257 and 3215 cm^{-1} and C=N stretching absorption between 1623 and 1603 cm^{-1}, whereas the C=O stretching absorption of our corresponding ketones occurred between 1689 and 1647 cm^{-1}. Further comparison of the infrared spectra of our ketimines with those of the corresponding ketones revealed that only the ketimines exhibit a strong absorption near 1350 cm^{-1} (range of 1372–1340 cm^{-1}); this band may be distinctive of the ketimines (probably C=NH bending). The assignment of this band to the Ar_2C=N grouping[14] cannot be reconciled with the fact that the absorption also appears in the spectra of our alkyl aryl ketimines.

Roberts[15] found N–H bands of three N^{14}-labeled ketimines to be about 9 ppm downfield from tetramethylsilane. In carbon tetrachloride, this peak broadened to a bump, which at times proved difficult to detect at room temperature; in other solvents, notably carbon disulfide, it sharpened, especially at low temperatures. The nmr spectra of our ketimines confirm the position of this N–H absorption and the difficulty in detecting it. Its extreme breadth tends to cause low integration values.

From a study of the infrared spectra of N-nitrososydnonimines, Hashimoto[16] concluded that they exist to a great extent in a 1,3-dipolar form and assigned bands at 1680–1665 and 1555 cm^{-1} to C=N^+ and $^+$N=N, respectively. Bellamy[17] indicates the existence of two absorptions distinctive of N–O^- between 1310 and 1250 cm^{-1}; our N-nitrosoketimines consistently exhibited a strong band toward the upper end of

(13) P. L. Pickard and G. W. Polly, *J. Amer. Chem. Soc.*, 76, 5169 (1954).

(14) H. B. Williams, P. E. Koenig, G. Huddleston, T. Couvillon, and W. Castille, *J. Org. Chem.*, 28, 463 (1963).

(15) J. B. Lambert, W. L. Oliver, and J. D. Roberts, *J. Amer. Chem. Soc.*, 87, 5085 (1965).

(16) M. Hashimoto, Ph.D. Thesis, Tokyo Institute of Technology, Tokyo, Japan, 1960.

(17) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1960, p 308.

TABLE II

N-NITROSOKETIMINES

Compd	Mp, °C[a]	Color	Yield, %	Principal ir[b] bands (1700–1000 cm^{-1})	Nmr[c] (δ) ArH[d]	ArCH$_3$	AlkCH$_3$
1a	Oil[e]	Red	51	1695, 1608, 1580, 1484, 1466, 1319	7.00 (4.0)	2.17 (2.4)	1.22 (6.2)[f]
1b	Oil[e]	Red	83	1698, 1610, 1580, 1481, 1466, 1321	6.88 (4.0)	2.17 (3.2)	1.23 (9.8)
1e[g]	50–53	Blue	25	1669, 1603, 1570, 1493, 1451, 1321	7.55		
1f[h]	61–63	Blue	41	1660, ——, 1587, 1497, 1485, 1312			
1h[i,j]	43[k]	Purple	68	1668, 1610, 1570, 1498, 1488, 1316	7.27 (8.0)	2.38 (3.0) 2.12 (2.5)	
1i[i,l]	69–71	Purple	76	1669, 1600, 1575, 1515, 1477, 1311			

[a] All samples melted with decomposition. [b] Spectra were determined in CCl_4 with a Beckman IR-5. [c] Nmr values were measured in parts per million (ppm) downfield from TMS as an internal standard; intensities (in parentheses) relative to phenyl H; CCl_4 solvent. [d] The approximate center of complex absorption for the diaryl compounds is listed. [e] An analytically pure sample was not obtained. [f] The isopropyl methyne absorption is at 2.27 (0.8). [g] Reaction with Et_3OBF_4 gave benzophenone (66% yield). [h] Reaction with Et_3OBF_4 gave 4,4′-dichlorobenzophenone (48% yield). [i] Mailed (air freight) for combustion analysis packed in Dry Ice. [j] Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.54, 75.62; H, 6.14, 6.30; N, 11.01, 11.24. [k] See ref 8. [l] Calcd for $C_{13}H_8N_2OCl_2$: C, 55.94; H, 2.89; N, 10.04; Cl, 25.41. Found: C, 55.76, 55.77; H, 3.15, 3.28; N, 9.68, 9.81; Cl, 25.22, 25.11.

TABLE III

1,1-DISUBSTITUTED PROPYLENE OXIDES

Compd	Bp (mm), °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Ir,[a] cm^{-1} Epoxy methyne stretch	Ir,[a] cm^{-1} Epoxide bend	Nmr[b] (δ) ArH[c]	Nmr[b] (δ) ArCH$_2$	Nmr[b] (δ) Oxide H	Nmr[b] (δ) Oxide CH$_3$
9a	77–78 (2.0)[d]	26						3236	1252	6.96 (4.0)	2.13 (2.7)[e]	3.45 (1.2)	1.17 (3.0)
9b	58–60 (0.5)	69	$C_{14}H_{20}O$	82.30	9.87	82.17, 82.34	9.78, 9.90	3226	1251	6.88 (4.0)	2.05 (3.1)[f]	2.87 (0.8)	1.12 (3.2)
9h	129–131 (0.8)	61	$C_{17}H_{18}O$	85.67	7.61	85.47	7.23	3236	1268	7.20 (8.0)	2.28 (3.6), 2.23 (1.9)	3.37 (0.9)	2.00 (2.8)
9i	172–173 (2.6)	40	$C_{15}H_{12}OCl_2$[g]	64.53	4.33	64.43	4.50	3247	1261	7.18 (8.0)		3.19 (0.9)	1.12 (3.0)

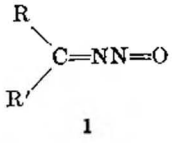
[a] Spectra determined with a Beckman IR-5; CCl_4 solvent for 9a and 9b; 9h and 9i neat. [b] Nmr spectra were measured in parts per million (ppm) downfield from TMS as an internal standard; intensities (in parentheses) relative to phenyl H. [c] The approximate center of complex absorption for the diaryl compounds is listed. [d] Not analytically pure. [e] The isopropyl methyne absorption is at 2.27 (0.9); the alkyl CH_3 absorption is at 1.17 (6.0). [f] The alkyl CH_3 absorption is at 1.15 (8.1). [g] Calcd: Cl, 25.40. Found: Cl, 25.27.

this region. Their most distinctive absorptions, however, are the pairs of strong bands at 1515–1451 cm^{-1}. Both the infrared and nmr spectra of our N-nitrosoketimines exhibited no absorption in the N—H region.

All the 1,1-disubstituted propylene oxides exhibited a sharp, weak band in the infrared at 3226–3247 cm^{-1}, which may be ascribed to the epoxy methyne hydrogen. Normal methyne absorption (where the other three bonds are all to carbon) is found at about 2960 cm^{-1}, and this would be expected if the product were the isomeric disubstituted acetone. The most distinctive epoxide absorption[18] also is present at 1251–1268 cm^{-1}.

The nmr spectra of these epoxides all contain two distinctive related absorptions: a quartet at 3.45–2.87 and a doublet at 2.00–1.12 ppm, of relative intensities 1:3. These cannot be explained on the basis of the product being either the isomeric 1,1-disubstituted acetone or the isomeric 2,2-disubstituted propionaldehyde. Furthermore, no aldehyde absorption was evident in the nmr spectrum.[19]

Three of the possible structures contributing to the resonance of N-nitrosoketimines are shown below. None of the physical measurements essential for the determination of their true structure has yet been made. Still, some evidence is provided by their chemical properties and physical characteristics.



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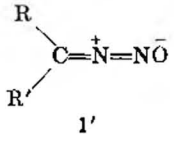
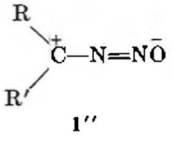


1′



1″

(18) See ref 17, pp 118, 119.

(19) Further chemical evidence that excludes these isomeric carbonyl compounds includes the failure of the product to form a 2,4-dinitrophenylhydrazone under ordinary conditions or to give the iodoform test.

The individual N-nitrosoketimines vary widely in stability. Within the two series of N-nitroso-4,4′- and 2,4′-disubstituted benzophenonimines (**1c–f** and **1g–i**), stability is increased by electron-withdrawing substituents and lowered by electron-donating ones, as is the case with corresponding diazonium salts.[20] Steric considerations, however, seem to be of even greater importance. **1h** can be isolated while **1d** (its (4,4′ analog) cannot, and **1i** treated with triethyloxonium fluoroborate forms an epoxide while **1f** decomposes under the same conditions to the corresponding ketone. The two highly hindered alkyl aryl N-nitrosoketimines (**1a, b**) are the most stable of those studied.

While chemical properties indicate only the structure of the transition state, the fact that intramolecular decomposition of unhindered N-nitrosoketimines occurs at room temperature, or even below, is consistent with a low activation energy and a substantial contribution of the 1,4-dipolar structure (**1″**) to the ground state. Also, the presence of bulky R groups around the ketimine carbon atom would be expected to impede the formation of the postulated four-membered cyclic intermediate (**8**) by attack of the nucleophilic nitroso oxygen atom. The nucleophilic nature of this oxygen atom also is shown by the reaction with triethyloxonium fluoroborate.

A characteristic property of the N-nitrosoketimines is their intense color, and this prompted the recording of their ultraviolet–visible absorption spectra (Table IV). The low extinction coefficients of all peaks in the visible region led us to suspect that the deep colors of the N-nitrosoketimines might be due to a surface phe-

(20) Z. E. Jolles in "The Chemistry of Carbon Compounds," Vol. IIIa, E. H. Rodd, Ed., Elsevier, New York, N. Y., 1954, p 266. *Cf.* also C. G. Snow, *Ind. Eng. Chem.*, **24**, 1420 (1932).

TABLE IV
ULTRAVIOLET–VISIBLE ABSORPTION SPECTRA OF N-NITROSOKETIMINES

Compd	Solvent	λ, mμ (log ε)
1a	CCl_4	254, 268, 273, 284, 500, 518
b	EtOH	226, 268, 275, 284, 502, 518
f	CCl_4	256 (3.993), 265 (4.001), 306 (3.943), 522 (2.033), 596 (2.033)
h	EtOH	259 (4.009), 312 (3.925), 494 (1 380), 520 (1.518)
i	EtOH	258 (3.596), 310 (3.721), 523 (2 079), 585 (2.033)

nomenon, though the intense colors of their solutions suggested otherwise.

The ordinary nitrosochromophore causes a blue or green color in the monomeric state corresponding to distinctive bands at 300 and 665 mμ; such bands are absent in the spectra of **1** (Table IV). The azo chromophore also produces intense colors, the wavelength of the absorption bands varying with the amount of conjugated unsaturation. Dialyl compounds **1** are blue or purple in color, indicating a high degree of conjugation. The less conjugated alkyl aryl **1** are red, revealing the expected hypsochromic effect.

Although both **1′** and **1″** contain the azo chromophore, the failure of the N-nitrosoketimines to undergo attempted 1,3-dipolar cycloadditions with ketene, ketene diethyl acetal, and dimethyl acetylenedicarboxylate is consistent with a low contribution of **1′** to the transition state of the molecule.

The 1,3-dipolar structure of the nitrosamines (**12′**), originally proposed on the basis of spectral evidence,[21] is consistent with the synthesis and isolation of a host of nitrosimmonium salts.[22] A major contribution of **1″** to the transition state, and probably to the ground



12 **12′**

state, of the N-nitrosoketimines would be directly analogous. Unfortunately, the nmr method, which worked so well in determining the structure of **12**, is incapable of distinguishing the relative contributions of **1**, **1′**, and **1″**. Structure **1″** emphasizes that N-nitrosoketimines usefully may be regarded as N-oxides of disubstituted diazomethanes.

Experimental Section[23]

General Synthesis of Ketimines (2).—A Grignard reagent was prepared by slowly adding about 0.4 mol of the appropriate halide in 100 ml of anhydrous ether to magnesium turnings (10 g, 0.41 g-atom) in 25 ml of anhydrous ether. The dark solution was allowed to stand for several hours until cool. In those reactions in which steric hindrance was a factor, dry toluene (150 ml) was added and the ether was distilled until the temperature had reached 100°; a light solid usually appeared in the toluene solution. The appropriate nitrile (about 0.36 mol) in 50 ml of solvent (or enough to effect solution) was added dropwise, and the resulting suspension refluxed for about 2 days. To the cooled suspension, anhydrous methanol (90 ml) was added with efficient stirring and the stirring continued for an additional 2 hr under gentle reflux. The hot suspension was filtered with suction and the solid, white methoxymagnesium halide was washed several times with anhydrous ether. Removal of the solvent from the filtrate at reduced pressure afforded the crude ketimine, from which the pure product was obtained by recrystallization or vacuum distillation. Data on the individual ketimines are found in Table I.

Nitrate Salt of 4,4′-Dimethoxybenzophenonimine.—4,4′-Dimethoxybenzophenonimine (2c) (0.5 g, 2 mmol) was suspended in 25 ml of petroleum ether (bp 30–60°) and nitrous fumes were introduced. A deep blue color developed immediately, but was replaced after about 3 hr by a clear brown solution containing a light yellow powder. Filtration followed by washing with petroleum ether left 0.54 g (85%) of a solid which gave a strong Liebermann test. Several recrystallizations from chloroform–petroleum ether afforded the analytical sample, mp 178–180° with sweating from 140°.

Anal. Calcd for $C_{15}H_{14}N_2O_6$: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.17, 59.33; H, 5.30, 5.33; N, 9.02, 9.14.

Nitrate Salt of 4,4′-Dimethylbenzophenonimine.—The crude yield of this compound, prepared as above from 4,4′-dimethylbenzophenonimine (2d), was 1.3 g (99%). Several recrystallizations from chloroform–petroleum ether produced the analytical sample, mp 190–192° with sweating from 150°.

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.14; H, 5.92; N, 10.29. Found: C, 66.68; H, 6.01; N, 9.91, 9.72.

Hydrolysis of 4,4′-Dimethoxybenzophenonimine (2c).—A suspension of 2c (0.50 g, 1.66 mmol) in 20 ml of 6 *N* hydrochloric acid was refluxed for 24 hr. The solution was cooled, filtered, and the gray solid (mp 145–147°) washed with ether. The yellow filtrate was extracted three times with ether, and the combined extracts were dried and evaporated to give 0.09 g of 4,4′-dimethoxybenzophenone as white needles, mp 142–144° (lit.[24] mp 143–144°). Total yield was 0.44 g (86%).

Hydrolysis of the Nitrate Salt of 2c.—A similar hydrolysis of the nitrate salt of 2c gave 0.32 g of a product that melted over a wide range. Fractional crystallization from cyclohexane gave very thin, colorless needles, mp 108–110°, and clusters of colorless rods, mp 137–139°. The infrared spectrum of the latter was identical with that of 4,4′-dimethoxybenzophenone[25] (lit.[24] mp 143–144°).

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83; O, 19.81. Found: C, 74.65; H, 5.68; O, 19.67.

The infrared spectrum of the colorless needles was similar to, but not identical with, the spectrum of 4,4′-dimethoxybenzophenone. No mention of a lower melting form of this ketone was found in the literature. These needles were also analyzed.

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83; O, 19.81. Found: C, 74.79; H, 5.34; O, 19.87.

Hydrolysis of 4,4′-Dimethylbenzophenonimine (2d).—A similar hydrolysis of 2d gave the corresponding ketone as white needles, mp 95–96° (lit.[26] mp 92–95°), whose infrared spectrum agreed with that in the literature.[25]

General Synthesis of N-Nitrosoketimines (1).—A suspension of sodium acetate (14.8 g, 0.145 mol) in 40 ml of dry carbon tetrachloride was cooled to below −10° (internal temperature) in a Dry Ice–acetone bath. Nitrosyl chloride (4.00 g, 60 mmol) was added with stirring, followed by a solution of the ketimine (2) (40 mmol) in 10 (more, if necessary) ml of dry carbon tetrachloride cooled to −10°, the internal temperature being kept at or below −10°. Addition of the ketimine caused the immediate appearance of a dark color. The mixture was stirred for 20 min at −10° and quickly washed with 200 ml of ice-cold 10% potassium bicarbonate, followed by 200 ml of ice-water. The dried (anhydrous magnesium sulfate) solution was evaporated under reduced pressure and the resultant, deeply colored oil was dis-

(21) C. R. Looney, W. D. Phillips, and E. L. Reilly, *J. Amer. Chem. Soc.*, **79**, 6163 (1957); G. J. Karabatsos and R. A. Taller, *ibid.*, **86**, 4373 (1964).

(22) S. Hünig, L. Geldern, and E. Lücke, *Rev. Chim.* (Bucharest), **7**, 935 (1962); *Angew. Chem.*, **75**, 476 (1963); A. Schmidpeter, *Tetrahedron Lett.*, 1421 (1963); *Chem. Ber.*, **96**, 3275 (1963); D. Klamann and W. Koser, *Angew. Chem.*, **75**, 1104 (1963).

(23) All melting points, which are uncorrected, were determined with a Kofler hot stage, except those (so designated) taken in sealed capillaries, which were determined with a Hershberg-type apparatus. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were obtained with a Beckman IR-5 or a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet and visible spectra were obtained with a Cary Model 14 recording spectrophotometer. Nuclear magnetic resonance spectra were determined with a Varian A-60 high-resolution spectrometer. The mass spectrograph was determined with a Hitachi Perkin-Elmer Model RMU-6A mass spectrophotometer.

(24) K. Auwers, *Ann. Chem.*, **356**, 127 (1907).

(25) N. Lozach and G. Guillonzo, *Bull. Soc. Chim. Fr.*, [5] **24**, 1221 (1957).

solved in 10 ml of anhydrous ether and cooled to −78° in Dry Ice. If a solid separated, it was recrystallized from petroleum ether by dissolution at 0° followed by cooling in Dry Ice to −78°. Data on the individual 1, including combustion analyses, are found in Table II. No way was found to purify the two red oils (1a, b), since they decomposed to the corresponding ketones on attempted vacuum distillation and on attempted chromatography on silica gel.

Kinetic Study of the Decomposition of N-Nitrosoketimines (1).—N-Nitroso-2,4'-dimethylbenzophenonimine (1h) (0.50 g, 2.1 mmol) was dissolved in 25 ml of cyclohexane at 23°; the gas evolved (N_2) was allowed to displace water from a gas measuring tube. A sample of the data collected was subjected to analysis for both first- and second-order kinetics. The linearity of the first-order curve and the constancy of the first-order rate constant and of the resultant first-order half-life (4.75 hr) all indicate a first-order mechanism for the decomposition.

General Synthesis of 1,1-Disubstituted Propylene Oxides (9).—Twenty milliliters of an ethylene chloride solution containing 1.17 mmol of triethyloxonium fluoroborate[26] per milliliter (4.45 g, 23.4 mmol) was cooled to 5° in a three-neck flask fitted with a reflux condenser, a dropping funnel, and an inlet tube for maintaining a nitrogen atmosphere, and treated dropwise with a solution of the N-nitrosoketimine (1) (16.8 mmol) in 10 ml of ethylene chloride. The resulting deeply colored solution was stirred at 0–5° for 1 hr and then allowed to warm slowly to room temperature. Gas evolution occurred during this warming, followed by a gradual change of the deep red or blue color to bright orange. After evolution of gas had ceased, the solvent was removed under reduced pressure and the residual orange-red oil was dissolved in 20 ml of anhydrous ether and washed twice with 5% sodium bicarbonate and twice with water. Evaporation of the dried (anhydrous magnesium sulfate) ether solution under reduced pressure and vacuum distillation of the resulting oil afforded the 1,1-disubstituted propylene oxide (9) as a colorless or pale yellow oil. Data on 9, including combustion analyses, are found in Table III.

Similar reactions of triethyloxonium fluoroborate with 1e and 1f produced only the corresponding ketones.

1-(2-Chlorophenyl)-1-(4-chlorophenyl)-1-propanol.—A Grignard reagent was prepared from magnesium turnings (2.75 g, 0.113 g-atom) in 10 ml of anhydrous ether and 2-bromochlorobenzene (21.00 g, 0.1097 mol) in 90 ml of anhydrous ether. After the dark solution was stirred for 2 hr under gentle reflux, a solution of 4-chloropropiophenone (16.86 g, 0.1000 mol) in 30 ml of anhydrous ether was added dropwise, and the resulting suspension was refluxed overnight, cooled in an ice bath, and treated with 50 ml of 20% sulfuric acid and 70 g of ice. The ether solution was separated, the aqueous layer was extracted twice with 20-ml portions of ether, the combined ether extracts were dried over anhydrous magnesium sulfate, and the ether was removed under reduced pressure to give a crude orange-brown oil, vacuum distillation of which afforded 17.8 g (63.4%) of a colorless oil, bp 138–140° (30 mm). Its infrared and nmr spectra coincided with expectations.

1-(2-Chlorophenyl)-1-(4-chlorophenyl)propene.—1-(2-Chlorophenyl)-1-(4-chlorophenyl)-1-propanol (17.80 g, 63.3 mmol) was refluxed overnight in a solution of 5 ml of phosphorus oxychloride in 25 ml of toluene. The solution was cooled and poured with stirring into 50 g of ice. After the ice had melted, the toluene was separated and the aqueous fraction was extracted three times with 10-ml portions of ether. The combined organic fractions were washed three times with 15-ml portions of 5% sodium bicarbonate and twice with 15-ml portions of water and dried over magnesium sulfate, and the solvents were removed at reduced pressure. Vacuum distillation of the deep orange oil yielded 10.9 g (65.5%) of a pale yellow oil, bp 132–134° (0.35 mm).

Anal. Calcd for $C_{15}H_{12}Cl_2$: C, 68.46; H, 4.60; Cl, 26.94. Found: C, 68.33, 68.57; H, 4.43, 4.37; Cl, 27.21, 27.08.

1-(2-Chlorophenyl)-2-(4-chlorophenyl)-1-propanone (10) or 1-(4-Chlorophenyl)-2-(2-chlorophenyl)-1-propanone (11).—A solution of *m*-chloroperbenzoic acid (4.47 g, 22.0 mmol) in 60 ml of methylene chloride was added dropwise to a solution of 1-(2-chlorophenyl)-1-(4-chlorophenyl)propene (4.20 g, 16.0 mmol) in 10 ml of methylene chloride, and the mixture was refluxed for 18 hr. After cooling, the excess per acid was decomposed by stirring with 25 ml of 10% aqueous sodium sulfite until no iodine was liberated from a sample on addition of a solution of potassium iodide in 95% ethanol. The methylene chloride layer was separated and washed twice with 15 ml of 5% aqueous sodium bicarbonate and twice with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. Vacuum distillation afforded 4.05 g (90.5%) of 10 or 11 as a yellow oil, bp 146–148° (0.35 mm).

Anal. Calcd for $C_{15}H_{12}OCl_2$: C, 64.53; H, 4.33; Cl, 25.40. Found: C, 64.43; H, 4.50; Cl, 25.27.

The yellow 2,4-dinitrophenylhydrazone of this oil, mp 156–158°, also was analyzed.

Anal. Calcd for $C_{21}H_{16}Cl_2N_4O_4$: C, 54.92; H, 3.51; N, 12.20; Cl, 15.44. Found: C, 54.79; H, 3.81; N, 12.11; Cl, 15.40.

Registry No.—**1a**, 16620-65-8; **1b**, 16620-66-9; **1e**, 16620-67-0; **1f**, 16620-68-1; **1h**, 16620-69-2; **1i**, 16620-70-5; **2a**, 16620-71-6; **2b**, 16620-72-7; **2c**, 5291-48-5; **2c** nitrate salt, 16620-74-9; **2d**, 16620-75-0; **2d** nitrate salt, 16620-76-1; **2e**, 1013-88-3; **2f**, 5526-10-3; **2g**, 16621-07-1; **2h**, 16621-08-2; **2i**, 16621-09-3; **9a**, 16621-10-6; **9b**, 16621-11-7; **9h**, 16621-12-8; **9i**, 16621-13-9; 1-(2-chlorophenyl)-1-(4-chlorophenyl)-1-propanol, 16621-14-0; 1-(2-chlorophenyl)-1-(4-chlorophenyl)propene, 16621-15-1.

(26) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

Reactions of Enamines. X. Methylene Bases in the Benzothiazole Series as Enamines[1]

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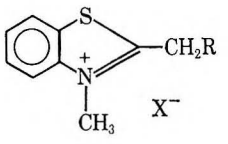
Received December 15, 1967

The methylene base 2-benzylidene-3-methylbenzothiazoline (**7**, R = H) has been shown to undergo alkylation, acylation, and reaction with trichloroacetic acid. The products are those characteristic of the reaction of **7** (R = H) as an enamine. 2-Diphenylmethylene-3-methylbenzothiazoline (**7**, R = C_6H_5), a methylene base disubstituted on the methylene carbon, proved to be unreactive compared with **7** (R = H).

The methylene bases derived from the quaternary salts of various nitrogen heterocyclic compounds have been shown to undergo many reactions characteristic of enamines.[1,2] In the case of the methylene base[3] derived from 2,3-dimethylbenzothiazolium salts (**1**, R = H), elucidation of the course of its reactions has been complicated by the fact that it exists as a dimer.[4] The correct structure **2** of this dimer was first proposed by Larive and Dennilauler[5] on the basis of chemical evidence and was later confirmed by nuclear magnetic resonance spectroscopy.[6] Many reactions of the dimer



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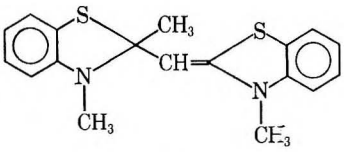
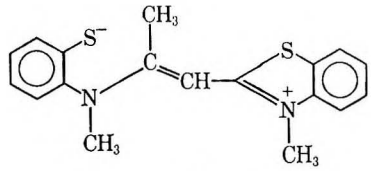


2

2 with electrophilic reagents have been reported.[4-12] These reactions are best rationalized on the basis of reaction at sulfur[13] of the mesomeric form **3** rather than reactions at the enamine carbon of **2**. Very little is recorded in the literature about the reactions of monomeric methylene bases in the benzothiazole series. The methylene base **4** is reported to acylate with boiling acetic anhydride[14] to give reaction at the enamine carbon. The methylene base **5** derived from 2-ethyl-3-methylbenzothiazolium iodide (**1**, R = CH_3; X = I) has been prepared and shown to be monomeric.[6] Alkylation of **5** with methyl iodide is reported[15] to give 2-isopropyl-3-methylbenzothiazolium iodide. It seemed of interest, therefore, to prepare a monomeric methylene base in the benzothiazole series and investigate its reactions as an enamine.



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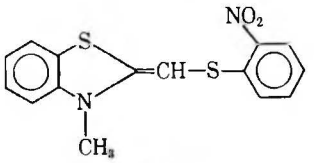

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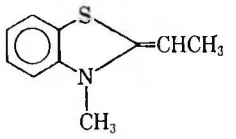

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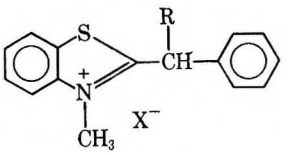
2-Benzylbenzothiazole[16] was converted into 2-benzyl-3-methylbenzothiazolium tosylate (**6**, R = H; X = tosyl) by reaction with methyl *p*-toluenesulfonate. Treatment of **6** (R = H; X = tosyl) with sodium methoxide in methanol gave the methylene base **7** (R = H) as a crystalline solid. The compound **7** (R = H) had



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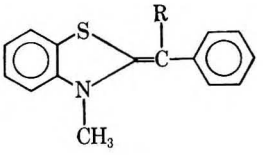


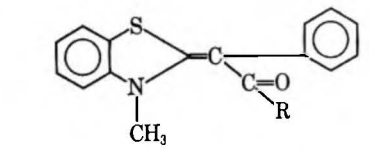
7

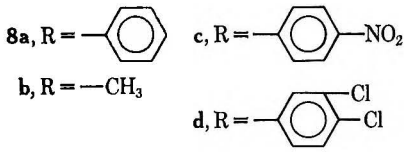
the correct elemental analysis and the nuclear magnetic resonance spectrum was consistent with the assigned structure showing a vinyl proton at τ 4.46. The nmr spectrum and a molecular weight determination showed **7** (R = H) to be monomeric.

Alkylation of **7** (R = H) with excess methyl iodide or *p*-nitrobenzyl bromide gave the expected products (**6**, R = CH_3; X = I) and (**6**, R = $CH_2C_6H_4NO_2$; X = Br) in high yield, respectively. Alkylation of **7** (R = H) with 2,4-dinitrofluorobenzene, however gave the new methylene base **7** (R = $C_6H_3(NO_2)_2$). Evidently **7** (R = H) was a stronger base and removed the elements of hydrofluoric acid from the intermediate **6** (R = C_6H_3-$(NO_2)_2$; X = F). In support of this, a salt was isolated from the reaction mixture which on treatment with sodium iodide was found to be **6** (R = H; X = I).

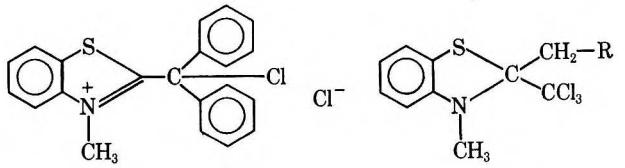
Acylation of **7** (R = H) with benzoyl chloride gave **8a** together with an equimolar amount of **6** (R = H; X = Cl). The formation of **6** (R = H; X = Cl) could be prevented and the yield of **8a** increased by adding triethylamine as base. In this way, **7** (R = H) was acylated by acetyl, *p*-nitrobenzoyl, and 3,4-dichlorobenzoyl chlorides to give **8b**, **c**, and **d**, respectively.

(1) Part IX: G. H. Alt, *J. Org. Chem.*, **31**, 2384 (1966).
(2) M. Coenen, *Angew. Chem.*, **61**, 11 (1949).
(3) W. König and W. Meier, *J. Prakt. Chem.*, **109**, 324 (1925).
(4) O. Mumm, H. Hinz, and J. Diederichsen, *Ber.*, **72**, 2107 (1939).
(5) H. Larive and R. Dennilauler, *Chimia*, **15**, 115 (1961).
(6) J. Metzger, H. Larive, E. Vincent, and R. Dennilauler, *J. Chem. Phys.*, **60**, 944 (1963).
(7) A. I. Kiprianov and F. S. Babichev, *J. Gen. Chem. USSR*, **20**, 145 (1950).
(8) F. S. Babichev, *ibid.*, **20**, 1904 (1950).
(9) V. I. Dénes, M. Fărcăsan, and G. Ciurdaru, *Ber.*, **97**, 1246 (1964); see also V. I. Dénes and M. Fărcăsan, *J. Gen. Chem. USSR*, **32**, 119, 654 (1962).
(10) L. M. Yagupolsky and M. S. Marenets, *ibid.*, **23**, 481 (1953).
(11) M. Coenen, *Ann.*, **633**, 78 (1960).
(12) M. T. LeBris, *Ann. Chim.* (Paris), [13] **1**, 328 (1956), and references there cited.
(13) In cases where the products from **2** are those which would be expected from the monomeric methylene base [*e.g.*, L. G. S. Brooker and F. L. White, U. S. Patent 2,112,139 (1938)], they are formed from the primary products by an intermolecular rearrangement under the reaction conditions (see ref 9).
(14) V. I. Dénes, M. Fărcăsan, and G. Ciurdaru, *Ber.*, **96**, 174 (1963).
(15) Unpublished work at Kodak-Pathé, Vincennes, France; see ref 5.
(16) F. L. Hamer, *J. Chem. Soc.*, 1487 (1956).





The disubstituted methylene base **7** (R = C_6H_5) was also prepared from the corresponding salt **6** (R = C_6H_5; X = tosyl) and shown to be monomeric. The compound **7** (R = C_6H_5) proved to be unreactive compared with **7** (R = H) owing to steric hindrance at the enamine carbon and/or to the electron withdrawing effect of the phenyl groups. However, **7** (R = C_6H_5) could be converted into **6** (R = C_6H_5; X = I) by treatment with hydriodic acid and was chlorinated[17] by chlorine in carbon tetrachloride to the salt **9**.



9 **10**

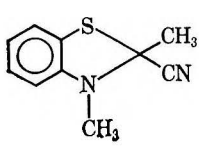
Enamines have been shown to add trichloroacetic acid to give α-trichloromethyl amine derivatives.[18] In the same way **7** (R = H) reacts with trichloroacetic acid to give the trichloromethyl derivative **10** (R = C_6H_5). The latter compound has an interesting nuclear magnetic resonance spectrum. The benzyl protons are in different environments due to the asymmetry of the molecule and appear as two doublets centered at τ 6.30 with J = 16 cps and at 6.55 with J = 16 cps. This reaction must have involved protonation of the methylene base **7** (R = H) to give **6** (R = H; X = Cl_3COO^-), followed by decarboxylation of the trichloroacetate anion to give trichloromethyl anion. Addition of the latter to the cation of **6** (R = H) then affords the observed product **10** (R = C_6H_5).

As the dimer **2** is reconverted to the benzothiazolium salt **1** (R = H) on protonation,[4] the dimer **2** was also subjected to reaction with trichloroacetic acid.[19] Reaction of **2** in benzene solution with trichloroacetic acid gave **10** (R = H). Compound **17** was characterized by elemental analysis, and had a nuclear magnetic resonance spectrum consistent with the assigned structure.

(17) Enamines have been shown to chlorinate [A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **28**, 3492 (1963)] and brominate [(a) R. L. Pedersen, J. L. Johnson, R. P. Holysz, and A. C. Ott, *J. Amer. Chem. Soc.*, **79**, 1115 (1957); (b) M. E. Kuehne, *ibid.*, **83**, 1492 (1961)], to give β-haliminium salts.

(18) G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **31**, 1340 (1966).

(19) H. Wahl and J. J. Voreanger [*Bull. Soc. Chim. Fr.*, 3359 (1965)] have isolated



from the reaction of sodium cyanide with **1** (X = $MeSO_4^-$).

In summary, it may be concluded that methylene bases in the benzothiazole series undergo reactions characteristic of enamines. Only when the methylene base exists as a dimer are anomalous reactions encountered and these are best rationalized as reactions on sulfur of a species such as **3**. The initially formed products from **3** occasionally undergo intermolecular rearrangements under the conditions of the reaction resulting in products which would be expected from the monomeric methylene base.

Experimental Section[20]

2-Benzylbenzothiazole.—This compound was prepared by the method of Hamer,[16] bp 165–170° (1.4 mm) [lit.[16] bp 157–163° (0.5 mm)]; $n^{24}D$ 1.6415; nmr, τ 5.79 (s, 2, CH_2Ph), 1.9–3.1 (m, 9, aromatic H).

2-Benzyl-3-methylbenzothiazolium Tosylate (6, **R** = **H**; **X** = **tosyl**).—2-Benzylbenzothiazole (11.3 g, 0.05 mol) and methyl *p*-toluenesulfonate (9.3 g, 0.05 mol) were heated at 180° for 3 hr. The solid residue was triturated with ether and filtered to give 20.5 g (99%) of crude product. Two recrystallizations from 2-propanol gave analytically pure **6** (R = H; m = tosyl), mp 175–177°.

Anal. Calcd for $C_{22}H_{21}NO_3S_2$: C, 64.20; H, 5.14; N, 3.40; S, 15.58. Found: C, 64.44; H, 5.21; N, 3.47; S, 15.74.

2-Benzyl-3-methylbenzothiazolium Iodide (6, **R** = **H**; **X** = **I**).—2-Benzylbenzothiazole (3.0 g; 0.013 mol) was dissolved in excess methyl iodide (10 ml) and heated at the reflux temperature overnight. On cooling, ether was added and the precipitate filtered. Recrystallization from ethanol gave **6** (R = H; X = I) as fine needles, mp 208–209° dec.

Anal. Calcd for $C_{15}H_{14}INS$: C, 49.05; H, 3.84; I, 34.56; N, 3.82; S, 8.73. Found: C, 49.04; H, 3.79; I, 34.65; N, 4.02; S, 8.75.

2-Benzylidene-3-methylbenzothiazoline (**7**, **R** = **H**).—Sodium methoxide solution (10 ml of 1.02 *N*; 0.01 mol) was added dropwise to an ice-cold solution of 2-benzyl-3-methylbenzothiazolium tosylate (4.1 g, 0.01 mol) in methanol (10 ml). The product separated as an oil which solidified on addition of water (30 ml). Recrystallization from ethanol gave 1.5 g (63%) of yellow needles: mp 74–75°; nmr, τ 6.87 (s, 3, CH_3N), 4.46 (s, 1, CH=C), 2.6–3.6 (m, 9, aromatic H).

Anal. Calcd for $C_{15}H_{13}NS$: C, 75.27; H, 5.47; N, 5.85; S, 13.40; mol wt, 239.32. Found: C, 75.31; H, 5.57; N, 5.78; S, 13.46; mol wt, 240.

2-α-Methylbenzyl-3-methylbenzothiazolium Iodide (6, **R** = CH_3; **X** = **I**).—2-Benzylidene-3-methylbenzothiazoline (1.2 g, 0.005 mol) was refluxed in methyl iodide (20 ml) for 18 hr. The methyl iodide was then removed *in vacuo*, and the residue was triturated with ether and filtered to give 1.7 g (89%) of a white salt. One recrystallization from ethanol gave pure material, mp 176–178° dec.

Anal. Calcd for $C_{16}H_{16}INS$: C, 50.40; H, 4.23; I, 33.29; N, 3.67. Found: C, 50.22; H, 4.24; I, 33.47; N, 3.66.

2-α-(*p*-Nitrobenzyl)benzyl-3-methylbenzothiazolium Bromide (6, **R** = $CH_2C_6H_4NO_2$; **X** = **Br**).—A mixture of 2-benzylidene-3-methylbenzothiazoline (2.4 g, 0.01 mol) and *p*-nitrobenzyl bromide (4.3 g, 0.02 mol) was refluxed in benzene (50 ml) for 2 hr. Cooling and filtering gave 1.4 g of pale yellow solid. The benzene mother liquors were returned to reflux for 18 hr from which a further 1.8 g of solid was obtained. The two portions were combined and purified by slurrying in hot acetone, to give 3.0 g of a pale yellow solid, mp 190° dec.

Anal. Calcd for $C_{22}H_{19}BrN_2O_2S$: C, 58.02; H, 4.21; Br, 17.55; N, 6.15. Found: C, 57.89; H, 4.31; Br, 17.81; N, 5.92.

2-α-(2,4-Dinitrophenyl)benzylidene-3-methylbenzothiazoline [**7**, **R** = $C_6H_3(NO_2)_2$].—2-Benzylidene-3-methylbenzothiazoline (1.2 g, 0.05 mol) and 2,4-dinitrofluorobenzene (0.9 g, 0.05 mol)

(20) Melting points were taken with a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Infracord Model 137 in chloroform solution. Nmr spectra were taken with a Varian A-60 instrument in deuteriochloroform solution using tetramethylsilane as an internal standard. Elemental analyses and molecular weights (by differential osmometry) were carried out by Galbraith Laboratories.

were refluxed in benzene (25 ml) for 1 hr. The deep purple mixture was cooled and filtered, and the filtrate was evaporated to dryness, giving a dark resin, which was chromatographed on 60 g of Woelm neutral alumina (grade I) in benzene. Elution with benzene afforded the product as 0.6 g, (28%) of dark purple solid. One recrystallization from ethanol gave pure material as dark purple, nearly black, crystals, mp 184–185°.

Anal. Calcd for $C_{21}H_{15}N_3O_4S$: C, 62.21; H, 3.73; N, 10.36. Found: C, 62.03; H, 3.82; N, 10.25.

The residue from the filtration above was taken up in a little hot ethanol and treated with a solution of sodium iodide in ethanol. On cooling, a salt, mp 207–209° dec, crystallized which was identified as 6 (R = H; X = I) by mixture melting point.

2-α-Benzoylbenzylidene-3-methylbenzothiazoline (8a). A.—Benzoyl chloride (1.4 g, 0.01 mol) in benzene (20 ml) was added dropwise to a solution of 7 (R = H) (4.8 g, 0.02 mol) in benzene (75 ml). The reaction mixture was heated at the reflux temperature for 3 hr, cooled, and filtered. The solid had mp 223–224° dec and the analysis fits the formula for 6 (R = H; X = Cl).

Anal. Calcd for $C_{15}H_{14}ClNS$: C, 65.32; H, 5.12; Cl, 12.86; N, 5.08; S, 11.63. Found: C, 65.38; H, 5.20; Cl, 13.03; N, 4.96; S, 11.62.

On treatment with aqueous sodium hydroxide 6 (R = H; X = Cl) gave 7 (R = H), mp 72–74° not depressed in admixture with authentic material. The filtrate above was evaporated to dryness under reduced pressure and the residue (2.0 g, 52.5%) recrystallized from ethanol to give 8a, mp 208–210°, not depressed in admixture with the material below.

B.—Benzoyl chloride (1.4 g, 0.01 mol) in benzene (25 ml) was added dropwise to a mixture of 2-benzylidene-3-methylbenzothiazoline (2.4 g, 0.01 mol) and triethylamine (1.0 g, 0.01 mol) in benzene (75 ml) at 25°. The mixture was then refluxed 2 hr. On cooling, the triethylamine hydrochloride was filtered off, the filtrate was evaporated to dryness, and the residue was crystallized from ethanol, affording the product as 2.2 g, (65%) of yellow prisms, mp 209–211°. The material showed no carbonyl absorption below 6.0 μ in the infrared spectrum.

Anal. Calcd for $C_{22}H_{17}NOS$: C, 76.93; H, 4.99; N, 4.08. Found: C, 76.78; H, 4.94; N, 4.13.

2-α-Acetylbenzylidene-3-methylbenzothiazoline (8b).—Acetyl chloride (0.8 g, 0.01 mol) in benzene (20 ml) was added dropwise to a mixture of 2-benzylidene-3-methylbenzothiazoline (2.4 g, 0.01 mol) and triethylamine (1.0 g, 0.01 mol) in benzene (70 ml) at 25°, stirred for 1 hr, then refluxed 1 hr. The mixture was then cooled and filtered. The filtrate was evaporated and the residue was crystallized from ethanol, giving 1.5 g (63%) of off-white solid, mp 154–157°. Two recrystallizations from aqueous methanol afforded pure material as yellow plates, mp 157–158°. The material showed no carbonyl absorption below 6.0 μ in the infrared spectrum.

Anal. Calcd for $C_{17}H_{15}NOS$: C, 72.56; H, 5.37; N, 4.98. Found: C, 72.37; H, 5.31; N, 5.19.

2-α-(*p*-Nitrobenzoyl)benzylidene-3-methylbenzothiazoline (8c).—*p*-Nitrobenzoyl chloride (0.9 g, 0.005 mol) in benzene (25 ml) was added dropwise to a mixture of 2-benzylidene-3-methylbenzothiazoline (1.2 g, 0.005 mol) and triethylamine (0.5 g, 0.005 mol) and triethylamine (0.5 g, 0.005 mol) at 25°. The mixture became quite dark on addition, but on refluxing for 3 hours turned bright orange. After this time, the mixture was filtered hot, and the filtrate concentrated to *ca.* 60 ml. On cooling, the product separated as 1.5 g (67%) of orange crystals, mp 247–249°. Recrystallization from chloroform–methanol gave bright orange plates, mp 249–250°. The material showed no carbonyl absorption below 6.0 μ in the infrared spectrum.

Anal. Calcd for $C_{22}H_{16}N_2O_3S$: C, 68.02; H, 4.15; N, 7.21. Found: C, 67.87; H, 4.17; N, 7.16.

2-α-(3,4-Dichlorobenzoyl)benzylidene-3-methylbenzothiazoline (8d).—3,4-Dichlorobenzoyl chloride (2.1 g, 0.01 mol) in benzene (20 ml) was added dropwise to a mixture of 2-benzylidene-3-methylbenzothiazoline (2.4 g, 0.01 mol) and triethylamine (1.0 g, 0.01 mol) and benzene (100 ml) at 25°. After refluxing for 3 hr, the mixture was filtered hot, the filtrate was evaporated, and the greenish residue was crystallized from benzene–methylcyclohexane. This material was washed well with hot ethanol, then recrystallized from chloroform–methanol to afford the pure product as 1.5 g (37%) of bright-yellow needles, mp 194–196°. The compound showed no carbonyl absorption below 6.0 μ in the infrared spectrum.

Anal. Calcd for $C_{22}H_{15}Cl_2NOS$: C, 64.08; H, 3.97; Cl, 17.20. Found: C, 64.26; H, 3.75; Cl, 17.15.

2-Diphenylmethylbenzothiazole.—Diphenylacetyl chloride (46.0 g, 0.2 mol) was added to *o*-aminothiophenol (25.0 g, 0.2 mol). The reaction mixture was heated to 90° and phosphorus pentoxide (9.5 g) was added portionwise with stirring. On completion of the addition the mixture was heated to 200° for 15 min. The reaction mixture was cooled to 100° and 10% sodium hydroxide solution (160 ml) was added. The reaction mixture was extracted with ether. The ethereal solution was dried ($MgSO_4$) and evaporated to give 57 g of crude product. Vacuum distillation afforded 37 g (61%) of product, bp 215–220° (1.0 mm). Crystallization from methanol gave 2-diphenylmethylbenzothiazole as prisms: mp 89–91°; nmr, τ 4.11 [s, 1, **CH**$(Ph)_2$], 1.9–3.05 (m, 14, aromatic H).

Anal. Calcd for $C_{20}H_{15}NS$: C, 79.70; H, 5.02; N, 4.65; S, 10.64. Found: C, 79.52; H, 5.01; N, 4.63; S, 10.91.

2-Diphenylmethyl-3-methylbenzothiazolium Tosylate (6, R = C_6H_5; X = Tosyl).—2-Diphenylmethylbenzothiazole (6.0 g, 0.02 mol) and methyl *p*-toluenesulfonate (3.7 g, 0.02 mol) were heated at 200° for 2 hr. The solid residue was triturated with ether and filtered to give 9.7 g (99%) of crude product. Two recrystallizations from 2-propanol gave analytically pure 6 (R = C_6H_5; X = tosyl), mp 181–182° dec.

Anal. Calcd for $C_{28}H_{25}NO_3S_2$: C, 68.96; H, 5.17; N, 2.87; S, 13.15. Found: C, 68.78; H, 5.40; N, 2.76; S, 12.95.

2-Diphenylmethyl-3-methylbenzothiazolium Iodide (6, R = C_6H_5; X = I). A.—The tosylate 6 (R = C_6H_5; X = tosyl) (2.45 g, 0.005 mol) in hot 50% aqueous ethanol (10 ml) was treated with 57% hydriodic acid (2 ml). The precipitated solid was filtered and recrystallized twice from methanol to give 6 (R = C_6H_5; X = I), mp 222–224° dec.

Anal. Calcd for $C_{21}H_{18}INS$: C, 56.89; H, 4.09; I, 28.63; N, 3.16; S, 7.23. Found: C, 56.83; H, 4.11; I, 28.51; N, 3.07; S, 7.16.

B.—Hydriodic acid, (0.1 ml of 57% aqueous acid, 0.0032 mol) was added to a warm solution of 2-diphenylmethylene-3-methylbenzothiazoline (0.1 g, 0.0032 mol) in ethanol (7 ml). On cooling, 0.1 g (71%) of colorless prisms formed, mp 222–224° dec, not depressed in admixture with authentic material above.

2-Diphenylmethylene-3-methylbenzothiazoline (7, R = C_6H_5).—Sodium methoxide solution (10 ml of 1.02 *N*, 0.01 mol) was added to an ice-cold solution of 6 (R = C_6H_5; X = tosyl) (4.9 g, 0.01 mol) in methanol (10 ml). The precipitated product was filtered to give 3.0 g (95%) of crude 7 (R = C_6H_5). One recrystallization from 2-propanol, then two from hexane, gave the product as bright yellow needles: mp 130–131°; nmr, τ 7.17 (s, 3, CH_3N), 2.6–3.6 (m, 14, aromatic H).

Anal. Calcd for $C_{21}H_{17}NS$: C, 79.96; H, 5.43; N, 4.44; S, 10.17; mol wt, 315.42. Found: C, 80.09; H, 5.56; N, 4.26; S, 10.44; mol wt, 330.

2-(Diphenylchloromethyl)-3-methylbenzothiazolium Chloride (9).—A carbon tetrachloride solution of chlorine (25 ml of 0.168 *M* solution, 0.0042 mol) was added dropwise to an ice-cold solution of 2-diphenylmethylene-3-methylbenzothiazoline (1.3 g, 0.0042 mol) in carbon tetrachloride. A salt immediately precipitated. Filtration and recrystallization from acetonitrile–ethyl acetate gave 0.6 g (37%) of almost colorless prisms, mp 163–165° dec.

Anal. Calcd for $C_{21}H_{17}Cl_2NS$: C, 65.28; H, 4.44; Cl, 18.35; N, 3.63; S, 8.30. Found: C, 65.09; H, 4.66; Cl, 18.57; N, 3.57; S, 8.14.

2,3-Dimethyl-2-(trichloromethyl)benzothiazoline (10, R = H).—To a solution of the dimer 2[5] (3.26 g, 0.01 mol) in boiling benzene (50 ml) was added a solution of trichloroacetic acid (3.30 g, 0.02 mol) in benzene (25 ml). The reaction mixture was heated at the reflux temperature for 1.5 hr. The benzene was removed under aspirator vacuum. The residue was recrystallized twice from aqueous acetone to give 17: mp 75–77° (4.0 g, 71%); nmr, τ 7.83 (s, 3, C-**CH**$_3$), 6.86 (s, 3, N-**CH**$_3$), 2.8–3.7 (m, 4, aromatic H).

Anal. Calcd for $C_{10}H_{10}Cl_3NS$: C, 42.49; H, 3.57; Cl, 38.64; N, 4.96. Found: C, 42.33; H, 3.51; Cl, 37.81; N, 5.05.

2-Benzyl-2-trichloromethyl-3-methylbenzothiazoline (10, R = C_6H_5).—A dried solution of 2-benzylidene-3-methylbenzothiazoline (1.0 g, 0.0042 mol) in benzene (20 ml) was added to a hot, anhydrous solution of trichloroacetic acid (0.7 g, 0.0042 mol) in benzene (20 ml). The mixture was refluxed 1.5 hr. Removal of the solvent *in vacuo* and recrystallization from ethanol afforded the product as 0.8 g (54%) of pale yellow needles: mp 104–105°; nmr, τ 6.87 (s, 3, N-**CH**$_3$), 6.55 (d, 1, J = 16 Hz, benzyl H), 6.00 (d, 1, J = 16 Hz, benzyl H), 2.8–3.7 (m, 9, aromatic H).

Anal. Calcd for $C_{16}H_{14}Cl_2NS$: C, 53.57; H, 2.93; Cl, 29.65; N, 3.91; S, 8.94; mol wt, 358.71. Found: C, 53.51; H, 3.92; Cl, 29.60; N, 3.70; S, 8.92; mol wt, 370.

Registry No.—**6** (R = H; X = tosyl), 16622-37-0; **6** (R = H; X = I), 16622-21-2; **6** (R = CH_3; X = I), 16622-22-3; **6** (R = $CH_2C_6H_4NO_2$; X = Br), 16622-23-4; **6** (R = H; X = Cl), 16622-24-5; **6** (R = C_6H_5; X = tosyl), 16622-25-6; **6** (R = C_6H_5; X = I), 16622-26-7; **7** (R = H), 16622-27-8; **7** [R = $C_6H_3(NO_2)_2$], 16622-28-9; **7** (R = C_6H_5), 16622-29-0; **8a**, 16622-30-3; **8b**, 16622-31-4; **8c**, 16622-32-5; **8a**, 16638-70-3; **9**, 16622-33-6; **10** (R = H), 16622-34-7; **10** (R = C_6H_5), 16622-35-8; 2-diphenylmethylbenzothiazole, 16622-36-9.

Acknowledgment.—Thanks are extended to Dr. A. J. Speziale for many helpful discussions and to Mr. F. B. Clark for technical assistance.

Synthesis of 11H-Indeno[1,2-*c*]isoquinoline Compounds Related to Chelerythrine

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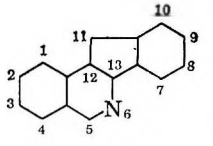
Received December 14, 1967

Reactions leading to the 11H-indeno[1,2-c]isoquinoline nucleus are described. 7,8-Dimethoxyisoquinoline was obtained by an acid-catalyzed cyclization of 2,3-dimethoxybenzylaminoacetal to 4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline followed by dehydration and dehydrogenation. Reductive condensation of the methiodide of 7,8-dimethoxyisoquinoline with benzaldehyde gave 2-methyl-4-benzyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline in low yield. The Bobbitt process, by which a benzylaminoacetal is condensed with an aromatic aldehyde, was employed effectively in producing several 4-benzylisoquinolines. Reduction of the corresponding methiodides with lithium aluminum hydride gave 1,2-dihydroisoquinolines, which cyclized under the proper acid conditions to give tetrahydro-11H-indeno[1,2-c]isoquinolines. Dehydrogenation with iodine completed the synthesis. In this way, 3,4-dimethoxy-6-methyl-8,9-methylenedioxy-11H-indeno[1,2-c]isoquinolinium iodide and 3,4,8,9-tetramethoxy-6-methyl-11H-indeno[1,2-c]isoquinolinium iodide—both related to chelerythrine—were prepared.

The authors wish to report a new synthesis for the little known 11H-indeno[1,2-*c*]isoquinoline system **1**.[1,2] The general purpose was to open a convenient way to compounds of this class; the particular purpose was to synthesize structural variations of the Sanguinaria alkaloids,[3] *e.g.*, chelerythrine (**2**).



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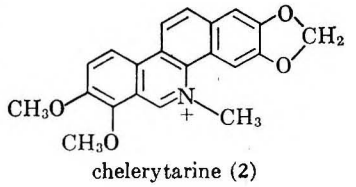


chelerytarine (**2**)

The plan of synthesis required 4-benzylisoquinolines (specifically **9**) as key intermediates. Such compounds should be accessible by reductively condensing an isoquinoline methiodide (specifically **7**) with an aromatic aldehyde.[4] The resulting 4-benzyltetrahydroisoquinoline products **8** could then be dehydrogenated to produce **9**. For the compounds of interest, this approach required 7,8-dimethoxyisoquinoline (**6**), which was prepared in two ways, both making use of 2,3-dimethoxybenzylaminoacetal (**3**) as the starting material. Treatment of acetal **3** with hydrochloric acid in the presence of hydrogen and a catalyst[5] gave tetrahydroisoquinoline (**5**). Treatment of acetal **3** with hydrochloric acid in the absence of hydrogen and catalyst gave 4-hydroxytetrahydroisoquinoline (**4**).[6] Structure **4** for the hydroxy compound is consistent with its nmr spectrum. Thus, the ratio of methoxy protons to aromatic protons is 6:2 as required, and the two-proton multiplet at 2.98 ppm corresponds to the methylene group at position 3. Formation of a dibenzoyl derivative of compound **4** is also consistent with its assigned structure. Catalytic dehydrogenation converted both tetrahydroisoquinolines **4** and **5** into the same compound, the fully aromatic 7,8-dimethoxyisoquinoline (**6**).[7] The isoquinoline preparation *via* hydroxy compound **4** gave good yields (*ca.* 60%) and was simpler to carry out than the alternate preparation involving **5**. Both methods were far superior to the Pomeranz–Fritsch synthesis.[8] (See Scheme I.)

Attachment of a 4-benzyl group[4] was tried with benzaldehyde itself as the aromatic aldehyde. When a mixture of methiodide **7** and benzaldehyde was exposed to hydrogenation conditions in acid solution, the expected product, 2-methyl-4-benzyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**8**, $R_1 = R_2 = H$), was obtained. However the low yield was discouraging and,

(1) The name and numbering follow the recommendations of "The Ring Index" [L. T. Capell and D. F. Walker, Jr., 2nd Suppl. to 2nd ed, American Chemical Society, Washington, D. C., 1964, p 189] in ring number 10815.

(2) Only three references could be found, *i.e.*, J. N. Chatterjea and H. Mukherjee, *J. Indian Chem. Soc.*, **37**, 379 (1960); S. Wawzonek, J. K. Stowell, and R. E. Karll, *J. Org. Chem.*, **31**, 1004 (1966); S. F. Dyke and D. W. Brown, *Tetrahedron*, **24**, 1455 (1968).

(3) R. H. F. Manske and H. L. Holmes, "The Alkaloids," Academic Press Inc., New York, N. Y., Vol. IV, 1954; p 253; Vol. VII, 1960, p 430.

(4) Method of R. Grewe, W. Krüger, and E. Vangermain, *Chem. Ber.*, **97**, 119 (1964).

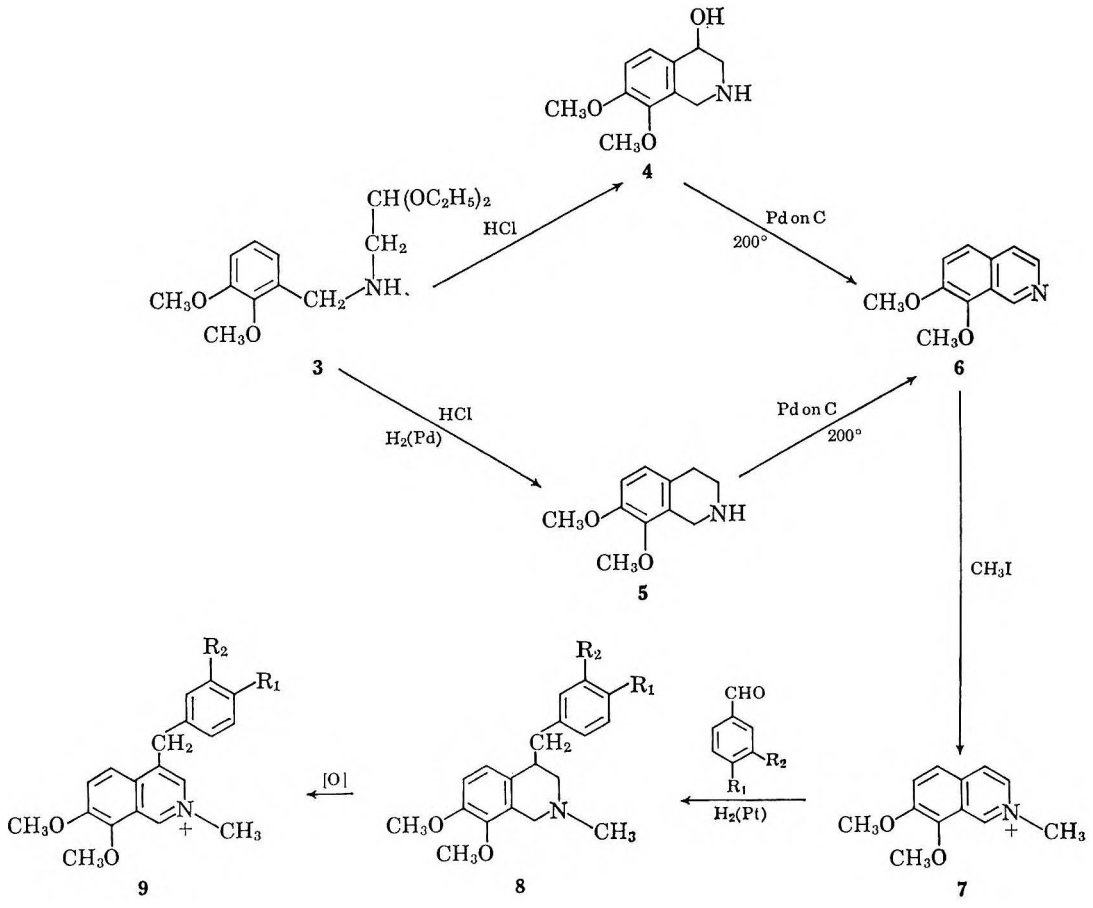
(5) J. M. Bobbitt, K. L. Khanna, and J. M. Kiely, *Chem. Ind.* (London), 1950 (1964); J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965).

(6) In independent work, J. M. Bobbitt and J. C. Sih, utilizing a similar procedure, have isolated several analogous 4-hydroxytetrahydroisoquinolines [*J. Org. Chem.*, **33**, 856 (1968)]. Also *cf.* I. G. Hinton and F. G. Mann, *J. Chem. Soc.*, 599 (1959); T. Kondo and S. Tanaka, *J. Pharm. Soc. Jap.*, **50**, 923 (1930); *Chem. Abstr.*, **25**, 515 (1931).

(7) Related aromatizations of 4-ethoxy-1,2,3,4-tetrahydroisoquinolines have been reported by N. Vinot, *Bull. Soc. Chim. Fr.*, 617 (1960); *Ann. Chim.* (Paris), [13], **3**, 461 (1958).

(8) *Cf.* W. J. Gensler, *Org. Reactions*, **6**, 191 (1951). W. H. Perkin, Jr., and R. Robinson [*J. Chem. Soc.*, **105**, 2376 (1914)], using sulfuric acid in the Pomeranz–Fritsch cyclization of 2,3-dimethoxybenzalaminoacetal obtained 7,8-dimethoxyisoquinoline (**6**) in about 5% yield. C. Djerassi, F. K. Markley, and R. Ehrlich [*J. Org. Chem.*, **21**, 975 (1956)] using polyphosphoric acid brought the yield to 12–17%. In our hands, a variety of conditions produced **6** in yields no better than 8%.

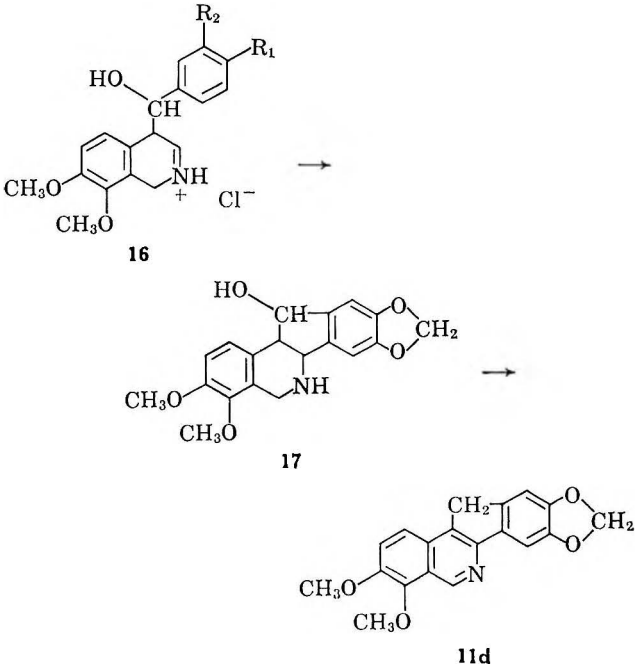
SCHEME I



when concurrent work on another approach began to show promising results, this plan was put aside.

In the alternate approach,[9] the starting material again was aminoacetal **3**. With benzaldehyde in the presence of hydrochloric acid, the aminoacetal furnished a solid hydrochloride (82%), evidently the same as that obtained by Dyke and Sainsbury[10] and formulated by them as **16a** ($R_1 = R_2 = H$). Exposing the hydrochloride to alkali generated the aromatic isoquinoline base **10a** in 72% yield. Methylation with methyl iodide formed the methiodide **9a**. The generality of this elegant method[9] was demonstrated by the use of *m*-anisaldehyde to give the corresponding 4-*m*-anisyl derivatives (**10b** and **9b**), of veratraldehyde to give the 4-veratryl derivatives (**10c** and **9c**), and of piperonal to give the 4-piperonyl derivatives (**10d** and **9d**). In every case, the acid-catalyzed condensation with the aromatic aldehydes precipitated product in the form of hydrochloride salts. The carbon content of the hydrochlorides from benzaldehyde and from piperonal was consistent with formulations **16a** and **16d**. The carbon content of the hydrochlorides from *m*-anisaldehyde and from veratraldehyde was consistent with that expected for the hydrochloride of the fully aromatic isoquinolines **10b** and **10c**. Whatever the nature of the precipitated hydrochlorides, alkali converted them smoothly into isoquinoline gases **10**.[10] (See Scheme II.)

In the reactions leading to the 4-piperonyl derivative **10d**, a side product was observed containing five aromatic protons instead of the expected seven. Methylation of this side product to indenoisoquinoline **15d** supported its formulation as **11d**. A reasonable sequence leading to **11d** would involve the intermediate condensation product **16d**,[4] which could cyclize to **17** by essentially the same mechanism as in the **12** to **13** conversion. Dehydration and dehydrogenation of **17** would lead to the observed side product.

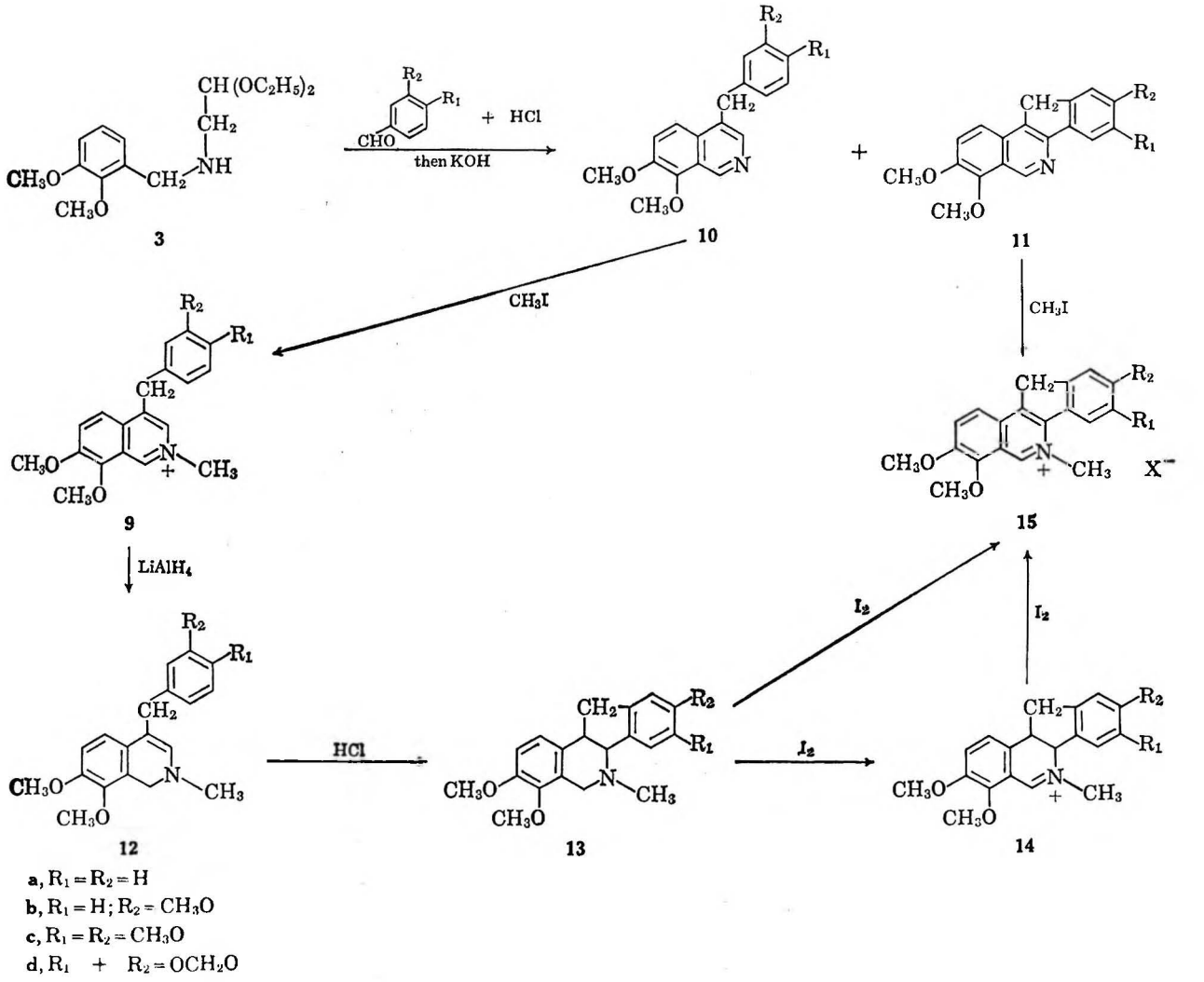


The final stages of the synthesis called for closing a ring on the 3 position of a 1,2-dihydroisoquinoline, as in

(9) J. M. Bobbitt, D. P. Winter, and J. M. Kiely, *J. Org. Chem.*, **30**, 2459 (1965).

(10) S. F. Dyke and M. Sainsbury, *Tetrahedron*, **23**, 3161 (1967).

SCHEME II



a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3O$
c, $R_1 = R_2 = CH_3O$
d, $R_1 + R_2 = OCH_2O$

12 to 13. Related ring closures from the 1 position and from the 2 position have been reported;[11] ring closure from the isoquinoline 4 position have been considered but, so far as it can be determined, have not been realized.[12] In the authors' hands, the cyclization, carried through with the veratryl and piperonyl derivatives, proved to be both possible and practical. The necessary 1,2-dihydroisoquinolines **12c** and **12d** were obtained by reducing the corresponding isoquinolinium quaternary salts **9c** and **9d** with lithium aluminum hydride.[13] The structures of the dihydroisoquinolines, which were isolated as crystalline solids, are supported by the nmr spectra. Thus, the presence of a vinyl proton in piperonyl-1,2-dihydroisoquinoline (**12d**) is substantiated by a three-proton singlet at 5.92 ppm (coinciding OCH_2O and C=CH). The location and integration values of the signals for two methoxy groups, an N-methyl group, and five aromatic protons are also in accord with structure **12d**. The veratryl derivative **12c** shows its vinyl proton as a one-proton signal at 5.80 ppm.

Tetrahydroindenoisoquinoline **13d** was obtained when the 4-piperonyl-1,2-dihydroisoquinoline **12d** was exposed to the action of hydrochloric acid in methanol or in acetic acid. Several other conditions were tried but unsuccessfully. The tetramethoxy-1,2-dihydroisoquinoline **12c** also cyclized under the proper conditions. The nmr spectra of **13d** and **13c** proved to be consistent with the assigned structures (see Experimental Section). *A priori*, cyclization could lead either to *cis* or *trans* geometry at the tetrahydroindenoisoquinoline 12 and 13 positions of **13**. The nmr spectra did not help in deciding on the geometry, but on the basis of mechanistic speculation, the authors favor the *cis* arrangement. Ring closure *para* rather than *ortho* to the substituent oxygens is highly likely; electrophilic substitutions on veratroles or on methylenedioxybenzenes avoid the positions next to oxygen.

Dehydrogenation with ethanolic iodine plus potassium acetate at 40° converted the methylenedioxytetrahydroindenoisoquinoline **13d** into the triiodide of the corresponding quaternary dihydro derivative **14d**. Treatment with sulfite produced the simple iodide. Iodine dehydrogenation at 80° oxidized tetrahydroindenoisoquinoline **13d** as well as dihydro derivative **14d** to the fully aromatic indenoisoquinolinium iodide **15d**. Iodine dehydrogenation of tetrahydroisoquino-

(11) For a brief review see S. F. Dyke and M. Sainsbury, *Tetrahedron*, **21**, 1907 (1965); also, *cf.* D. W. Brown and S. F. Dyke, *ibid.*, **22**, 2429 (1966).

(12) A. R. Battersby, R. Binks, and P. S. Uzzell, *Chem. Ind.* (London), 1039 (1955); M. Sainsbury, S. F. Dyke, and A. R. Marshall, *Tetrahedron*, **22**, 2445 (1966); S. P. Pappas, Ph.D. Dissertation, University of Wisconsin, 1963; *Dissertation Abstr.*, **23**, 3125 (1963); S. F. Dyke, M. Sainsbury, and B. J. Moon, *Tetrahedron*, **24**, 1467 (1968).

(13) An adaptation of the procedure of H. Schmid and P. Karrer [*Helv. Chim. Acta*, **32**, 960 (1949)] who reduced 2-methylisoquinolinium iodide to 2-methyl-1,2-dihydroisoquinoline.

lines to 3,4-dihydroisoquinolines, as in **13** to **14**, observed before.[14] Structure **14d** is supported by the fact that further oxidation with iodine is possible to give **15d**, by the sharp infrared absorption peak at 1665 cm^{-1} ($C{=}N^+$), and by the nmr singlet for one proton at 9.40 ppm, expected for the olefinic proton adjacent to nitrogen. The dehydrogenation of the tetramethoxy derivative **13c** was performed so as to lead directly to the indenoisoquinolinium iodide **15c**. Anion exchange conveniently converted the rather insoluble iodides **15d** and **15c** into the more soluble nitrates.

In summary, a six-step process has been described by which indeno[1,2-*c*]isoquinolines can be synthesized from readily available starting materials. One of the steps—cyclization of **12** to **13**—provides a further example of the versatility of the 1,2-dihydroisoquinoline system in permitting attachment of an activated aryl group to the isoquinoline 3 position. The new synthesis has been applied to the preparation of two indenoisoquinoline derivatives related to chelerythrine (2).

Experimental Section

General.—All melting points were determined in open capillary tubes in a melting point apparatus calibrated against standard samples. Infrared curves were taken with a recording spectrophotometer (Perkin-Elmer 137 and 237). Ultraviolet absorption curves were obtained with the help of a Bausch and Lomb 505 scanning spectrophotometer using 1-cm path length quartz cells. The nmr spectra were taken on a 60-Mc instrument (Varian A-60). For gas–liquid partition chromatography, we relied on an F & M dual column apparatus.

Analyses for elements were performed by Microchemical Laboratories, Massachusetts Institute of Technology, Cambridge, Mass., by Scandinavian Microanalytical Laboratory, Herlev, Denmark, by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Galbraith Laboratories, Inc., Knoxville, Tenn.

2,3-Dimethoxybenzylaminoacetal (3).[5,9]—Over a 6-hr period of stirring in an atmosphere of hydrogen, a mixture of *o*-veratraldehyde (3.3 g, 0.02 mol), aminoacetal (2.7 g, 0.02 mol), platinum oxide (0.2 g), and absolute alcohol (200 ml) absorbed 0.02 mol of hydrogen. Removal of catalyst and solvent left pale yellow 2,3-dimethoxybenzylaminoacetal (**3**) as a yellow oil (5.7 g, 99%), which was used without further purification.

2-Methyl-7,8-dimethoxyisoquinolinium Iodide (7) from 4-Hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4).—A solution of 2,3-dimethoxybenzylaminoacetal (**3**) in 6 *N* hydrochloric acid (5.7 g or 0.020 mol in 200 ml) was stirred for a day and then stored in the cold for 3 days. Adding crushed sodium hydroxide to the cold stirred mixture to pH >10 precipitated the 4-hydroxy compound **4**. Most of the product was collected by filtration; additional quantities were obtained by extracting the filtrate with ether. The total yield of product in the form of a dull white powder, mp 140–142°, was 3.0 g (70%). A sample of this 4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4**), prepared for elemental analysis by recrystallization from 1:1 ethanol–benzene, melted constantly at 141–142.5°.

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.80; H, 6.99; N, 6.52.

The nmr spectrum, taken in deuteriochloroform, showed signals at 2.98 (2 H, m, position 3), 3.24 (3 H, broad singlet, position 1 plus OH), 3.78 and 3.83 (6 H, 2 s, 2 OCH_3), 3.8–4.6 (2 H, m, positions 2 and 4), and 6.80 and 7.12 ppm (2 H, 2 d, $J's$ = 8 cps, positions 5 and 6).

A dibenzoyl derivative was prepared by vigorously shaking a mixture of 4-hydroxy compound **4** (51 mg), benzoyl chloride (280 mg), and 2.5 *N* aqueous sodium hydroxide solution (1 ml) for 10 min. The gummy brown precipitate was crystallized by gradually cooling its ethanolic solution. The fluffy white crystalline dibenzoyl derivative of **4** (37 mg) showed mp 125–126°.

Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36. Found: C, 71.63; H, 5.60; N, 3.40.

A solution of the dibenzoyl derivative in chloroform showed no infrared absorption in the 3400–3600-cm^{-1} region but did show carbonyl maxima at 1720 (ester) and 1660 cm^{-1} (amide).

The 4-hydroxytetrahydroisoquinoline **4** (1.3 g, 7.5 mmol) was aromatized by boiling its solution in decalin (15 ml) containing 0.3 g of 30% palladium-on-carbon at 200° for 4 hr. An atmosphere of nitrogen was maintained over the reaction mixture. After catalyst was removed by filtering the cooled mixture, the filtrate was diluted with 10 ml of benzene and was extracted with several small volumes of 4 *N* hydrochloric acid. The combined aqueous acid extracts were rinsed once with benzene and then treated with 10% aqueous sodium hydroxide (cooling) until the mixture was strongly alkaline. Several extractions with ether removed the product as an ether solution, which was washed first with small portions of water and then with saturated potassium chloride. The ethereal solution, dried with magnesium sulfate, was stripped of solvent at room temperature under aspirator pressures. The yellow residual oil (1.1 g) was taken as 7,8-dimethoxyisoquinoline (**6**).

The nmr spectrum of **6** as a 10% solution in trifluoroacetic acid showed signals at 4.24 and 4.36 (two 3 H, 2 s, 2OCH_3), 8.16 and 8.38 (4 H, two broad singlets, positions 3, 4, 5, 6), and 9.77 ppm (1 H, broad singlet, position 1). For comparison, the spectrum of unsubstituted isoquinoline dissolved in trifluoroacetic acid was taken and was found to show a complex of signals at 8.00–8.85 (6 H, positions 3, 4, 5, 6, 7, 8) and a broad singlet at 9.73 ppm (1 H, position 1).

Treating the 7,8-dimethoxyisoquinoline (**6**) with methyl iodide (2.8 g) produced the lumpy yellow methiodide **7**. Washed once with a small volume of absolute alcohol, this product weighed 1.7 g (83% from the 4-hydroxy derivative **4**) and showed mp 181–183° with slight preliminary sintering. The same methiodide from authentic 7,8-dimethoxyisoquinoline prepared according to the Pomeranz–Fritsch procedure[3] melted at 182–183°; a mixture of the methiodides melted at 181–183° with sintering at 176°. The two methiodides as mulls with mineral oil gave identical infrared absorption curves.

Recrystallizations from methylene chloride–benzene furnished analytically pure 2-methyl-7,8-dimethoxyisoquinolinium iodide (**7**), mp 182–183° dec.

Anal. Calcd for $C_{12}H_{14}INO_2$: C, 43.51; H, 4.26; I, 38.32; N, 4.23. Found: C, 43.31; H, 4.35; I, 38.32; N, 4.24.

2-Methyl-7,8-dimethoxyisoquinolinium Iodide (7) from 7,8-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (5).[5]—A solution of 2,3-dimethoxybenzylaminoacetal (5.7 g, 0.020 mol) in 150 ml of 8 *N* hydrochloric acid was added to a suspension prepared by saturating a stirred mixture of 10% palladium on carbon (0.2 g) and ethanol with hydrogen. Stirring the reaction mixture for 10 hr under hydrogen resulted in the uptake of 1 molar equiv of hydrogen; hydrogen uptake stopped after this period. Removal of the catalyst and all solvent left a yellow pasty mass, which solidified on treatment with a few drops of ethanol. This crude product (3 g, mp 185–190°) on crystallization from absolute alcohol furnished 2.1 g (42%) of pale green crystalline hydrochloride of 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5**), mp 192.5–193° dec.

The free base **5** was used for aromatization. A mixture of the hydrochloride (1.5 g, 7.0 mmol) in 15 ml of water was made strongly alkaline (pH >10) with sodium hydroxide, and the free base was extracted with several portions of decalin. The decalin solution was dried with potassium carbonate, mixed with 30% palladium on carbon, and boiled at 200° for 4 hr. Subsequent treatment, essentially the same as described above, gave rise to 1.2 g of 7,8-dimethoxyisoquinoline (**6**) as a yellow oil. The derived methiodide **7** weighed 1.8 g (79% from 5·HCl) and melted either alone or mixed with authentic material at 180–183° (preliminary sintering). Mineral oil mulls of the two samples gave identical infrared absorption spectra.

2-Methyl-4-benzyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8a).[1]—Benzaldehyde (320 mg, 3.0 mmol) and 0.2 ml of 2 *N* NaOH solution were added to 2-methyl-7,8-dimethoxyisoquinolinium iodide (**7**, 820 mg, 2.5 mmol) in 25 ml of absolute alcohol. The mixture was subjected without delay to hydrogenation at atmospheric pressure over a catalyst prepared by saturating 30 mg of platinum oxide in 25 ml of alcohol with hydrogen. In 2.5 hr, 2.9 molar equiv of hydrogen was absorbed, after which time hydrogenation stopped. Aqueous 2 *N* sodium hydroxide (15 ml) was added, the turbid mixture was filtered, and

(14) W. J. Gensler in "Heterocyclic Compounds," Vol. IV, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p 396.

the filtrate was extracted with ether. The ether solution was washed with two small portions of water, dried with magnesium sulfate, and stripped of solvent. The brown residue was dissolved in concentrated hydriodic acid, and the solution was washed once with ether and then evaporated to dryness at moderate temperatures. Recrystallization of the crude residual iodide from absolute alcohol furnished 255 mg (24%) of bright yellow crystalline 2-methyl-4-benzyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinolinium iodide (**8a**·HI), mp 187–189°. Further crystallizations gave product melting no higher than 188–189°.

Anal. Calcd for $C_{19}H_{24}INO_2$: C, 53.66; H, 5.69; N, 3.29. Found: C, 53.47; H, 5.81; N, 3.38.

4-Benzyl-7,8-dimethoxyisoquinoline (10a).[9,10]—A mixture of benzaldehyde (2.12 g, 0.020 mol), 2,3-dimethoxybenzylaminoacetal (**3**, 2.85 g, 0.010 mol), ethanol (15 ml), and concentrated hydrochloric acid (15 ml) was boiled gently for 30 min. Cooling the mixture for 1 hr precipitated a yellow solid, which after crystallization from absolute ethanol appeared as bright yellow needles (2.8 g or 82%), mp 102–103° (sintering at 100°). Further crystallization did not change the melting point.

Anal. Calcd for $C_{18}H_{20}ClNO_3$: C, 64.77; H, 6.04; Cl, 10.62; N, 4.20. Found: C, 64.70; H, 6.30; Cl, 10.63; N, 4.15.

This solid in a mineral oil mull showed infrared absorption peaks at 1660 and 3350 (broad) cm^{-1}. With the exception of the color, these data correspond well to those reported for compound **16a**.[10]

Isoquinoline base **10a** was obtained by stirring a suspension of the above hydrochloride (1.25 g, 3.76 mmol) in aqueous alkali (pH >10) for 30 min. The precipitate was washed with cold water, dried, and then crystallized from ethanol to give 0.75 g (72%) of white crystalline 4-benzyl-7,8-dimethoxyisoquinoline (**10a**), mp 95–98° (sintering at 92°). The analytically pure material melted at 98–99°.

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.62; H, 6.29; N, 4.94.

Compound **10a** as a 10% solution in trifluoroacetic acid showed the following nmr signals: 4.21 and 4.36 (two 3 H, 2 s, $2OCH_3$), 4.62 (2 H, s, $ArCH_2$), 7.38 (5 H, two peaks, benzyl ArH's), 8.05 (1 H, d, J = 7 cps, position 3), 8.21 (2 H, two peaks, positions 5 and 6), and 9.67 ppm (1 H, d, J = 8 cps, position 1).

4-Piperonyl-7,8-dimethoxyisoquinoline (10d).—When the directions given above were followed with piperonal (3.0 g or 0.020 mol) taken in place of benzaldehyde, bright orange crystals (2.7 g, 68%), mp 100–102° (sintering at 98°), precipitated from the hydrochloric acid reaction mixture. Recrystallizations from ethanol gave crystals (**16d**·H_2O) with mp 102.5–103° (sintering at 100°).

Anal. Calcd for $C_{19}H_{20}ClNO_5 \cdot H_2O$: C, 57.65; H, 5.60; Cl, 8.96; N, 3.54. Found: C, 57.54; H, 5.97; Cl, 8.92; N, 3.28.

The crystals in a mineral oil mull showed infrared absorption peaks at 1660 and 3300 cm^{-1}.

Stirring a suspension of this material (3.50 g) in aqueous sodium hydroxide (pH >10) for 1–2 hr furnished a dull white solid, which after drying weighed 2.80 g. Fractional crystallization from absolute alcohol afforded two materials. The more soluble component was isolated as white powdery crystals (2.1 g, 65%) of 4-piperonyl-7,8-dimethoxyisoquinoline (**10d**), mp 124–125° (slight preliminary sintering). Further crystallizations brought the melting point to 124–125° (no sintering).

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.58; H, 5.29; N, 4.32.

A 15% solution of **10d** in deuteriochloroform showed nmr signals at 3.98 (3 H, s, OCH_3), 4.09 (3 H, s, OCH_3), 4.25 (2 H, s, $ArCH_2$), 5.89 (2 H, s, OCH_2O), 6.70 (3 H, s, 3 ArH), 7.60–7.90 (2 H, m, 2 ArH), 8.30 (1 H, s, position 3), and 9.50 ppm (1 H, broad singlet, position 1).

The less soluble component (0.21 g, 6.5%, mp 238–242°), which was taken as 3,4-dimethoxy-8,9-methylenedioxy-11H-indeno[1,2-c]isoquinoline (**11d**), was crystallized from 1:1 ethanol–chloroform to a constant melting point of 242–243.5°.

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.10; H, 4.81; N, 4.33.

A 15% solution of this indenoisoquinoline **11d** in trifluoroacetic acid showed the following nmr signals: 4.24 (5 H, s, OCH_3 plus $ArCH_2$), 4.39 (3 H, s, OCH_3), 6.17 (2 H, s, OCH_2O), 7.28 (1 H, s, position 7 or 10), 7.60 (1 H, s, position 7 or 10), 8.12 (2 H, s, positions 1 and 2), and 9.52 ppm (1 H, d J = 8 cps, position 5).

4-Veratryl-7,8-dimethoxyisoquinoline (10c).—Use of veratraldehyde in place of benzaldehyde in the above condensation furnished a red crystalline hydrochloride precipitate (70%) showing a color transformation to yellow at 135–140° and melting at 171–173°. Recrystallizations from absolute alcohol gave analytically pure 4-veratryl-7,8-dimethoxyisoquinoline hydrochloride (**10c**·HCl), mp 172–173°, with the same color change at 135–140°.

Anal. Calcd for $C_{20}H_{22}ClNO_4$: C, 63.91; H, 5.90; Cl, 9.43; N, 3.73. Found: C, 63.70; H, 6.08; Cl, 9.21; N, 3.84.

This compound as a mineral oil mull showed infrared absorption peaks at 1650, 2600 broad (unexplained), and 3400 cm^{-1}.

The free base **10c** in the form of white powdery crystals from benzene was obtained in 85% yield. The melting point, 251–252° (sintering at 233°), could not be improved by further recrystallizations.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.68; H, 6.01; N, 4.13.

A 15% solution of 4-veratryl-7,8-dimethoxyisoquinoline (**10c**) in trifluoroacetic acid showed nmr signals at 3.78 and 3.91 (8 H, two singlets, two benzyl OCH_3 plus $ArCH_2$), 4.17 and 4.31 (6 H, two singlets, two isoquinoline OCH_3 groups), 6.68–8.60 (7 H, complex), and 9.64 ppm (1 H, d, J = 3 cps, position 1).

4-*m*-Anisyl-7,8-dimethoxyisoquinoline Hydrochloride (10b·HCl).—The crystalline yellow hydrochloride obtained when *m*-anisaldehyde was taken as starting aldehyde melted at 104–105° (sintering at 93°). A sample, prepared for analysis by recrystallization from ethanol, showed mp 104–105° (sintering at 100°).

Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; Cl, 10.25; N, 4.05. Found: C, 65.68; H, 5.84; Cl, 10.19; N, 4.17.

A mineral oil mull of this hydrochloride showed infrared absorption peaks at 1670 and 3400 cm^{-1}.

A 20% solution of 4-*m*-anisyl-7,8-dimethoxyisoquinoline hydrochloride in trifluoroacetic acid showed nmr signals at 4.04, 4.06, and 4.10 (9 H, 3 s, 3 OCH_3), 5.33 (2 H, s, $ArCH_2$), 7.21 s, 7.38 s, and 7.4–8.2 m (6 H, 6 ArH's), 8.59 (1 H, s, position 3), and 9.05 ppm (1 H, d, J = 10 cps, position 1).

2-Methyl-4-piperonyl-7,8-dimethoxyisoquinolinium Iodide (9d).—A mixture of the 4-piperonylisoquinoline **10d** (2.0 g, 6.2 mmol) and methyl iodide (9.0 g, 63 mmol) in 50 ml of 1:1 ethanol–benzene was boiled for 5 min. The mixture was cooled, and the orange upper layer was decanted from the underlying dark, viscous layer. The upper layer to which a few drops of alcohol was added was brought to a boil and then cooled. The precipitated crystals were collected by filtration, and the filtrate, treated with 3 g of methyl iodide, was allowed to react at room temperature for an hour. Cooling produced another crop of crystals. The mother liquor was combined with the original lower layer. Concentration and cooling deposited more product, which was crystallized from ethanol (decolorizing carbon used) before it was combined with the first two crops. The combined yellow methiodide **9d** (2.3 g or 81%) showed mp 190–192° with preliminary sintering. A sample prepared for analysis by recrystallization from ethanol melted at 192–193° (sintering at 183°).

Anal. Calcd for $C_{20}H_{20}INO_4$: C, 51.63; H, 4.33; I, 27.27; N, 3.01. Found: C, 51.86; H, 4.48; I, 27.16; N, 3.09.

2-Methyl-4-veratryl-7,8-dimethoxyisoquinolinium Iodide (9c).—A solution of the isoquinoline base **10c** (3.4 g, 0.010 mol) and methyl iodide (13.5 g, 0.095 mol) in 80 ml of benzene was boiled for 5 min. Ethanol (10 ml) was added, and the mixture processed for recovery of the iodide in a manner similar to that described above. Yellow crystals of methiodide **9c** (3.6 g, 75%) were obtained that gradually decomposed at temperatures over 160°. Recrystallization from ethanol changed the melting point behavior only slightly.

Anal. Calcd for $C_{21}H_{24}INO_4$: C, 52.40; H, 5.03; I, 26.36; N, 2.91. Found: C, 52.13; H, 4.94; I, 26.35; N, 2.91.

2-Methyl-4-*m*-anisyl-7,8-dimethoxyisoquinolinium Iodide (9b).—Treatment of the hydrochloride of isoquinoline **10b** (2.77 g, 8.0 mmol) with water at pH >10 released the free base, which was isolated in the usual way to give a dark, viscous oil (2.1 g). This oil was dissolved in benzene (100 ml) containing 12.0 g (0.090 mol) of methyl iodide, and the solution was boiled for 5 min. Two crops of yellow crystalline product **9b** were taken and were recrystallized from alcohol to give 2.53 g (70%) of yellow 2-methyl-4-*m*-anisyl-7,8-dimethoxyisoquinolinium iodide, mp 161–162° (red at 148°; sintering at 160°). Further crystallization did not affect the melting point significantly.

Anal. Calcd for $C_{20}H_{22}INO_3$: C, 53.23; H, 4.92; I, 28.12; N, 3.10. Found: C, 53.21; H, 5.05; I, 27.95; N, 3.08.

A 20% solution in trifluoroacetic acid showed nmr signals at 3.90, 4.18, 4.31, 4.54 (4 s, 4 CH_3), 4.58 (s, $ArCH_2$), and 6.80–8.35 ppm (complex, ArH).

2-Methyl-4-benzyl-7,8-dimethoxyisoquinolinium Iodide (9a).—This methiodide was formed in ethanol solvent. The two crops isolated melted at 295–298°. Recrystallization from ethanol raised the melting point to 297–298°.

Anal. Calcd for $C_{19}H_{20}INO_2$: C, 54.17; H, 4.79; I, 30.12; N, 3.33. Found: C, 53.96; H, 4.81; I, 30.30; N, 3.26.

2-Methyl-4-piperonyl-7,8-dimethoxy-1,2-dihydroisoquinoline (12d).—The mixture obtained on adding powdered dry 2-methyl-4-piperonyl-7,8-dimethoxyisoquinolinium iodide (9d, 0.91 g or 1.96 mmol) to an ice-cold suspension of lithium aluminum hydride (0.72 g or 19 mmol) in 100 ml of dry ether was stirred at room temperature for 12 hr. A slow stream of nitrogen blanketed the green reaction mixture. With the stirred mixture maintained at 0°, drops of ice–water were added until no hydrogen was evolved. Filtration through a layer of filter aid removed the gelatinous precipitate. The clear ethereal filtrate was extracted with 10-ml portions of cold 6 *N* hydrochloric acid until the aqueous layer was colorless. The combined acid extracts, after one washing with ether, was cooled and was added dropwise to 15 ml of ice-cold, stirred 28% aqueous ammonia. The precipitate was collected, washed with a small amount of cold water, and air-dried on the funnel. The gray 1,2-dihydroisoquinoline product 12d obtained in this way weighed 0.47 g (71%) and melted at 95–98° (sintering at 90°). After crystallization from 1:1 aqueous alcohol, a sample appeared as shiny, off-white crystals, mp 97–98°.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13; double bonds, 1.0. Found: C, 70.61; H, 6.21; N, 4.17; hydrogen absorbed on catalytic hydrogenation, 0.98 molar equiv.

The infrared absorption spectrum of this compound as a mineral oil mull showed a sharp peak at 1660 cm^{-1}, which was associated with C=C.

This dihydroisoquinoline as a 10% deuteriochloroform solution gave nmr signals at 2.75 (3 H, s, $N-CH_3$), 3.54 (2 H, s, position 1), 3.83 (6 H, s, 2 $-OCH_3$), 4.23 (2 H, s, $ArCH_2$), 5.92 (3 H, s, OCH_2O+ position 3), 6.69 (2 H, s, positions 5 and 6), and 6.80 ppm (3 H, s, piperonyl ArH's).

2-Methyl-4-veratryl-7,8-dimethoxy-1,2-dihydroisoquinoline (12c).—2-Methyl-4-veratryl-7,8-dimethoxyisoquinolinium iodide (9c, 0.96 g or 2.0 mmol) was added to a cold, stirred suspension of lithium aluminum hydride (0.76 g or 20 mmol) in 100 ml of ether. The procedure thereafter was essentially the same as for the piperonyl analog. The light gray dihydroisoquinoline product 12c weighed 0.62 g (85%) and showed mp 92–94° (sintering at 85°). Crystallization from chloroform produced dull white crystals, mp 96–97°.

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.82; H, 7.10; N, 3.88.

A mineral oil mull showed the expected infrared absorption peak for C=C at 1640 cm^{-1}.

A 20% deuteriochloroform solution of 2-methyl-4-veratryl-7,8-dimethoxy-1,2-dihydroisoquinoline (12c) revealed absorptions at 2.70 (3 H, s, $N-CH_3$), 3.55 (2 H, s, position 1), 3.78, 3.80, 3.82 (12 H, 3 s, 4 $-OCH_3$), 4.21 (2 H, s, $ArCH_2$), 5.80 (1 H, s, position 3), 6.66 (2 H, s, positions 5 and 6), and 6.82 ppm (3 H, s, veratryl ArH's).

Cyclization of 2-Methyl-4-piperonyl-7,8-dimethoxy-1,2-dihydroisoquinoline (12d) to 3,4-Dimethoxy-6-methyl-8,9-methylenedioxy-5,6,12,13-tetrahydro-11H-indeno[1,2-c]isoquinoline (13d).

A. Cyclization in Methanol–Hydrochloric Acid.—A solution of dihydroisoquinoline 12d (0.30 g or 0.89 mmol) in a mixture of 5 ml of methanol plus 5 ml of concentrated hydrochloric acid was boiled under nitrogen for 0.5 hr and then allowed to cool to room temperature. The light orange precipitate was collected. Dilution of the filtrate with 3 ml of water produced more of this solid, which was combined with the first precipitate. The treatment of this orange solid (27 mg) is described below.

In a similar experiment starting with 0.5 g of dihydroisoquinoline 12d, the cooled filtrate remaining after the orange precipitate had been removed, was treated with ice-cold aqueous ammonia until basic. The brown turbid mixture was extracted with three 15-ml portions of 1:1 chloroform–benzene. The combined extracts were washed with a small volume of water, dried with magnesium sulfate, and stripped of solvent at room temperature and under reduced pressure. The brown semisolid residue (0.3 g from 0.5 g of dihydroisoquinoline 12d) was dissolved in 2 ml of chloroform and chromatographed through a 10 in. column of acid-washed Merck alumina (25 g). The developing solvents were first, 500 ml of benzene, and then three 250-ml portions of 1:1 benzene–chloroform. The last two 250-ml portions of eluate, containing material from a yellow band on the column, were combined and stripped of solvent to leave 105 mg (21%) of brown, semisolid tetrahydroindeno[1,2-c]isoquinoline 13d.

This compound as a 15% carbon tetrachloride solution showed nmr signals as follows (see 1 for numbering): 2.35 (3 H, s, $N-CH_3$), 2.82 (2 H, s, position 5), 3.75 and 3.79 (6 H, 2 s, 2 $-OCH_3$), other peaks between 2.00 and 4.35 (4 H, complex, positions 11, 12, 13), 5.86 (2 H, s, OCH_2O), and 6.66 and 6.70 ppm (4 H, 2 s, 4 ArH's). The same material in trifluoroacetic acid (10% solution) gave peaks at 3.13 (3+ H, s, $N-CH_3$), 3.61 (2+ H, s, position 5), 4.04 (6 H, s, 2 $-OCH_3$), other peaks between 2.8–4.2 (4 H, complex, positions 11, 12, 13), 6.02 (2 H, s, OCH_2O), and 6.5–7.1 ppm (4 H, complex, 4 ArH's).

A solid derivative of tetrahydroindenoisoquinoline 13d was prepared by allowing a solution of the brown semisolid (0.10 g) in 0.5 ml of trifluoroacetic acid to stand for 1 hr, adding 2 ml of ethanol, and cooling at 0° for several hours. The crystals were removed. A second crop could be isolated from the filtrate after it had been diluted with ether. The combined solids were crystallized from 1:1 ethanol–ether to give silky white crystals of the trifluoroacetate salt of tetrahydroindenoisoquinoline 13d, mp 180–182°. The yield was 0.12 g, *i.e.*, 90% from the free base or 20% from precursor dihydroisoquinoline 12d. Further crystallization brought the melting point to 182–182.5° (sintering at 181°).

Anal. Calcd for $C_{22}H_{22}F_3NO_6$: C, 58.28; H, 4.89; N, 3.09. Found: C, 58.52; H, 5.04; N, 3.33.

When the above-mentioned orange solid (mp 230–233° with preliminary changes) was crystallized from ethanol–ether, it melted at 232–233°. A sample was dried *in vacuo* at room temperature before analysis.

Anal. Calcd for $C_{19}H_{18}ClNO_5$ (*i.e.*, 11d·HCl·H_2O): C, 60.73; H, 4.83; Cl, 9.43; N, 3.73. Found: C, 60.61; H, 5.30; Cl, 9.43; N, 3.98.

The nmr spectrum of this material dissolved in trifluoroacetic acid was identical with that of 3,4-dimethoxy-8,9-methylenedioxy-11H-indeno[1,2-*c*]isoquinoline (11d) in the same solvent. The trifluoroacetate salt of the orange side product was compared with the same salt of 11d. The salts were prepared by allowing a solution of 20 mg of solid in 0.2–0.3 ml of trifluoroacetic acid plus 0.5 ml of ethanol to stand for a short while. The precipitate was collected, washed on the funnel with a few drops of ether–ethanol, and air dried. The two solids melted separately or when mixed in equal amounts at 238–240° (sintering at 237°). The infrared spectra of the two trifluoroacetate salts (mineral oil mulls) were identical.

Although the formulation of the side product as the hydrochloride of 3,4-dimethoxy-8,9-methylenedioxy-11H-indeno[1,2-*c*]-isoquinoline (11d) is consistent with its properties, how it appears at this point in the synthesis remains speculative. The compound was encountered in only one preparation.

B. Cyclization in Acetic Acid–Hydrochloric Acid.—A solution of 0.3 g (0.89 mmol) of 2-methyl-4-piperonyl-6,7-dimethoxy-1,2-dihydroisoquinoline (12d) in 10 ml of acetic acid containing 0.5 ml of concentrated hydrochloric acid was boiled under nitrogen for 1.5 hr. Cold 28% aqueous ammonia added in portions to the reaction mixture at temperatures below 15° made the mixture alkaline. Thereafter the processing was essentially the same as described above. The product, 3,4-dimethoxy-6-methyl-8,9-methylenedioxy-5,6,12,13-tetrahydro-11H-indeno-[1,2-*c*]isoquinoline (13d), weighed 0.23 g (75%). Its nmr spectrum was exactly the same as that obtained for the same compound from the methanol–hydrochloric acid cyclization. This material was suitable for use in the subsequent stages.

C. Unsuccessful Cyclizations.—When the 12d to 13d conversion was attempted with mixtures of 98% formic acid and 85% phosphoric acid at 100 or 80° and for periods ranging from 6–24 hr, no recognized product was isolated. Boiling a solution of dihydroisoquinoline 12d in concentrated hydrochloric acid for 6, 3, or 1 hr again gave no useful product.

Cyclization of 2-Methyl-4-veratryl-7,8-dimethoxy-1,2-dihydroisoquinoline (12c) to 3,4,8,9-Tetramethoxy-6-methyl-5,6,12,13-tetrahydro-11H-indeno[1,2-c]isoquinoline (13c). A. Cyclization in Ethanol–Hydrochloric Acid.—A solution of the dihydroisoquinoline 12c (0.20 g or 0.56 mmol) in 20 ml of concentrated hydrochloric acid and 5 ml of ethanol was boiled in an atmosphere

of nitrogen for 2 hr. The cooled mixture was extracted with small portions of ether to remove nonbasic materials and then made basic with ammonia in a manner similar to that already described for the piperonyl analog. The crude product **13c** (0.18 g) in 500 ml of 1:1 benzene–chloroform was passed through a 1 × 22 cm column of acid-washed alumina. The column was then washed with an additional 100 ml of the same solvent. The combined eluates, stripped of solvent under reduced pressures at room temperature, left 0.175 g (88%) of 3,4,8,9-tetramethoxy-6-methyl-5,6,12,13-tetrahydro-11H-indeno-[1,2-c]isoquinoline (**13c**) as a brown viscous oil, which was suitable for use in the next step.

As a 10% solution in carbon tetrachloride, this material showed nmr signals at 2.40 (2 H, m, positions 12 and 13), 3.30 (2 H, s, position 5), 3.68–4.00 (17 H, 5 s, 4 $-OCH_3$ plus $N-CH_3$ plus position 11), and 6.50–6.90 ppm (4 H, m, 4 ArH's).

B. Cyclization in Acetic Acid–Hydrochloric Acid.—A mixture of dihydroisoquinoline **12c** (0.20 g or 0.56 mmol), 0.3 ml of concentrated hydrochloric acid, and 10 ml of glacial acetic acid was boiled under nitrogen for 4 hr. The cooled reaction mixture, after dilution with 200 ml of water, was washed with several small portions of ether, and thereafter processed essentially as described above. The crude tetramethoxy cyclization product **13c** was obtained as a brown viscous oil (0.17 g, 86%) suitable for use without purification.

3,4-Dimethoxy-6-methyl-8,9-methylenedioxy-12,13-dihydro-11-H-indeno[1,2-c]isoquinolinium Salt of 14d.—A mixture of tetrahydro derivative **13d** (0.10 g, 0.30 mmol), iodine (0.23 g, 1.8 mmol), potassium acetate (0.35 g, 3.6 mmol), and 10 ml of ethanol was held at 40° with occasional swirling for 10 min. The initial turbidity disappeared on warming to 40°. Cooling the reaction mixture to room temperature deposited the black crystalline periodide of dihydroindenoisoquinolinium cation **14d**. Crystallization from ethanol furnished shiny orange crystals (0.132 g or 62%), mp 148.5–149°. Further crystallization did not affect the melting point.

Anal. Calcd for $C_{20}H_{20}I_3NO_4$: C, 33.41; H, 2.80; I, 52.94; N, 1.95. Found: C, 33.66; H, 2.74; I, 52.95; N, 1.97.

To get the simple iodide, the periodide (87 mg or 0.12 mmol) in 5 ml of warm methanol was treated with solid sodium sulfite in small portions until the red-brown color changed to bright orange-yellow. Cooling gave bright yellow crystals of 3,4-dimethoxy-6-methyl-8,9-methylenedioxy-12,13-dihydro-11H-indeno[1,2-c]isoquinolinium iodide of **14d**, (44 mg or 80%), mp 168.5–169° (sintering at 166°). Recrystallization did not change the melting point.

Anal. Calcd for $C_{20}H_{20}INO_4$: C, 51.63; H, 4.33; I, 27.27; N, 3.01. Found: C, 51.56; H, 4.09; I, 27.51; N, 2.87.

This dihydro iodide as a mull with mineral oil showed an infrared absorption peak at 1665 cm^{-1} attributable to $C{=}N^+$.

A 7% solution of the iodide of **14d** in deuteriochloroform was scanned in the nmr spectrophotometer. The signals were weak, so that a time-averaging computer had to be used. Peaks appeared as follows: 2.85 (2 H, m, positions 12 and 13), 3.78 (8 H, s, 2 $-OCH_3$ plus position 11), 4.12 (3 H, s, $N-CH_3$), 5.84 (2 H, s, OCH_2O), 6.2–7.5 (4 H, m, positions 1, 4, 7, 10), and 9.40 ppm (1 H, broad s, position 5).

3,4-Dimethoxy-6-methyl-8,9-methylenedioxy-11H-indeno-[1,2-c]isoquinolinium Iodide (15d). A. By Methylation of Free Base 11d.—A mixture of 3,4-dimethoxy-8,9-methylenedioxy-11H-indeno[1,2-c]isoquinoline (**11d**, 1.0 g, or 3.1 mmol) and methyl iodide (4.5 g or 31 mmol) in 25 ml of ethanol plus 25 ml of benzene was boiled for 2.5 hr. Allowing the yellow reaction mixture to stand overnight at room temperature produced bright yellow crystals. Recrystallization from ethanol afforded the methiodide **15d** (0.98 g or 71%), mp 248–250° (preliminary sintering). Further recrystallization from the same solvent brought the melting point to a constant value of 249–250° (preliminary sintering).

Anal. Calcd for $C_{20}H_{18}INO_4$: C, 51.85; H, 3.92; I, 27.39; N, 3.02. Found: C, 52.12; H, 4.02; I, 27.15; N, 3.19.

B. By Iodine Dehydrogenation of Dihydro Compound 14d.—Iodine (80 mg or 0.30 mmol) in 10 ml of ethanol was added to a solution of dihydroindenoisoquinolinium iodide of **14d** (50 mg or 0.15 mmol) in 10 ml of ethanol, and the mixture was boiled gently for 2 hr. Solvent was removed under vacuum at room temperature. Allowing the brown residue to stand overnight in 2 *N* sulfurous acid furnished a dull yellow powder, which on crystallization from 1:1 ethanol–acetone gave 3,4-dimethoxy-6-methyl-8,9-methylenedioxy-11H-indeno[1,2-c]isoquinolinium iodide (**15d**, 31 mg or 60%) as bright yellow crystals, mp 243–245° (sintering at 197°). Mixed with the same product from part A, this compound melted at 244–247° (sintering at 197°). The infrared absorption spectra of the two materials were identical.

C. By Iodine Dehydrogenation of Tetrahydroindenoisoquinoline 13d.—A mixture of tetrahydro compound **13d** (100 mg or 0.30 mmol), iodine (230 mg or 1.8 mmol), potassium acetate (350 mg or 3.6 mmol), and 10 ml of absolute alcohol was treated essentially as described in part B. The bright yellow crystals of the methiodide product **15d** (106 mg or 60% calculated from dihydroisoquinoline **12d**) showed mp 245–248° (sintering at 198°) by itself and mp 246–248° (sintering at 198°) when mixed with the product from part A. The two materials showed identical infrared absorption spectra.

3,4,8,9-Tetramethoxy-6-methyl-11H-indeno[1,2-c]isoquinolinium Iodide (15c).—A solution of tetramethoxytetrahydroindenoisoquinoline **13c** (0.175 g or 0.48 mmol), iodine (0.45 g or 1.77 mmol), potassium acetate (0.50 g or 5.1 mmol), and 1:1 methanol–ethanol (50 ml) was boiled for 2 hr. Treatment with 2 *N* sulfurous acid changed the dark color to bright orange. Cooling the concentrated mixture gave the desired iodide. A second crop could be obtained by further concentration. Recrystallization of the combined solids from ethanol afforded dark yellow crystals of 3,4,8,9-tetramethoxy-6-methyl-11H-indeno-[1,2-c]isoquinolinium iodide (**15c**, 0.18 g or 79%), mp 219–220° dec. Further crystallization did not change the melting point.

Anal. Calcd for $C_{21}H_{22}INO_4$: C, 52.62; H, 4.63; I, 26.48; N, 2.92. Found: C, 52.80; H, 4.80; I, 26.42; N, 2.89.

3,4-Dimethoxy-6-methyl-8,9-methylenedioxy-11H-indeno-[1,2-c]isoquinolinium Nitrate (15d).—Dowex 1 X-8, the ion-exchange resin used here, contains quaternary ammonium groups attached to a partially cross-linked styrene–divinylbenzene copolymer. A 1.25 × 40 in. column was prepared by adding a suspension of 400 g of thoroughly washed resin (100–200 mesh) in its chloride form to a glass tube. Care was taken to exclude air bubbles. Sodium nitrate solution (0.5 *M*) was passed through the column until the emergent liquid gave no precipitate with silver nitrate. The column was then washed with 2 l. of water.

A solution of **15d** iodide (1.4 g or 3.1 mmol) in 4 l. of distilled water was passed through the column at the rate of 200 ml/hr. This was followed by 2 l. of water. The combined solution and washings were evaporated under reduced pressure at room temperature. The residual orange solid was crystallized from absolute alcohol to give the desired indenoisoquinolinium nitrate **15d** (1.08 g or 90%), which decomposed in the range 200–220°. Further crystallization from the same solvent gave an analytically pure sample.

Anal. Calcd for $C_{20}H_{18}N_2O_7$: C, 60.30; H, 4.55. Found: C, 60.46; H, 4.79.

3,4,8,9-Tetramethoxy-6-methyl-11H-indeno[1,2-c]isoquinolinium Nitrate (15c).—The iodide of **15d** was converted to its nitrate essentially according to the above directions. Crystallization of the crude product from ethanol gave small golden yellow flakes of the nitrate (75%), mp 229–231° dec. Further crystallizations gave a sample for analysis still with the same melting point characteristics.

Anal. Calcd for $C_{21}H_{22}N_2O_7$: C, 60.86; H, 5.35. Found: C, 60.64; H, 5.48.

Registry No.—**4**, 16503-92-7; **4** dibenzoyl derivative, 16503-93-8; **5**·HCl, 15365-56-7; **6**, 16503-95-0; **7**, 16503-96-1; **8a**·HI, 16503-97-2; **9a**, 16503-98-3; **9b**, 16503-99-4; **9c**, 16520-66-4; **9d**, 16504-00-0; **10a**, 15539-33-0; **10b**·HCl, 16504-02-2; **10c**, 16504-03-3; **10c**·HCl, 17520-67-5; **10d**, 16504-04-4; **11d**, 16504-05-5; **11d**·HCl, 16504-06-6; **12c**, 16504-07-7; **12d**, 16504-08-8; **13c**, 16504-09-9; **13d**, 16504-10-2; **14d** periodide, 16482-30-7; **14d** iodide, 16504-11-3; **15c** iodide, 16504-12-4; **15d** iodide, 16504-13-5; **15d** nitrate, 16504-14-6; **15c** nitrate, 16504-15-7; **16a**, 15539-31-8; **16d**, 16503-34-7; chelerythrine, 2870-15-7.

Acknowledgment.—We wish to thank the American Cancer Society for a grant (T-300A) in support of this

work and the National Science Foundation for Research Equipment Grant GP3618 that provided funds for the purchase of a Varian A-60 nmr spectrometer. Also, we wish to acknowledge the kind cooperation of Dr. J. M. Bobbitt in informing us of his work before publication and of Mr. D. W. Smith, Monsanto Chemical Company, Everett, Mass., for taking some of the nmr spectra.

Acylindoles. I. The Synthesis and Transformations of 3-(2-Aminobenzoyl)indoles

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Received January 12, 1968

The acid-catalyzed rearrangement of appropriately substituted 3-(2-aminobenzoyl)indoles and 5-(3-indolyl)-2,3-dihydro-1,4-benzodiazepines was found to result in the formation of indolo[3,2-*c*]quinolines, 3-(2-aminophenyl)-4(1H)-quinolones, and an imidazo[1,2-*a*]indolo[3,2-*c*]quinoline. An independent synthesis of the 3-(2-aminophenyl)-4(1H)-quinolones is described. The requisite indolylbenzodiazepines were prepared from the corresponding 3-(2-fluorobenzoyl)indoles by treatment with ethylenediamine.

The synthesis of heterocyclic systems such as dibenzodiazocines,[1] quinazolines,[2] benzodiazepines,[3] indoles,[4] and quinolones[5] from aromatic *o*-amino ketones has now been well established, and consequently we have investigated the synthesis and subsequent transformations of some 3-(2-aminobenzoyl)indoles. While these compounds can be utilized as starting materials for the synthesis of other heterocyclic moieties, we have found that these indoles readily undergo acid-catalyzed rearrangements to give quinolones and indoloquinolines.

The preparation of the aminobenzoylindoles was effected by a nucleophilic exchange of fluorine for amines on 3-(2-fluorobenzoyl)indole (**1**)[6] (Scheme I). Compound **1** was obtained by the acylation of indolylmagnesium bromide with *o*-fluorobenzoyl chloride. Also isolated from this reaction was 1,3-di(2-fluorobenzoyl)indole which was readily converted into **1** by treatment with aqueous alkali. A Vilsmeier type of reaction carried out as described by Anthony,[7] for the synthesis of 3-benzoylindole was also utilized, but the yield of **1** was, in this instance, much lower than that obtained from the Grignard reaction. Alkylation of **1** with dimethyl sulfate in the presence of sodium hydroxide afforded the N-methyl derivative **2**.

Treatment of **1** with ethylenediamine gave the corresponding indolylbenzodiazepine **3**, while the amination of **2** with benzylamine gave the substituted aminobenzoylindole **4**. Treatment of these acyl- or iminoindoles with acid resulted in both cases in rearrangement. Thus, compound **4** when treated with hot aqueous acid afforded a mixture of the quinolone **5** and the indoloquinoline **6**.[8] Under somewhat similar conditions, compound **3** gave the corresponding quinolone **7**.

More energetic treatment of **3** with acid gave the indoloquinoline **8**, which could also be obtained from compound **7** under similar conditions. By heating **7**, in high-boiling solvents, either the previously described indoloquinoline **9**[9] or a mixture of **9** and the dealkylated quinolone **10** was obtained. Thus, by heating a solution of **7** in diphenyl ether under reflux, compound **9** was the only detectable product, while in nitrobenzene both **9** and **10** were obtained.

The mechanism of the rearrangement of **4** to the quinolone **5** can be explained by the initial protonation of **4** at the carbonyl oxygen[10] to give the indolenine intermediate A (Scheme II). Nucleophilic addition of the anilino N–H function to the polarized C=N bond of A, as shown, followed by hydrolytic cleavage of the resultant intermediate B at the C–N bond of the five-membered ring would then lead directly to the observed quinolone **5**.

Evidence that the mechanism for the conversion of **3** into **7** is similar and initially involves the hydrolytic cleavage of the azomethine bond was given by the observation that base cleavage of the 4-methyl quaternary salt of **3** (compound **11**) gave the corresponding methylaminoethylaminoindole **12**, which when subjected to hot mineral acid, underwent a similar rearrangement to give a 60% yield of the quinolone **13** (Scheme III). A minor product isolated from the reaction mixture was the indoloquinoline **14**, isolated as the dihydrochloride hemihydrate. The formation of the indoloquinolines from the intermediate quinolones is self-explanatory and would involve condensation of the anilino amine with the quinolone carbonyl group.

The proof of structure for the quinolones **5**, **7**, and **10** was given by the following unequivocal syntheses. Ethyl 2-nitrophenylacetate upon treatment with N,N-dimethylformamide diethyl acetal[11] afforded the aminoacrylate **15**. This was not isolated but was directly converted by acid treatment into the acrylate **16**[12] (Scheme IV).

(1) W. Metlesics, T. Resnick, G. Silverman, R. Tavares, and L. H. Sternbach, *J. Med. Chem.*, **9**, 633 (1966).

(2) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.* **30**, 3957 (1965).

(3) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962).

(4) R. I. Fryer, J. V. Earley, and L. H. Sternbach, *ibid.*, **32**, 3728 (1967).

(5) R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, 3057 (1964).

(6) The susceptibility of a fluorine *ortho* to a carbonyl group toward nucleophilic exchange with amines has previously been demonstrated by R. I. Fryer, J. V. Earley, and L. H. Sternbach, *ibid.*, 4979 (1963). See also H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **31**, 2319 (1966).

(7) W. C. Anthony, *ibid.*, **25**, 2049 (1960).

(8) For convenience and simplicity, the compounds described throughout the discussion will be referred to by number or letter corresponding to their correct structures.

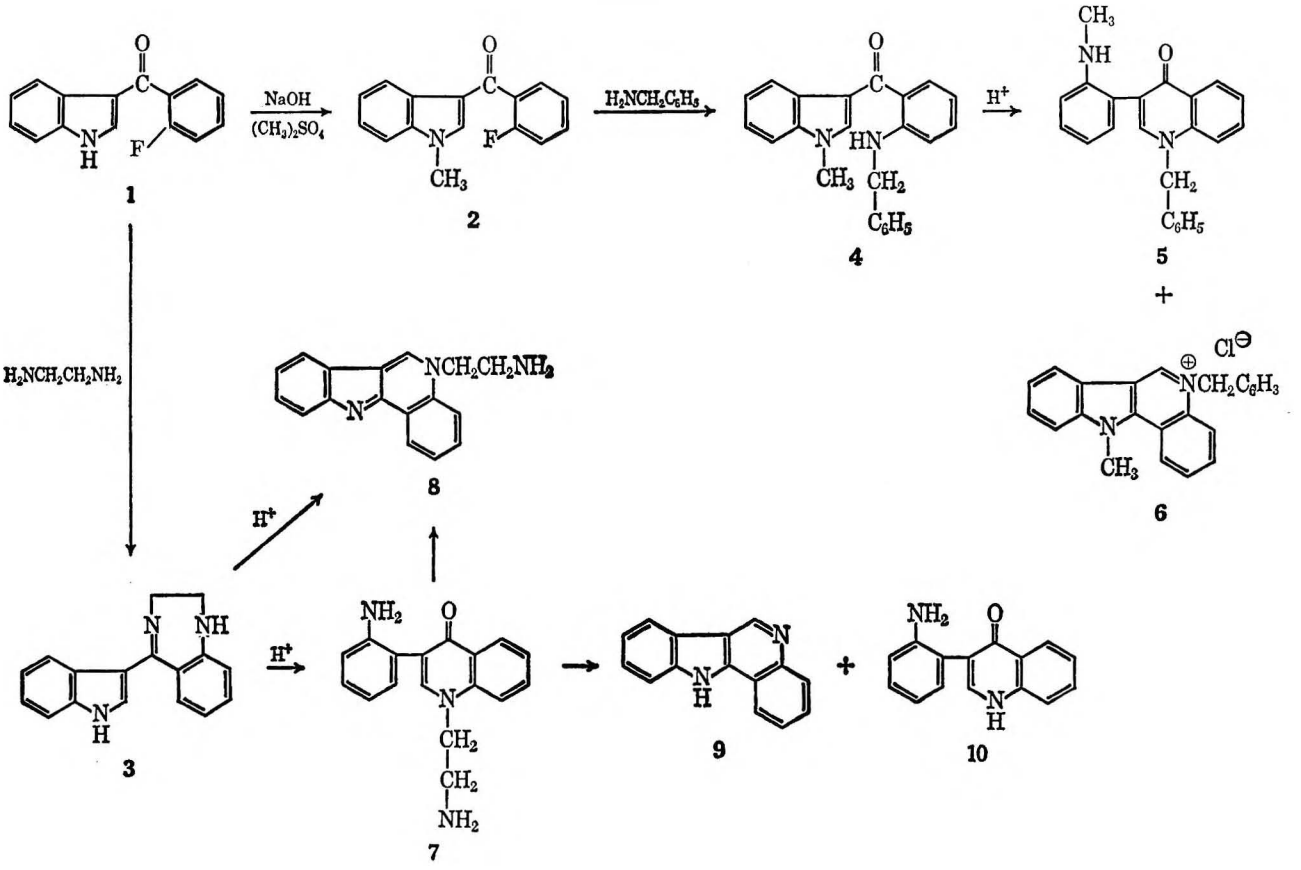
(9) W. O. Kermack and N. E. Storey, *J. Chem. Soc.*, 607 (1950).

(10) R. L. Hinman and E. B. Whipple [*J. Amer. Chem. Soc.*, **84**, 2534 (1962)] have established that the principal conjugate acid of indole in strong acid is the 3-protonated isomer. The 3-acylindoles have been found to protonate primarily at the acyl oxygen [G. Berti and A. da Settimo, *Gazz. Chim. Ital.*, **91**, 728 (1961)].

(11) H. Meerwein, *Angew. Chem.*, **71**, 530 (1959).

(12) Formylation of ethyl 2-nitrophenylacetate with sodium and ethyl formate was unsuccessful.

SCHEME I



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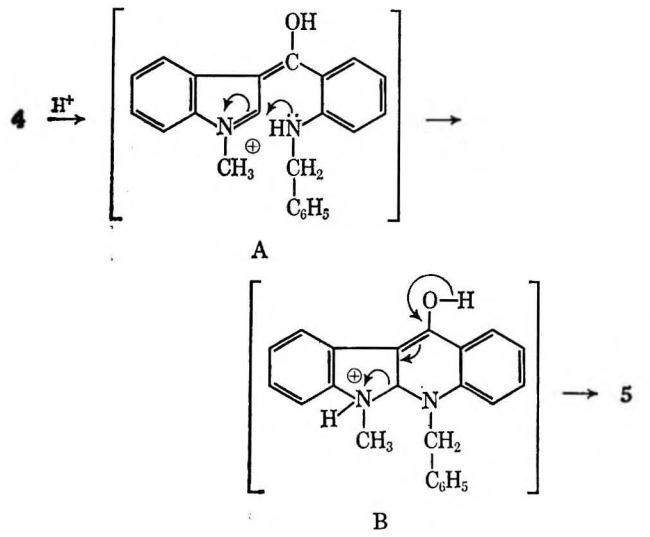
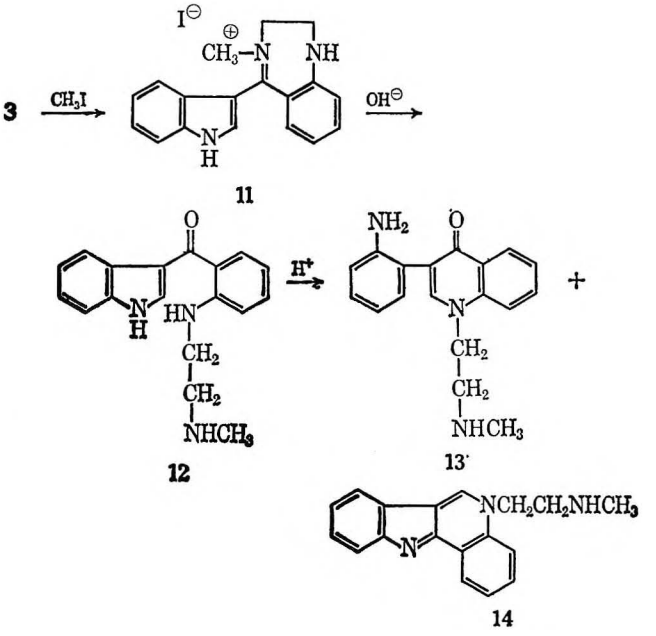


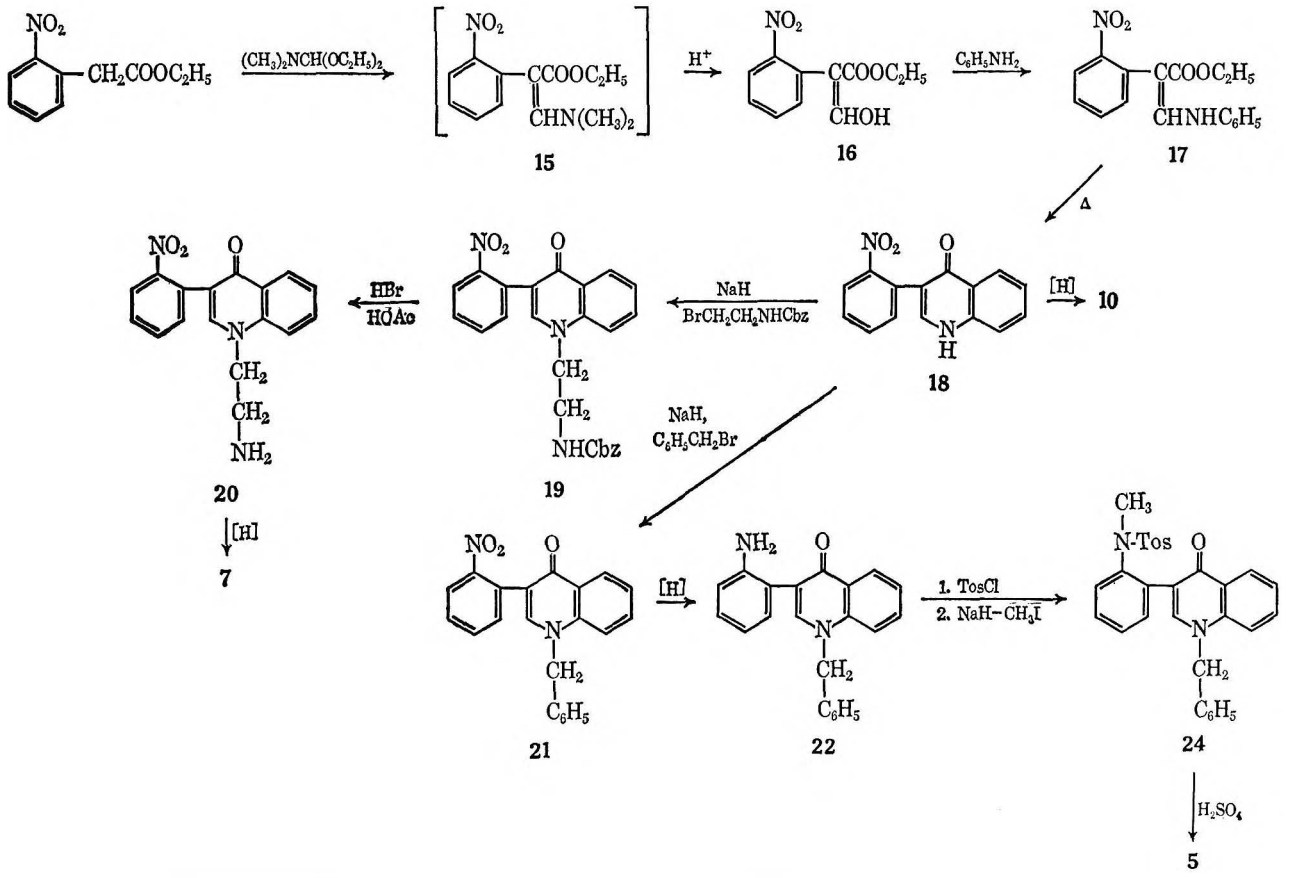
SCHEME III



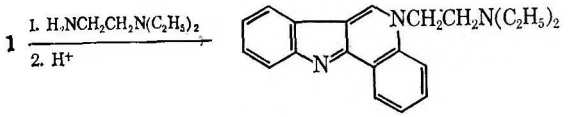
Treatment of **16** with aniline gave **17** as a mixture of *cis* and *trans* isomers. The isomers were not characterized and, in general, were not separated since both could be cyclized by heating under reflux in diphenyl ether to give the desired quinolone (compound **18**). Catalytic reduction of the nitro group gave an authentic sample of the corresponding aminoquinolone **10** which was identical in all respects with the substance obtained by subjecting **7** to prolonged heating in nitrobenzene. Treatment of **18** with sodium hydride followed by the addition of carbobenzoxy-2-bromoethylamine gave compound **19**. Cleavage of the carbobenzoxy group with hydrogen bromide in acetic acid gave the free amino derivative **20**. Reduction of **20** then gave an authentic sample of **7** which was identical with the product obtained by acid-catalyzed rearrangement of **3**. By forming the N-benzyl derivative of **18** (compound **21**), carrying out the reduction and alkylation steps as shown in Scheme IV, an authentic sample of **5** was also obtained.

The structure of the indoloquinoline **9** was confirmed by a comparison with an authentic sample.[9] The structures of the substituted indoloquinolines **8** and **14**

SCHEME IV



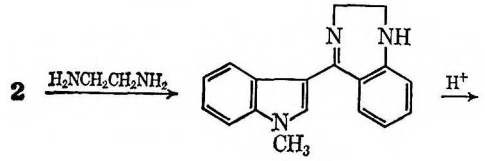
were assigned primarily on the basis of compatible physical data. However, both compounds have ultraviolet spectra almost superimposable on that of the previously described N,N-diethylaminoethyl derivative, compound **25**.[9] Furthermore, treatment of compound **1** with N,N-diethylethylenediamine followed by acid-catalyzed rearrangement of the product gave compound **25** which was then converted into the dimethiodide and



25

was compared with and shown to be identical with an authentic sample.[9] Compound **6** upon heating at reduced pressure readily underwent debenzylation to yield 11-methyl-11H-indolo[3,2-*c*]quinoline.[13]

An analogous rearrangement of an indolodiazepine was observed when **26**, prepared by treatment of **2** with



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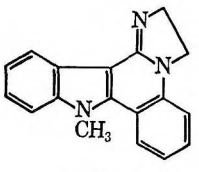

27

ethylenediamine, was subjected to acid hydrolysis. In this instance the imidazoindoloquinoline **27** was the only product isolated. The assignment of the imidazoindoloquinoline structure follows by analogy and also from consistent spectral data. For example, the mass spectrum showed the parent ion at *m/e* 273, compatible with structure **27**, in addition to the strong loss of one and two hydrogens (*m/e* 272 and 271). Also in accord with structure **27** were the infrared and nmr spectra which were completely devoid of any N–H absorption.

Experimental Section[14]

3-(2-Fluorobenzoyl)indole (1). A. From *o*-Fluoro-N,N-dimethylbenzamide, Indole, and Phosphorus Oxychloride.—A solution of 15.9 g (0.135 mol) of indole, 44.8 g (0.268 mol) of *o*-fluoro-N,N-dimethylbenzamide, and 15 ml of $POCl_3$ was heated with vigorous stirring. After reaching 88° a vigorous exothermic reaction occurred and ice-bath cooling was applied. The temperature rose to 150° and then gradually fell to below 60°. The mixture was then heated for 3 hr at 80°. The brown solution was cooled in ice, basified carefully with 3 *N* NaOH and extracted with CH_2Cl_2. After washing with 0.1 *N* HCl and water, the organic layer was separated, dried (Na_2SO_4), and filtered through 100 g of Florisil. Evaporation of the solvent gave an amber oil which was treated with ether and refrigerated. Filtration gave 6.4 g (17%) of pale yellow prisms, mp 195–199°. Recrystallization from ethanol gave white prisms, mp 195–198°.

Anal. Calcd for $C_{15}H_{10}FNO$: C, 75.30; H, 4.21. Found: C, 75.10; H, 4.29.

(13) A. K. Kiang, F. G. Mann, A. F. Prior, and A. Topham, *J. Chem. Soc.*, 1319 (1956).

(14) All melting points are corrected and were taken in capillary tubes on a Thomas–Hoover melting point apparatus. Infrared spectra were determined using a Beckman IR-9 spectrophotometer, nmr spectra with a Varian A-60 spectrometer, mass spectra with a CEC 21-100 spectrometer, and ultraviolet spectra with a Cary Model 14 spectrophotometer. The ultraviolet ϵ values refer to $\epsilon \times 10^{-3}$.

B. From Indolylmagnesium Bromide and o-Fluorobenzoyl Chloride.—To phenylmagnesium bromide, prepared from 24.3 g (1 g-atom) of magnesium and 176 g (1.1 mol) of bromobenzene in 300 ml of ether, was added dropwise with stirring, 130 g (1.1 mol) of indole in 300 ml of benzene. The resultant solution was heated under gentle reflux for 1 hr and cooled in ice, and 179 g (1.1 mol) of o-fluorobenzoyl chloride in 200 ml of benzene was added with vigorous stirring during 2 hr. The resultant mixture was heated under gentle reflux for 45 min, then cooled in ice, and hydrolyzed by the addition of 400 ml of 10% NH_4Cl in water. The reddish solid[15] was filtered, washed with water and ether, and then hydrolyzed by heating on the steam bath for 20 min with a mixture of 600 ml of acetone–100 ml of methanol and 200 ml of 5% NaOH. The resultant mixture was poured into 1800 ml of water and, after cooling, was filtered and recrystallized from acetone–methanol to yield 54 g of 1 as off-white prisms, mp 195–197°.

The filtrate obtained after separating the red solid and its ether washings were combined and the organic layer was separated, washed, dried, and concentrated. The resultant red, viscous mixture was triturated with hot ethanol, cooled, and filtered to give white crystals of 1,3-di(o-fluorobenzoyl)indole, mp 132–134°.

Anal. Calcd for $C_{22}H_{13}F_2NO_2$: C, 73.13; H, 3.63; N, 3.85. Found: C, 73.25; H, 3.72; N, 3.90.

The solid was hydrolyzed by warming it on the steam bath for 20 min in a mixture of 300 ml of acetone and 150 ml of 10% NaOH. After pouring into water the mixture was filtered to give 56 g of 1, mp 195–198°. The total yield of product was 110 g (46%).

1-Methyl-3-(2-fluorobenzoyl)indole (2).—A stirred solution of 9 g (0.038 mol) of 1 in 450 ml of acetone was treated with a solution of 41 g of KOH in 200 ml of water followed by the dropwise addition of 36 ml of dimethyl sulfate. After stirring for 30 min at room temperature the acetone was removed at reduced pressure, and the resultant precipitate was filtered, washed with water, and recrystallized from methanol to yield 6.1 g (63%) of white needles, mp 105–107°.

Anal. Calcd for $C_{16}H_{12}FNO$: C, 75.87; H, 4.78. Found: C, 76.05; H, 4.59.

5-(3-Indolyl)-2,3-dihydro-1H-1,4-benzodiazepine (3).—A solution of 100 g (0.436 mol) of 1, 500 ml of pyridine, and 234 ml of ethylenediamine was heated under reflux for 20 hr. The solution was concentrated at reduced pressure, and the resultant oily residue was dissolved immediately in 1 l. of hot CH_2Cl_2. After overnight refrigeration, filtration gave 49 g of 3 as pale yellow needles, mp 212–216°. Recrystallization from ethanol–water raised the melting point to 223–225°.

Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.09; H, 5.46; N, 16.09.

The dichloromethane filtrate was concentrated to dryness and the residue hydrolyzed by heating under reflux for 5 hr with a mixture of 250 ml of ethanol and 250 ml of 2 *N* H_2SO_4. After cooling, the precipitate was filtered and washed to give 17 g of 1. On the basis of recovered starting material, the yield of 3 was 54%.

1-Methyl-3-[2-(benzylamino)benzoyl]indole (4).—A solution of 20 g (0.08 mol) of 2 in 50 ml of pyridine and 36 ml of benzylamine was heated under reflux for 20 hr. The mixture was concentrated under reduced pressure to remove excess solvent, and the residue was treated with 100 ml of ethanol and 100 ml of 2 *N* sulfuric acid. The resultant mixture was refluxed for 8 hr and then concentrated to small volume. The residue was extracted with CH_2Cl_2, washed with water, dried over sodium sulfate, and concentrated to a yellow oil. This oil was dissolved in 75 ml of 2-propanol and refrigerated. Filtration gave 13.4 g of impure yellow solid. The solid was dissolved in benzene and placed on silica gel, and the silica gel was washed with *ca.* 2 l. of methylene chloride. Evaporation of the solvent gave 8.9 g (33%) of yellow solid, mp 133–135°. Recrystallization from 2-propanol yielded yellow prisms, mp 133–135°.

Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.29; H, 5.86; N, 8.11. Found: C, 81.15; H, 5.92; N, 8.23.

1-Benzyl-3-(2-methylaminophenyl)-4(1H)-quinolone (5) and 5-Benzyl-11-methyl-11H-indolo[3,2-c]quinolinium Chloride (6).—A solution of 10.2 g (0.03 mol) of 4 in a mixture of 175 ml of 6 *N* HCl and 200 ml of methanol was heated under reflux for 4 hr. The methanol was removed under reduced pressure, and the residue was cooled in ice and basified with 10% NaOH. The resultant precipitate was filtered. This precipitate was suspended in hot CH_2Cl_2 and filtered, and the undissolved solid was washed with additional CH_2Cl_2. The organic filtrate was dried over sodium sulfate and filtered through 120 g of neutral Woelm alumina, and the alumina was washed with 500 ml of CH_2Cl_2 and then 500 ml of $CHCl_3$. Evaporation of the solvent and addition of 50 ml of ether to the residue gave 4.4 g of 5 as a pale yellow solid, mp 205–211°. Recrystallization from methanol–dichloromethane gave white prisms: mp 213–215°; nmr (DMSO-d_6), δ 8.33 (s, 1, C=CH—N—$CH_2C_6H_5$), 5.03 (m, 1, J = 4.5 Hz, H–N–CH_3), and 2.72 (d, 3, J = 4.5 Hz, NH–CH_3); uv max (2-propanol), 213 mμ (ϵ 46.1), 241 (28.7), 296 (infl) (9.8), 326 (14.0), and 340 (infl) (12.5); (0.1 *N* HCl), 214 (32.9), 261 (32.5), 310 (infl) (8.7), 329 (13.4), and 339 (12.1); (0.1 *N* KOH), 242 (31.0), 296 (infl) (8.5), 327 (13.1), and 339 (33.9).

Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.03; H, 6.06; N, 8.02.

The solid (1.5 g) undissolved by the CH_2Cl_2 was recrystallized from methanol–ether to give white needles, mp 278–284°. This quaternary salt failed to give satisfactory microchemical data, and therefore it was converted into its chloride by suspending it in water with 5 g of freshly prepared silver chloride. After heating at 55° for 1 hr, the mixture was filtered and the filtrate was concentrated to give white crystals, mp 278–282°. Recrystallization from methanol gave colorless needles, mp 288–291°.

Anal. Calcd for $C_{23}H_{19}ClN_2$: C, 76.98; H, 5.34; N, 7.81. Found: C, 77.11; H, 5.35; N, 7.87.

Vacuum sublimation of 6 at 210–220° (0.1 mm) gave 11-methyl-11H-indolo[3,2-c]quinoline, as the sublimate, mp 142–144° (lit.[12] mp 146°); when mixed with an authentic sample, the melting point was 140.5–142°; the infrared spectra were identical.

Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.84; H, 5.25; N, 11.89.

1-(2-Aminoethyl)-3-(2-aminophenyl)-4(1H)-quinolone (7). A. By Hydrolysis of 3.—A solution of 5 g (0.019 mol) of 3 dissolved in a mixture of 25 ml of ethanol and 25 ml of 2 *N* sulfuric acid was heated under reflux for 32 hr and concentrated. The residual solid was dissolved in water, basified with 2 *N* NaOH and extracted with CH_2Cl_2. The organic layers were combined, washed with water, and dried over sodium sulfate. The solvent was concentrated to a small volume and ether was added until a solid began to separate. Refrigeration and filtration gave 3.5 g (70%) of yellow crystals, mp 163–165°. Recrystallization twice from ethanol–ether gave pale yellow needles: mp 162.5–163.5; ir (KBr), 3370, 3350, 3300 (NH_2), and 1610 cm^{-1} (C=O); nmr (DMSO-d_6), δ 8.05 (s, 1, =CH—N—CH_2—), 4.82 (s, 2, H_2N—C$\leq$), and 2.13 (broad, 2, H_2N—CH_2—); uv max (2-propanol), 215, mμ (ϵ 36.5), 235 (sh) (24.0), 255 (sh) (19.8), 297 (10.3), 333 (11.0), and 343 (sh) (10.55); (0.1 *N* HCl), 216 (25.4), 258 (32.2), 300 (sh) (6.2), 327 (12.0), and 338 (11.5); (0.1 *N* KOH) 235 (26.3), 245 (sh) (25.0), 294 (sh) (7.8), 328 (11.1), and 340 (10.7).

Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04. Found: C, 72.85; H, 6.24; N, 15.25.

B. By Reduction of 20.—A solution of 1.0 g (0.003 mol) of 20, prepared as described below, in 25 ml of ethanol was hydrogenated at 25° and atmospheric pressure using 0.5 g of Raney nickel. The reduction was stopped after 204 ml (0.09 mol) of hydrogen had been absorbed. The catalyst was removed by filtration and the solvent was concentrated to small volume, diluted with ether until slightly turbid, and refrigerated. Filtration gave 0.8 g (89%) of pale yellow prisms, mp 85–95° (possibly an etherate). Upon vacuum drying at 70° overnight, the melting point was raised to 159–160.5°. The mixture melting point with the product obtained by hydrolysis of 3 was 161–163°.

5-(2-Aminoethyl)-5H-indolo[3,2-c]quinoline (8). A.—A solution of 20 g (0.075 mol) of 3 dissolved in a mixture of 200 ml of 6 *N* HCl and 150 ml of ethanol was heated under reflux for 9 days and then concentrated to remove the alcohol. The residue was basified with concentrated NH_4OH, and the resultant oily suspension was refrigerated for several days. Filtration gave a yellow-brown solid which was recrystallized by dissolving it in methanol (a small amount of undissolved oil was discarded) and adding water until the mixture was slightly turbid (a small quantity of dark, amorphous solid which separated during the addition of water was discarded). After refrigeration, filtration yielded 11.3 g of yellow-green solid, mp (softens at 80°) 162–164°. The analytical sample was recrystallized from tetrahydrofuran–ether to give

(15) Tlc on silica gel G using ethyl acetate–hexane (1:1) showed this solid to be a mixture of compound 1 plus 1,3-di(o-fluorobenzoyl)indole.

yellow needles: melting point softens from *ca.* 150° until completely melted at 175°; nmr (DMSO-d_6), δ 9.20 (s, 1, =CH—N—CH_2); uv max (2-propanol), 220 mμ (ϵ 22.9), 237 (23.8), 248 (20.7), 280 (infl) (29.5), 291 (53.9), 303 (infl) (14.0), 318 (14.4), 340 (6.9), 363 (infl) (7.3), and 380 (7.6); (0.1 *N* HCl), 223 (22.5), 234 (28.7), 254 (infl) (21.4), 275 (32.7), 284 (33.4), 300 (13.0), and 350 (10.3); (0.1 *N* KOH) 219 (22.9), 241 (28.75), 280 (infl) (32.0), 288 (55.2), 312 (15.0) 330 (flat) (6.3), and 372 (9.5).

Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.03; H, 6.07; N, 16.04.

B.—A solution of 9.7 g of **7** in 100 ml of ethanol and 100 ml of 2 *N* H_2SO_4 was heated under reflux for 66 hr and then concentrated to remove the alcohol. The residue was basified and the precipitate filtered and air dried. Recrystallization from chloroform–ether gave yellow needles, mp 165–169°, identical in all respects with the product obtained by procedure A.

11H-Indolo[3,2-*c*]quinoline (9) and 3-(2-Aminophenyl)-4(1H)-quinolone (10).—A solution of 11.2 g of **7** in 100 ml of nitrobenzene was heated under reflux for 21.5 hr. The black solution was cooled to room temperature and 100 ml of ether added. After refrigeration the mixture was filtered to give 3.9 g of a dark brown solid. This solid was dissolved in methanol, filtered from an undissolved residue (discarded), and the filtrate diluted with ether. The precipitated brown solid was recrystallized several times from benzene–methanol to give 290 mg of **10** as pale yellow plates: mp 258–260°; ir (KBr), 3390, 3200 (NH_2, NH) and 1620 cm^{-1} (C=O); nmr (DMSO-d_6), δ 4.83 (broad s, 2, $-NH_2$), 7.95 (s, 1, =CH—N—), and 4.83 (broad s, 1, HN—CH=); uv max (2-propanol), 235 mμ (ϵ 22.5), 251 (22.3), 280 (infl) (20.2), 300 (10.5), 323 (10.8), and 335 (9.75).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.24; H, 5.12; N, 11.86. Found: C, 76.31; H, 5.39; N, 11.77.

The nitrobenzene–ether filtrate was concentrated at reduced pressure and the residue was dissolved in dichloromethane. This solution was extracted with 2 *N* hydrochloric acid and the acid layer was basified and extracted with dichloromethane. Concentration to small volume gave *ca.* 100 mg of **9**: mp 339–341° (lit.[3] mp 342°); mixture melting point with an authentic specimen, 341–343°.

5-(3-Indolyl)-2,3-dihydro-4-methyl-1H-1,4-benzodiazepinium Iodide (11).—A stirred solution of 26 g (0.1 mol) of **3** in 300 ml of warm tetrahydrofuran was treated with 30 ml (excess) of methyl iodide and heated under reflux for 2.5 hr. After cooling to room temperature, the suspension was filtered to give an orange solid. Recrystallization from methanol gave 23.5 g (58%) of yellow plates, mp 255–263°. An additional recrystallization from methanol raised the melting point to 259–263°.

Anal. Calcd for $C_{18}H_{18}N_3I$: C, 53.61; H, 4.50; N, 10.42. Found: C, 53.61; H, 4.25; N, 10.05.

3-[2-(2-Methylaminoethylamino)benzoyl]indole (12).—To a suspension of 32 g (0.08 mol) of **11** in 400 ml of methanol was added with swirling 160 ml (0.16 mol) of 1 *N* NaOH. After approximately 30–40 min at room temperature, the resultant solution began to deposit a yellow solid. The suspension was allowed to stand for an additional hour at room temperature and then refrigerated. The precipitate was separated by filtration, washed with water, and dried to yield 20.6 g of bright yellow crystals, mp 144–146°. Upon standing the filtrate gave an additional 2 g of product. The total yield was 22.6 g (96.5%). The analytical sample was obtained by recrystallization from benzene to give yellow plates: mp 146–147°; ir ($CHCl_3$), 3470, 3340 (NH_2), and 1620 cm^{-1} (C=O); uv max (2-propanol), 209 mμ (ϵ 41.9), 235 (26.1), 270 (infl) (11.6), 311 (10.2), and 377 (7.85); (0.1 *N* NaOH) 235 (infl) (2.0), 271 (15.15), and 343 (14.2).

Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 74.05; H, 6.56; N, 14.27.

1-(2-Methylaminoethyl)-3-(2-aminophenyl)-4(1H)-quinolone (13) and 5-(2-methylaminoethyl)-5H-indolo[3,2-*c*]quinoline (14) Dihydrochloride.—A solution of 10 g (0.034 mol) of **12** in 150 ml of 2 *N* H_2SO_4 and 100 ml of methanol was heated under reflux for 8.5 hr and then concentrated to remove the alcohol. The residue was basified with 10% sodium hydroxide and extracted with chloroform. The organic layer was separated, washed with water, dried over sodium sulfate, and evaporated. The residual yellow solid was suspended in 50 ml of ether, heated to boiling, and filtered. The separated solid was washed with an additional 200 ml of ether and then recrystallized from benzene to give 6 g (60%) of **13** as colorless plates: mp 175–176°, ir ($CHCl_3$), 3410, 3360 (NH_2), and 1620 cm^{-1} (C=O); uv max (2-propanol), 214 mμ (ϵ 35.1), 234 (infl) (21.7), 250 (sh) (8.9), 294 (9.9), 330 (10.9), and 340 (sh) (10.0); (0.1 *N* HCl), 215 (25.7), 259 (32.25), 304 (sh) (7.0), 327 (12.5), and 339 (11.1).

Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.67; H, 6.30; N, 14.21.

Evaporation of the combined ether washes gave 0.7 g of a yellow oil. This oil was covered with an excess of methanolic hydrogen chloride and refrigerated. The solid was filtered to give 0.6 g of **14** as the hemihydrate of the dihydrochloride. Recrystallization from methanol gave white needles: mp (darkening *ca.* 280°) 292–297° dec; uv max (H_2O), 216 mμ (infl) (ϵ 20.4), 223 (infl) (23.4), 235 (30.3), 254 (infl) (22.0), 275 (34.6), 283 (35.7), 299 (infl) (14.4), and 350 (10.9); (0.1 *N* KOH), 218 (23.9), 241 (30.0), 278 (infl) (33.0), 288 (57.9), 300 (infl) (16.2), 317 (16.15), 334 (6.75), and 370 (9.9); (0.1 *N* HCl), 215 (infl) (20.5), 223 (infl) (24.0), 235 (30.75), 254 (infl) (22.7), 275 (35.4), 283 (36.5), 300 (15.0), and 350 (11.4); nmr (D_2O), δ 9.42 (s, 1, =CH—N—CH_2).

Anal. Calcd for $C_{18}H_{19}Cl_2N_3 \cdot 0.5H_2O$: C, 60.50; H, 5.59; N, 11.75. Found: C, 60.34; H, 5.47; N, 11.84.

Ethyl 3-Hydroxy-2-(2-nitrophenyl)acrylate (16).—A solution of 104.5 g (0.5 mol) of ethyl 2-nitrophenylacetate and 104.5 g (0.71 mol) of the diethyl acetal of N,N-dimethylformamide[11] was heated under reflux for 3 days and concentrated. The residual brown oil was dissolved in a mixture of 150 ml of ethanol and 150 ml of 12 *N* H_2SO_4 and let to stand at room temperature for 3 hr. The solution was then diluted with 500 ml of ether and 300 ml of water. The dark red organic layer was separated, washed with water, and then extracted with a saturated sodium carbonate solution until all of the red color was in the aqueous phase. The ether layer was concentrated to give 16 g of starting material. The alkaline extracts were combined, neutralized with acid, and extracted with ether. The organic layer was separated, washed, dried, and concentrated to give 70.1 g (70%, based upon unrecovered starting material) of yellow prisms, mp 95.5–98°. Recrystallization from benzene gave yellow prisms: mp 95.5–98°; nmr (DMSO-d_6), δ 7.88 (s, 1, =CH—O—H) and 9.67 (broad s, 1, $\geqslant$C—OH).

Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.69; H, 4.67; N, 5.91. Found: C, 55.76; H, 4.32; N, 5.68.

Ethyl 3-Anilino-2-(2-nitrophenyl)acrylate (17).—A mixture of 100 g (0.422 mol) of **16** and 39.5 g (0.422 mol) of aniline was heated on a steam bath until solution occurred, 100 ml of ethanol was added, and the solution was let to stand overnight at room temperature. The precipitate was filtered to give 106 g of **17** as red prisms, mp 130–135°. The analytical sample was obtained by recrystallization from ethanol to give orange rods, mp 135–138°.

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.46; H, 5.02; N, 9.03.

Evaporation of the ethanol filtrate gave a yellow-orange solid which was washed with ether to give 22.5 g of the second isomer of **17**, mp 115–120°. Recrystallization from ethanol gave orange plates, mp 115–117°; total yield, 128.5 g (97%).

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.60; H, 5.03; N, 9.09.

3-(2-Nitrophenyl)-4(1H)-quinolone (18).—A solution of 17.5 g (0.056 mol) of **17** in 200 ml of diphenyl ether was heated under reflux for 4 hr. The ethanol generated during the reaction was removed using a Dean–Stark trap. After standing overnight at room temperature, the product was separated by filtration. The precipitate was washed with ether and dried to give 3.6 g (24%) of yellow crystals, mp 286–288°. Recrystallization from ethanol gave yellow microneedles, mp 287–288°.

Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79; N, 10.52. Found: C, 67.45; H, 3.38; N, 10.32.

3-(2-Aminophenyl)-4(1H)-quinolone (10) by Reduction of 18.—A solution of 0.8 g of **18** in 150 ml of methanol was treated with 1.5 g of Raney nickel and reduced at atmospheric pressure until the theoretical uptake of hydrogen had been absorbed. The mixture was filtered over Celite and the filtrate concentrated to give 0.6 g of white plates, mp 267–269°. This product was identical in all respects with the product obtained by pyrolysis of **3** in nitrobenzene.

1-[2-(Benzyloxycarbonylamino)ethyl]-3-(2-nitrophenyl)-4(1H)-quinolone (19).—A solution of 8.6 g (0.032 mol) of **18** in 50 ml of dry DMF was treated under nitrogen with 1.62 g (0.032 mol) of a 50% dispersion of sodium hydride in mineral oil. The resultant solution was stirred at room temperature for 1 hr and then

treated with a solution of 11.6 g (0.043 mol) of carbobenzoxy-2-bromoethylamine[15] in 10 ml of DMF. The reaction mixture was then heated at 80° for 66 hr, poured into a stirred mixture of 300 g of cracked ice and 300 ml of water, and filtered. The precipitate was washed with water and dried to yield 4.9 g (34%) of yellow solid, mp 172–177°. Recrystallization from benzene–methanol gave bright yellow rods, mp 174.5–175.5°.

Anal. Calcd for $C_{25}H_{21}N_3O_5$: C, 67.71; H, 4.77; N, 9.48. Found: C, 67.78; H, 4.85; N, 9.32.

1-(2-Aminoethyl)-3-(2-nitrophenyl)-4(1H)-quinolone (20).—A saturated solution (50 ml) of hydrogen bromide in glacial acetic acid was treated with 4.9 g (0.011 mol) of **19**. The reaction mixture was stirred overnight at room temperature and then diluted with ether. The product, as the hydrobromide salt, was removed by filtration and dissolved in 1500 ml of water, basified with concentrated NH_4OH, and extracted with CH_2Cl_2. The organic layer was washed with water, dried over sodium sulfate, filtered, and evaporated. The crystalline residue was filtered and the precipiate was washed with dichloromethane to yield 2.7 g (79%) of product, mp 202–204°. Recrystallization from ethanol gave yellow prisms, mp 203–204°.

Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.59. Found: C, 66.32; H, 5.09; N, 13.44.

1-Benzyl-3-(2-nitrophenyl)-4(1H)-quinolone (21).—To a stirred solution of 11.5 g (0.044 mol) of **18** in 200 ml of DMF was added, under nitrogen, 2.2 g (0.046 mol) of 50% sodium hydride. After stirring at room temperature for 1 hr, 7.4 g (0.044 mol) of benzyl bromide was added and the mixture was stirred for an additional 2 hr and then poured into ice–water. The precipitate was filtered, washed with water, and recrystallized from methanol–dichloromethane to yield 13.3 g (86.5%) of yellow crystals, mp 186–187.5°.

Anal. Calcd for $C_{22}H_{16}N_2O_3$: C, 74.15; H, 4.53; N, 7.86. Found: C, 74.35; H, 4.72; N, 8.12.

3-(2-Aminophenyl)-1-benzyl-4(1H)-quinolone (22).—A solution of 8.3 g (0.023 mol) of **21** in 600 ml of methanol was hydrogenated at 25° and atmospheric pressure using 1 g of Raney nickel. The reduction was stopped after 1500 ml (theoretical 1570 ml) of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate concentrated. The residue was recrystallized from methanol to give 6.6 g (87%) of yellow prisms: mp 189–191°; ir ($CHCl_3$), 3410 and 3300 cm^{-1} (NH_2).

Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.88; H, 5.76; N, 8.30.

1-Benzyl-3-[2-(*p*-toluenesulfonamido)phenyl]-4(1H)-quinolone (23).—To a solution of 5 g (0.015 mol) of **22** in 50 ml of pyridine was added 3 g (0.015 mol) of *p*-toluenesulfonyl chloride. After standing overnight at room temperature, the resultant mixture was poured into water, let stand for 2 hr, and filtered. The solid was washed thoroughly with water recrystallized twice from methanol to yield white prisms, mp 188–190°.

Anal. Calcd for $C_{29}H_{24}N_2O_3S$: C, 72.48; H, 5.03; N, 5.83. Found: C, 72.17; H, 4.91; N, 5.83.

1-Benzyl-3[2-(N-methyl-*p*-toluenesulfonamido)phenyl]-4(1H)-quinolone (24).—To a solution of 3.5 g (0.008 mol) of **23** in 20 ml of DMF was added, under nitrogen, 0.35 g (0.008 mol) of 50% sodium hydride. After stirring at room temperature for 1 hr, 1.03 g (0.008 mol) of methyl iodide was added, and the mixture was stirred for 2 hr at room temperature and then poured into ice–water. The precipitate was recrystallized from 2-propanol to yield 3.5 g (87%) of off-white prisms, mp 171–174°.

Anal. Calcd for $C_{30}H_{26}N_2O_3S$: C, 72.85; H, 5.30; N, 5.66. Found: C, 72.70; H, 5.39; N, 5.62.

1-Benzyl-3-(2-methylaminophenyl)-4(1H)-quinolone (5) by Hydrolysis of 24.—A mixture of 3 g (0.006 mol) of **24** in 15 ml of concentrated H_2SO_4 was heated on the steam bath for 15 min and poured into ice. The resultant solution was neutralized with concentrated NH_4OH, and the precipitate was filtered and washed thoroughly with water. Recrystallization from methanol gave colorless prisms, mp 212–214°; the mixture melting point with the product obtained by hydrolysis of **4** was 212–215°.

5-(2-Diethylaminoethyl)-5H-indolo[3,2-*c*]quinoline (25) Dimethiodide.—A solution of 40 g (0.17 mol) of **1** in a mixture of 50 ml of N,N-diethylethylenediamine and 100 ml of pyridine was refluxed for 17.5 hr and concentrated under reduced pressure. The viscous, oily residue was dissolved in CH_2Cl_2, washed thoroughly with water, dried, and concentrated. This residue was covered with 100 ml of ethanol and 100 ml of 2 *N* H_2SO_4 and refluxed, with stirring, for 5 hr. After cooling to room temperature, the precipitate was filtered, washed with 2 *N* H_2SO_4, water, and then recrystallized from methanol to yield 17.5 g of unreacted **1**. The alcohol–sulfuric acid filtrate was concentrated to remove the alcohol and the residue basified with 10% NaOH and extracted with dichloromethane. The organic layer was separated, washed (water, brine), and dried (Na_2SO_4). Evaporation of the solvent yielded 12.3 g of viscous oil. The oil was dissolved in benzene and chromatographed on 500 g of grade I neutral Woelm alumina. Elution of the column with benzene–dichloromethane (1:1) gave 5 g of **25**; uv max (2-propanol), 217 mμ (ε 15.0), 236 (14.8), 248 (sh) (12.9), 280 (infl) (19.0), 291 (30.9), 305 (infl) (8.6), 316 (8.7), 339 (4.8), and 365–380 (4.8); (0.1 *N* HCl), 215 (infl) (15.5), 222 (infl) (17.0), 235 (19.8), 255 (15.1), 276 (21.8), 284 (22.2), 300 (9.6) and 351 (7.25); (0.1 *N* KOH), 218 (13.9), 242 (18.0), 278 (infl) (19.0), 288 (33.6), 312 (9.9), 335 (infl) (4.4), and 372 (6.2).

Continued elution with ethyl acetate gave a mixture of **25** plus several other compounds, as observed by tlc. Evaporation of the ethyl acetate and addition of ether precipitated 200 mg of indolo[3,2-*c*]quinoline (**9**), mp 337–339°, undepressed when mixed with an authentic specimen. The remaining products could not be separated and identified.

Compound **25** was converted into its dimethiodide by treating 0.5 g of this compound, as an oil, with 0.4 g of methyl iodide in 10 ml of nitrobenzene. After warming on the steam bath for 20 min, the mixture was cooled and filtered. The precipitate was washed with ether and recrystallized from water to give white needles, mp 250–252° dec (lit.[9] mp 263–264°); mixture melting point with an authentic sample (mp 245–246° dec) was 247–248° dec; infrared spectra were identical.

5-(1-Methyl-3-indolyl)-2,3-dihydro-1H-1,4-benzodiazepine (26).—A solution of 5.5 g (0.02 mol) of **2** in 20 ml of ethylenediamine and 40 ml of pyridine was refluxed for 18 hr and evaporated. The residue was partitioned between CH_2Cl_2 and water. The organic layer was separated, washed, and extracted with three 100-ml portions of 1 *N* HCl. The acid extract was basified with NH_4OH and extracted with dichloromethane. After being washed and dried the dichloromethane was concentrated to a small volume, petroleum ether (bp 30–60°) was added until faintly turbid and the mixture was refrigerated. Filtration gave 2.7 g (46%) of bright yellow solid, mp 142–146°. An additional recrystallization from dichloromethane–petroleum ether gave small yellow plates, mp 144–148° (sinters prior to melting).

Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.51; H, 6.22; N, 15.26. Found: C, 78.48; H, 6.34; N, 15.23.

2,3-Dihydro-9-methyl-9H-imidazo[1,2-*a*]indolo[3,2-*c*]quinoline (27).—A solution of 10.3 g of **26** in 110 ml of ethanol and 110 ml of 6 *N* HCl was refluxed for 20.5 hr. After standing at room temperature overnight, the suspension was filtered to give 8 g of solid. Concentration of the filtrate to an oily solid and addition of a few milliliters of methanol gave an additional 1.6 g of solid. The two solids were combined, basified with a slight excess 1 *N* NaOH, and extracted with chloroform. The organic layer was separated, washed with a small amount of water, dried, and concentrated. The residual oil upon trituration with hot benzene gave a yellow solid. Recrystallization from 2-propanol–dichloromethane gave yellow needles: mp 257–260° dec; nmr (DMSO-d_6), δ 4.09 (s, 3, CH_3—N) and 3.96 (s, 4, =N—CH_2—CH_2—N).

Anal. Calcd for $C_{18}H_{16}N_3$: C, 79.09; H, 5.53; N, 15.38. Found: C, 79.06; H, 5.71; N, 15.36.

Registry No.—**1**, 16273-87-3; **2**, 16273-88-4; **3**, 16274-02-5; **4**, 16273-89-5; **5**, 16273-90-8; **6**, 16273-91-9; **7**, 16273-92-0; **8**, 16273-93-1; **10**, 16273-94-2; **11**, 16273-95-3; **12**, 16273-96-4; **13**, 16273-97-5; **14** dihydrochloride, 16273-98-6; **16**, 16273-99-7; **17** (*cis*), 16274-00-3; **17** (*trans*), 16274-01-4; **18**, 16273-20-4; **19**, 16273-22-6; **20**, 16273-24-8; **21**, 16273-26-0; **22**, 16273-28-2; **23**, 16273-30-6; **24**, 16273-31-7; **25**, 16273-32-8; **26**, 16273-33-9; **27**, 16273-34-0; 1,3-di-(*o*-fluorobenzoyl)indole, 16273-36-2.

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Acknowledgment.—We are indebted to Dr. V. Toome for the ultraviolet spectra, to Dr. T. Williams for the nmr spectra, to Dr. F. Vane for the mass spectra, to Mr. S. Traiman for the infrared spectra, and to Dr. A. Steyermark and Dr. F. Scheidl for the microanalyses.

The Condensation of *o*-Benzoylbenzaldehyde with Aliphatic Diamines

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Received March 6, 1968

The reaction of *o*-benzoylbenzaldehyde (II) with aliphatic diamines gave condensation products of type V which could readily be oxidized *via* peroxides of type VI to the carbinolamine derivatives of type IXa. The equilibrium between the tautomeric imidazoline derivatives IXa and IXb was investigated.

The reaction of aromatic *o*-dialdehydes with aromatic *o*-diamines gives derivatives containing the imidazo[2,1-*a*]isoindole[1] ring system rather than eight-membered heterocyclic compounds claimed in some cases.[2] This reaction has recently been reinvestigated and Thiele's original assignment was confirmed.[3] A similar problem had arisen concerning the structure of the products obtained by condensation of *o*-benzoylbenzoic acid with ethylenediamine.[4] This led us to study the condensation of *o*-benzoylbenzaldehyde with aliphatic diamines.

The *o*-benzoylbenzaldehyde, compound II, was obtained in over 50% yield by the oxidation of the benzhydrol derivative I (Scheme I). On reaction with ethylenediamine in aqueous ethanolic solution the known phthalimidine derivative III[4b] was formed. This result is analogous to the formation of N-phenylphthalimidine on reaction of *o*-phthalaldehyde with aniline.[5]

When the condensation of *o*-benzoylbenzaldehyde with ethylenediamine was performed under anhydrous conditions, a product was obtained[6] to which we assigned structure V in analogy to the results obtained with phthalaldehyde and *o*-phenylenediamine.[1] Proof for this structure was supplied by preparing the same compound by cyclization of the phthalimidine derivative III using titanium tetrachloride as condensing agent. Compound III was not cyclized to V in boiling ethylenediamine and, therefore, is not an intermediate in the reaction II → V.

The free base V was rapidly oxidized by exposing it in various solvents to air or, more conveniently, by using hydrogen peroxide as the oxidant. The primary reaction product was the peroxide VI which could be isolated by chromatographic separation. The crude oxidation product always contained compound IX, which is most likely formed by a reduction of the intermediate peroxide VI. This peroxide liberated iodine from an acidified potassium iodide solution and was readily reduced to compound IX which on mild hydrolysis yielded the known 3-hydroxyphthalimidine derivative XIII.[4b] Confronted with the problem of deciding between structure a and b for IX, we found that infrared absorption at 1660 cm^{-1} could not be accepted as proof for the presence of a carbonyl function since compounds V and VI also showed strong absorption at 1660 cm^{-1} obviously due to C=N stretching. Near-infrared spectra[7] were measured in chloroform and the overtones of OH and NH absorption at 1.4 and 1.5 μ, respectively, were found to be of equal intensity, indicating the presence of a 1:1 mixture of the forms IXa and b. As expected, this equilibrium proved to be pH dependent as shown by the ultraviolet spectra. On acidification a maximum at 251 mμ (ϵ 13,600) appeared which was attributed to the benzophenone chromophor and allowed the determination of a pK 8.6.[8] This constant describes the equilibrium between the carbinolamine base IXa and the protonated keto form IXb. To remove all remaining doubt about the structure of IX, its hydrobromide was subjected to single crystal X-ray structure analysis[9] which showed that compound IX in its protonated form has the keto structure b. The formation of the ether XII observed on treatment of IX with methanol is a reaction typical for carbinolamines and proves the presence of the tautomer IXa in the equilibrium.

We propose that the equilibrium of IXa with IXb is determined by the competition between the intermolecular association of the amidine functions[10] and the intramolecular interaction of amine and carbonyl groups.

Ring homologs of IX were prepared by condensation of *o*-benzoylbenzaldehyde with the appropriate diamines and subsequent oxidation. As indicated by ultraviolet and near-infrared spectra, the increased size of the heterocyclic ring changes the character of the amidine functions sufficiently to force the expected equilibrium to the side of the carbinolamine structures (VII and VIII).

Another route for the preparation of compound IX was found by treating the condensation product of phthaldehydic acid and ethylenediamine (X) with phenyllithium. This reaction which presumably proceeds *via* the hypothetical intermediate d gave only a poor yield of IX. We, therefore, oxidized X with

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(4) (a) T. Sulkowski, M. Wille, A. Mascitti, and J. Diebold, *ibid.*, **32**, 2180 (1967); (b) W. Metlesics, T. Anton, and L. H. Sternbach, *ibid.*, **32**, 2185 (1967).

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(6) The sulfate of this compound was isolated since the base was found to be unstable in air (*vide infra*).

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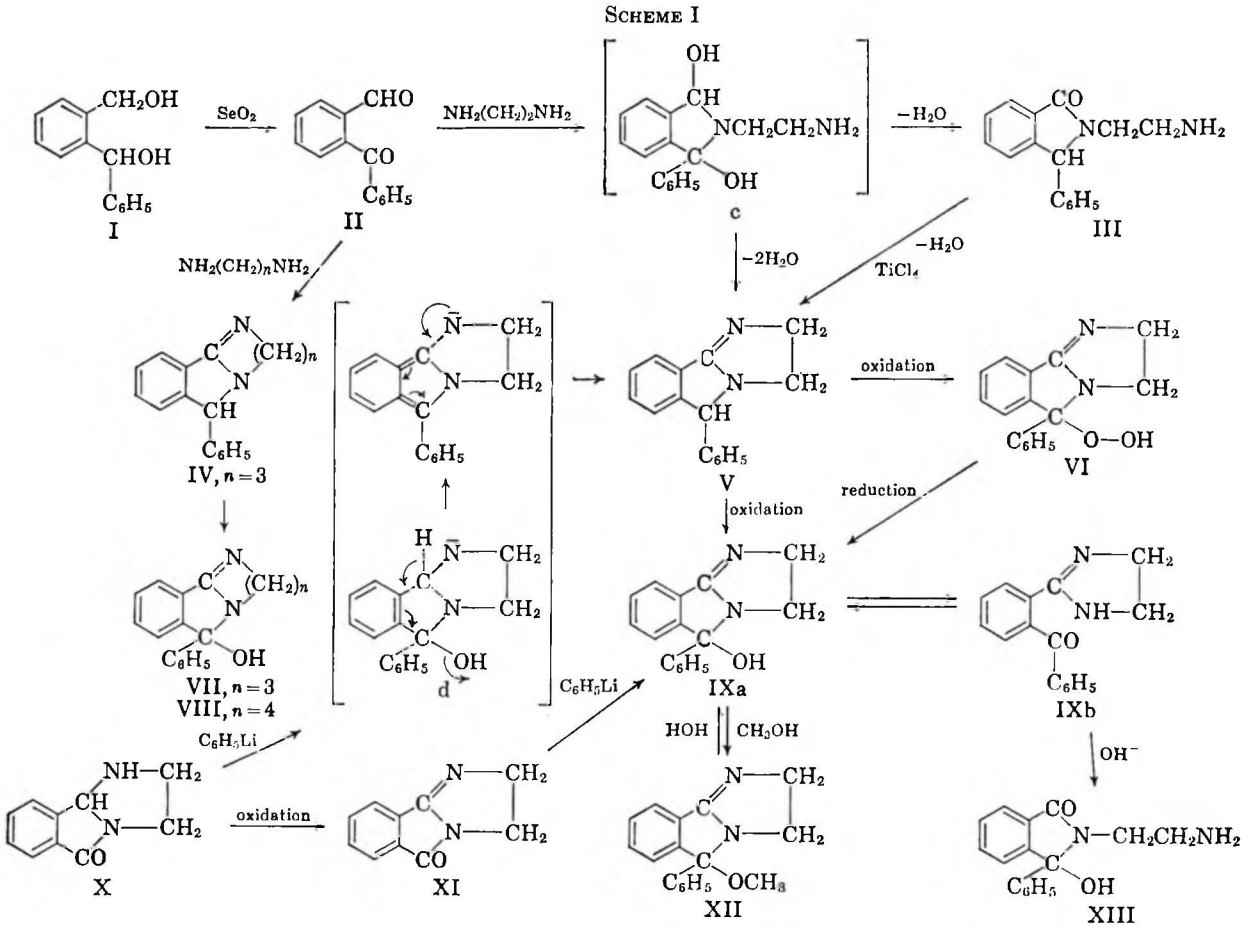
SCHEME I



diethyl azodicarboxylate to compound XI (mp 139–141°)[11] which on treatment with phenyllithium afforded IX in 49% yield.

Experimental Section[12]

o-Benzoylbenzaldehyde (II).—A suspension of 41.7 g (0.376 mol) of selenium dioxide in 147 ml of acetic acid and 294 ml of xylene was refluxed for 15 min and any water present was removed in a Dean–Stark receiver. To this mixture was added dropwise a solution of 64.2 g (0.3 mol) of *o*-hydroxymethylbenzhydrol (I)[13] in 86 ml of acetic acid and 258 ml of xylene in the course of 1 hr. During this time 25 ml of an aqueous phase was removed by cooling the distilling trap. During continued refluxing another 50–70 ml of an aqueous phase was removed. After 20 hr the solution was cooled and filtered from selenium. The filtrate was poured into ice water, basified with sodium hydroxide, and extracted with ether. Concentration of the extract yielded a yellow oil which on addition of petroleum ether (bp 30–60°) gave 33.5 g (53%) of white prisms melting at 64–67°: uv max (2-propanol) 226–227 mμ (ε 15,750), 251–252 (18,500), infl 294 (2600); ir ($CHCl_3$) 1665 (PhCOPh) and 1705 cm^{-1} (CH=O).

Anal. Calcd for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79. Found: C, 80.00; H, 4.68.

2-(2-Aminoethyl)-3-phenylphthalimidine (III).—A solution of 4.2 g (0.02 mol) of II in 85 ml of ethanol, 50 ml of water, and 6.8 ml (0.1 mol) of ethylenediamine was refluxed for 18 hr. The solution was concentrated to remove the alcohol and diluted with 160 ml of water. A solid product was collected on a filter and dried. A maleate was prepared in a mixture of methylene chloride, methanol, and ether. After recrystallization from a mixture of methanol and ether 2.6 g of a maleate melting at 184–187° dec was obtained. This salt was suspended in water and after basification gave 1.2 g (24%) of III melting at 88–91° (lit.[4b] mp 90–93°).

2,3,4,6-Tetrahydro-6-phenylpyrimido[2,1-*a*]isoindole Sulfate (IV·H_2SO_4).—A solution of 10.5 g (0.05 mol) of II in 22 ml (0.26 mol) of 1,3-propanediamine in 125 ml of toluene was refluxed for 3 hr. During this time 3.2 ml of an aqueous phase had separated in a Dean–Stark receiver. The solution was cooled, washed with water, and concentrated *in vacuo*. The residue crystallized, was collected on a filter, and washed with a small amount of ethyl acetate. This crop was dissolved in 100 ml of ethanol and a solution of 3 ml of concentrated sulfuric acid in 50 ml of ethanol was added. On addition of ethyl acetate a solid was obtained which after recrystallization from a mixture of ethanol and petroleum ether gave 12.7 g (73%) of white prisms melting at 170–172° dec: uv max (2-propanol) 238 mμ (ε 18,200), infl 246 (16,000), 265 (5600), 276 (3400), 285 (2100); ir (KBr) 1675 cm^{-1} (C=N); nmr (DMSO) δ 2.1 (m, 2, C—CH_2—C), 3.0–4.0 (m, 4, 2N—CH_2), 6.23 [s, 1, $(Ph)_2C$—H], 7.1–8.3 (m, 9).

Anal. Calcd for $C_{17}H_{16}N_2 \cdot H_2SO_4$: C, 58.94; H, 5.24. Found: C, 58.62; H, 5.49.

2,3-Dihydro-5-phenyl-5H-imidazo[2,1-*a*]isoindole Sulfate (V·H_2SO_4). A. From II.—A solution of 10.5 g (0.05 mol) of II in 125 ml of toluene and 17 ml (0.25 mol) of ethylenediamine was refluxed for 18 hr. During this time 4.5 ml of an aqueous phase was separated in a Dean–Stark receiver. The reaction mixture was cooled, washed with water, and concentrated *in vacuo* to an orange oil which was dissolved in a mixture of 35 ml of ethanol and 50 ml of ethyl acetate. A solution of 2.5 ml of concentrated sulfuric acid in 50 ml of ethanol was added and a crystalline precipitate was collected which after recrystallization from a mixture of methanol and ethyl acetate gave 7.2 g (43%) of white prisms melting at 221–223° dec. A sample was recrystallized again for analytical purposes and melted at

(11) A compound with structure XI had been described in the literature,[2a] mp 229–230°. In agreement with a previous investigation,[3a] we were also unable to reproduce this result and have to conclude that the compound previously described has a different structure.

(12) The melting points were determined with a Mettler FP-1 melting point apparatus by raising the temperature 2°/min from 10° below the melting or decomposition point. Ultraviolet and near-infrared spectra were determined with a Cary 14 spectrophotometer, infrared spectra using a Beckman IR-9 spectrophotometer, and nmr spectra on a Varian A-60 spectrometer at 60 Mc/sec [$(CH_3)_4Si$ internal standard]. The purity of compounds was established by thin layer chromatography. The identity of compounds was proved by comparison of spectral properties and mixture melting point.

(13) W. A. Bonner, *J. Amer. Chem. Soc.*, **85**, 439 (1963).

226–229° dec: uv max (2-propanol) 240 mμ (ε 15,000), 276 (5400); ir (KBr) 1660 cm^{-1} (C=N).

Anal. Calcd for $C_{16}H_{14}N_2 \cdot H_2SO_4$: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.61; H, 4.81; N, 8.73.

The hydrochloride was prepared from the corresponding base with aqueous 1 *N* hydrochloric acid. On recrystallization from a mixture of methanol and toluene, white prisms melting at 226–228° dec were obtained: nmr (DMSO) δ 3.6–4.3 (m, 4 $-CH_2-CH_2$), 6.13 (s, 1, CH), 7.3–7.9 (m, 9); mass spectrum (70 eV), *m/e* 234 ($C_{16}H_{14}N_2$).

Anal. Calcd for $C_{16}H_{14}N_2 \cdot HCl$: Cl, 13.09. Found: Cl, 13.22.

B. From III.—A solution of 1.2 ml of titanium tetrachloride in 30 ml of xylene was added at 25° to a stirred solution of 2.5 g of III in 150 ml of xylene. The mixture was refluxed for 18 hr, cooled, and washed with an aqueous solution of sodium carbonate. The xylene solution was extracted with 2 *N* hydrochloric acid. The acidic extract was poured on ice and made alkaline with sodium hydroxide. The solution was extracted with ethyl acetate and the extract was concentrated. Addition of a solution of sulfuric acid in a mixture of ethanol and tetrahydrofuran and further dilution with ethyl acetate gave a crystalline precipitate. Recrystallization from a mixture of methanol and ethyl acetate gave 0.5 g (15%) of white prisms melting at 225–228° dec ($V \cdot H_2SO_4$).

2,3-Dihydro-5-hydroperoxy-5-phenyl-5H-imidazo[2,1-*a*]isoindole (VI).—The crude base liberated from 16.6 g (0.05 mol) of $V \cdot H_2SO_4$ was dissolved in 50 ml of ethanol and 11 ml of a 30% aqueous solution of hydrogen peroxide was added. The mixture was stirred at 25° for 40 hr. A crystalline crop (8.6 g) was collected and placed on a column containing 250 g of silica gel. Elution with a mixture of one part of methanol and one part of chloroform gave fractions from which on concentration a crystalline residue was obtained. Recrystallization from a mixture of methanol and chloroform gave 2.3 g of white prisms melting at 165–167° dec: uv infl (2-propanol) 232 mμ (ε 14,000), 290 (2600), max 269 (4000), 275 (4400); ir (KBr) 1665 cm^{-1} (C=N).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.09; H, 5.39; N, 10.22.

Hydrochloride of VI.—This compound was prepared with methanolic hydrogen chloride and after recrystallization from a mixture of methanol and ether gave white platelets melting at 165–168° dec: uv max (2-propanol) 245 mμ (ε 14,800), 278 (5200); ir (KBr) 1680 cm^{-1} (C=N).

Anal. Calcd for $C_{16}H_{14}N_2O_2 \cdot HCl$: C, 63.47; H, 4.99; Cl, 11.71. Found: C, 63.63; H, 4.83; Cl, 11.79.

2,3,4,6-Tetrahydro-6-phenylpyrimido[2,1-*a*]isoindol-6-ol (VII).—A solution of 10 g of $IV \cdot H_2SO_4$ in water was basified with 2 *N* sodium hydroxide and extracted with methylene chloride. The extract was concentrated and the residue was dissolved in 50 ml of ethanol and 3 ml of 30% hydrogen peroxide. The solution was stirred at 25° for 12 hr and diluted with ether. A precipitate was collected and suspended in a refluxing mixture of 35 ml of methanol, 3.5 g of sodium sulfite heptahydrate, and 15 ml of water. After 15 min the suspension was cooled and diluted with water. The solid was collected and after recrystallization from a mixture of methylene chloride and methanol gave 2.2 g (29%) of white prisms melting at 227–230° dec: uv infl (2-propanol) 230 mμ (ε 15,000), 262 (4400) max 266 (4600), 271 (4800), infl 279 (3200), 285 (2400); uv max (0.1 *N* HCl) 239 mμ (ε 15,200), infl 266 (4500); near-ir ($CHCl_3$) max 1.43 μ (ε *ca.* 1) (OH); ir (KBr) 1655 cm^{-1} (C=N).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10. Found: C, 77.38; H, 6.15.

2,3,4,5-Tetrahydro-7-phenyl-7H-diazepino[2,1-*a*]isoindol-7-ol (VIII).—A solution of 10.5 g of II and 28.5 ml of 1,4-diaminobutane in 125 ml of toluene was refluxed for 2.5 hr, during which 3 ml of an aqueous phase had separated in a Dean–Stark receiver. The solution was cooled, washed with sodium chloride solution, and concentrated *in vacuo*. The residue was an orange oil which was dissolved in 150 ml of ethanol and 5 ml of 30% hydrogen peroxide was added. The solution was stirred at 25° for 18 hr. A solid precipitate was collected, washed with a mixture of ether and ethanol, and suspended in 25 ml of methanol. The mixture was refluxed and a solution of 5 g of sodium sulfite heptahydrate in 15 ml of water was added. After refluxing for 15 min the mixture was cooled, diluted with 30 ml of water, and filtered. The solid crop was washed with water, dried, and recrystallized from a mixture of chloroform and ether to give 4.5 g (32%) of white prisms melting at 216–218° dec: uv max (2-propanol) 258 mμ (ε 5000), 265 (5100), 273 (4800), infl 230 (15,000) 290 (2400); near-ir ($CHCl_3$) max 1.43 μ (ε *ca.* 1) (OH); ir (KBr) at 1650 cm^{-1} (C=N); nmr (DMSO) δ 1.84 (broad, 4), 3.12 (broad, 2), 3.70 (broad, 2), 6.75 (1), 7.1–7.8 (m, 9).

Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; O, 5.75. Found: C, 77.64; H, 6.75; O, 5.64.

2,3-Dihydro-5-phenyl-5H-imidazo[2,1-*a*]isoindol-5-ol and/or 2-(2-Imidazolin-2-yl)benzophenone (IX). A. From V.—To a suspension of 3 g of $V \cdot H_2SO_4$ in water was added 2 *N* aqueous sodium hydroxide. Extraction with methylene chloride and concentration gave an orange oil (2 g) which was dissolved in 20 ml of ethanol. To this solution was added 1 ml of 30% hydrogen peroxide. After stirring at 25° for 18 hr 1.3 g of a precipitate was collected. This crop was refluxed in 5 ml of methanol and a solution of 1.2 g of sodium sulfite heptahydrate in 5 ml of water was added. After 15 min the mixture was cooled, diluted with 10 ml of water, and filtered. The collected solid was recrystallized from methanol to give 0.8 g (35%) of white prisms melting at 194–196° dec: uv infl (2-propanol) 225 mμ (ε 15,500), 290 (2250), max 269 mμ (ε 4100), 275 (4250); near-ir ($CHCl_3$) max 1.40 (ε *ca.* 0.5), 1.42 (*ca.* 0.5) (OH), and 1.48 μ (*ca.* 0.4) (NH); ir (KBr) 1660 cm^{-1}; nmr (CF_3CO_2H) δ 4.12 (s, 4, $-CH_2CH_2-$), 7.35–8.0 (m, 9), 8.31 [2, $(NH^+)_2$].

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 56.4; N, 11.19. Found: C, 76.42; H, 5.79; N, 11.13.

B. From VI.—A solution of 0.7 g of sodium sulfite heptahydrate in 3 ml of water was added to 0.5 g of VI in 7 ml of dimethylformamide. The solution was heated to 100° for 15 min. On cooling and addition of 20 ml of water 0.3 g (45%) of IX was obtained.

C. From VI.—A solution of 0.1 g of VI and 0.33 g of triethylphosphite in 20 ml of ethanol was kept on a steam bath for 5 min, then 18 hr at 25°. The solution was concentrated *in vacuo*, and on addition of water 0.07 g (75%) of IX was obtained.

D. From X.—To a solution of 1.75 g of X in a mixture of 50 ml of benzene and 50 ml of ether was added 25 ml of a 2 *N* solution of phenyllithium in a mixture of benzene and ether (7:3). After stirring at 25° for 18 hr the solution was poured into ice water and extracted with ether. This extract was dried and concentrated and the residue was dissolved in a mixture of benzene and ethanol (1:1). A stream of air was bubbled through the solution for 60 hr. The solution was concentrated and the crystalline residue was collected and washed with methylene chloride and ether. Recrystallization from a mixture of methylene chloride and methanol gave 0.2 g (10%) of IX melting at 192–196° dec.

E. From XI.—To a solution of 0.85 g (0.005 mol) of XI in 15 ml of benzene cooled to 5–10° was added 12 ml (0.024 mol) of a 2 *N* solution of phenyllithium in a mixture of seven parts of benzene and three parts of ether. The mixture was stirred at 20° for 1 hr and poured into ice water. Extraction with methylene chloride gave a crystalline crop which after recrystallization from a mixture of methanol and methylene chloride gave 0.6 g (49%) of white prisms of IX melting at 194–196° dec.

Hydrochloride of IX.—To a suspension of IX in methanol was added a solution of hydrogen chloride in methanol. Ether was added and the crystalline precipitate was collected. Recrystallization from a mixture of methanol and ether gave white prisms melting at 173–175° dec: uv max (2-propanol) 251 mμ (ε 13,600); ir (KBr) 1665 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{14}N_2O \cdot HCl$: Cl, 12.36. Found: Cl, 12.22.

On prolonged heating in methanol this salt is transformed into the salt of the carbinolamine ether XII.

Hydrobromide of IX.—To a suspension of IX in ethanol was added an aqueous solution of hydrobromic acid. Addition of ether gave a precipitate which after recrystallization from a mixture of ethanol and ether gave white platelets melting at 184–186° dec.

Anal. Calcd for $C_{16}H_{14}N_2O \cdot HBr$: Br, 24.13. Found: Br, 24.15.

This product was submitted for X-ray structure analysis.[9]

1,2,3,9b-Tetrahydro-5H-imidazo[2,1-α]isoindol-5-one (X).—A solution of 100 g (0.67 mol) of phthalaldehydic acid in 1200 ml of methanol and 225 ml of ethylenediamine was refluxed for 17 hr. The solution was concentrated *in vacuo* and the residual oil was dissolved in 1000 ml of chloroform. This solution was washed successively with concentrated aqueous solutions of potassium carbonate and sodium chloride, dried, and concen-

trated. The residual yellow oil was dissolved in ethanol, a solution of 37 g of maleic acid in ethanol was added, and on addition of ether a crystalline crop of a maleate was obtained which after recrystallization from a mixture of methanol and ether gave 43 g of white prisms. This product was suspended in an ice-cold aqueous solution of potassium carbonate. Extraction with methylene chloride gave a product which after recrystallization from a mixture of benzene and petroleum ether yielded 20.1 g (17%) of white needles melting at 130–132°: uv max (2-propanol) 223 mμ (ε 9300), infl 245 (4500), shoulder 278 (1300); ir ($CHCl_3$) 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.17; H, 5.76; N, 15.99.

2,3-Dihydro-5H-imidazo[2,1-*a*]isoindol-5-one (XI).—From a solution of 17.4 g (0.1 mol) of X in 350 ml of benzene 25 ml of solvent was removed by distillation. After cooling 25 g (0.14 mol) of diethylazodicarboxylate was added and the solution was refluxed for 65 hr. The mixture was chilled and the hydrazo ester was removed by filtration. The orange filtrate was concentrated *in vacuo* and the residue was recrystallized from a mixture of tetrahydrofuran and petroleum ether to give 10.6 g (62%) of white needles melting at 139–141°: uv max (2-propanol) 215 mμ (ε 37,000), 218 (36,900), 252 (12,500), 303 (4300), infl 246 (11,500), 260 (9500); ir ($CHCl_3$) 1670 (C=N) and 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.49; H, 4.54; N, 15.98.

2,3-Dihydro-5-methoxy-5-phenyl-5H-imidazo[2,1-*a*]isoindole Hydrochloride (XII·HCl).—A solution of 5 g of IX hydrochloride in 50 ml of methanol was refluxed for 18 hr. The solution was concentrated *in vacuo* dissolved in 20 ml of methanol and 60 ml of ether was added. Crystals (0.5 g) precipitated and were identified as starting material. The mother liquor was concentrated and the residue was recrystallized from a mixture of methanol, methylene chloride and ether to give 3.1 g (59%) of white prisms melting at 139–141° dec: uv max (2-propanol) 244 mμ (ε 14,400), 278 (5100); ir (KBr) 1670 cm^{-1} (C=N).

Anal. Calcd for $C_{17}H_{16}N_2O \cdot HCl$: C, 67.83; H, 5.70; OCH_3, 10.32. Found: C, 67.84; H, 5.63; OCH_3, 10.44.

The corresponding base was obtained as a colorless oil on treatment with alkali: uv infl (0.1 *N* KOH) 230 mμ (ε 14,600), 290 (2700), max 269 (4200), 275 (4600); ir (smear) 1660 cm^{-1} (C=N); nmr ($CDCl_3$) δ 3.12 (s, 3, OCH_3), 2.6–3.5 (m, 2, —N—CH_2), 4.2–4.5 (m, 2, =N—CH_2), 7.1–8.0 (m, 9).

Hydrolysis of XII·HCl to IX.—A solution of 0.2 g of XII·HCl in 10 ml of water was kept at 25° for 48 hr. The solution was basified with 2 *N* aqueous sodium hydroxide and the precipitate (0.14 g, 84%) was collected and identified as IX.

2-(2-Aminoethyl)-3-hydroxy-4-phenylphthalimidine (XIII).—A solution of 0.5 g of IX in 50 ml of tetrahydrofuran, 10 ml of methanol and 5 ml of aqueous 2 *N* sodium hydroxide was refluxed for 48 hr. The yellow solution was concentrated, diluted with water, and extracted with methylene chloride. The extract was dried and concentrated to give 0.35 g (65%) of white prisms which after washing with ether melted at 172–176° (lit.[4b] mp 175–176°).

Registry No.—II, 16780-82-8; IV·H_2SO_4, 16780-83-9; V·H_2SO_4, 16780-84-0; V·HCl, 16780-85-1; VI, 16780-86-2; VI·HCl, 16780-87-3; VII, 16780-98-6; VIII, 16780-97-5; IXa, 16780-88-4; IXa·HCl, 16780-89-5; IXa·HBr, 16797-48-1; IXb, 16780-90-8; IXb·HCl, 16780-91-9; IXb·HBr, 16780-92-0; X, 16780-93-1; XI, 16780-94-2; XII, 16780-95-3; XII·HCl, 16780-96-4.

Acknowledgment.—We are indebted to Mr. S. Traiman, Dr. F. Vane, and Dr. T. Williams for spectroscopic data and interpretations and to Dr. Al Steyermark and Dr. F. Scheidel for microanalytical data. We wish to thank Professor G. Büchi for valuable advice and stimulating discussions.

The Reaction of Active Methylene Compounds with Carbon Disulfide in the Presence of Ammonia. II. The Reaction of Acetone and Methyl Ethyl Ketone

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Received October 18, 1967

The title reaction was extended to acetone and methyl ethyl ketone as the active methylene compound. Acetone, in the presence of ammonia, reacted with carbon disulfide to give a series of thiazine and diazine compounds. The most stable compound obtained was 3,4-dihydro-4,4,6-trimethyl-2(1H)-pyrimidinethione (V). Methyl ethyl ketone yielded 2-ethyldihydro-2,5,6-trimethyl-4H-3,1-thiazine-4-thione (X) and 4-ethyl-3,4-dihydro-4,5,6-trimethyl-2(1H)-pyrimidinethione (XI). A dithiole (XII) also was isolated from the reaction products of methyl ethyl ketone. The structures of these new compounds were proposed. The interrelation of a series of compounds which were obtained from the reaction product of acetone was described.

In previous research,[2] it was found that cyclohexanone, in the presence of ammonia and treated with carbon disulfide, gives 4(1H)-thiono-5,6,7,8-tetrahydro-2H-3,1-benzothiazine-2-spirocyclohexane and the related compounds. The reaction has now been extended to acetone and methyl ethyl ketone as the active methylene compound.

First, it was found that acetone, in contrast with cyclohexanone, did not give the corresponding thiazine derivative. Instead, a series of thiazine and diazine compounds of a different type was isolated. For example, when a mixture of acetone, carbon disulfide, and aqueous ammonia was shaken at room temperature for 20 hr, 6-hydroxy-4,4,6-trimethyltetrahydro-2H-1,3-thiazine-2-thione (I), 6-amino-4,4,6-trimethyltetrahydro-2H-1,3-thiazine-2-thione (II), 6-amino-4,4,6-trimethyltetrahydro-2(1H)-pyrimidinethione (III), and 3,4-dihydro-4,4,6-trimethyl-2(1H)-pyrimidinethione (V) were isolated from the reaction mixture.

Among these compounds, V was the most stable and thus could be most easily obtained from the reaction mixture. Compound I proved to be identical with the compound which was synthesized by Jansen and Mathes[3] from diacetonamine and carbon disulfide or from 2-methyl-2-isothiocyano-4-pentanone and dithiocarbamic acid. Compound II also was obtained from the reaction of diacetone alcohol or mesityl oxide.

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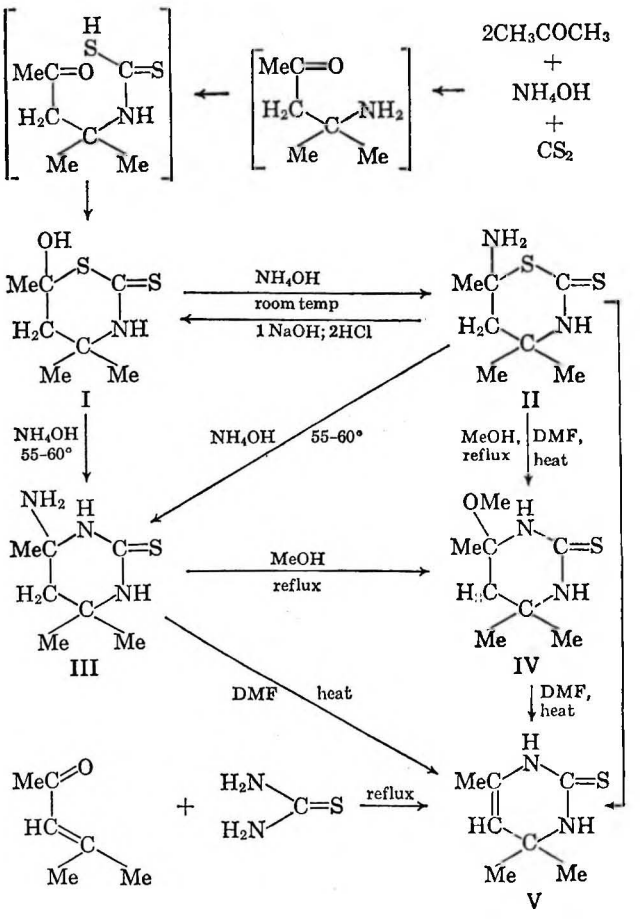
(2) T. Takeshima, T. Hayashi, M. Muraoka, and T. Matsuoka, *J. Org. Chem.*, **32**, 980 (1967).

(3) J. E. Jansen and R. A. Mathes, *J. Amer. Chem. Soc.*, **77**, 5431 (1955).

Interconversion of these compounds are as described in Scheme I (see Experimental Section).

SCHEME I

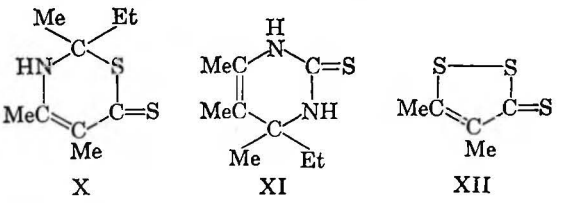


The structure of V was inferred from the following facts. (1) The reaction of mesityl oxide with thiourea gave the compound. (2) It was obtained from I by way of different routes (Scheme I). (3) Upon degradation with hydrochloric acid the compound afforded acetone. (4) Agreement of infrared, ultraviolet, and nmr spectra, the elemental analysis, and the molecular weight measurement. All agreed with the structure formulated for V (consult Experimental Section). The structure of II, III, and IV (see Experimental Section) were inferred from the interrelation between I, II, III, IV, and V, and the absorption spectra.

It is of interest that, when I and 6-hydroxy-4,4,6-trimethyltetrahydro-2H-3,1-thiazine-2-thione (VI) were treated with hot morpholine, elimination of the dithiocarboxyl group occurred to give morpholinium morpholine-N-dithiocarboxylate (IX),[4] which is now fully characterized (see Experimental Section).

Second, it was found that methyl ethyl ketone reacted in two ways. When the reaction was conducted below 0°, the main product was 2-ethyldihydro-2,5,6-trimethyl-4H-3,1-thiazine-4-thione (X, the pattern of cyclohexanone); when it was run at or above room temperature (*ca.* 25°), the main product was 4-ethyl-3,4-dihydro-4,5,6-trimethyl-2(1H)-pyrimidinethione (XI, the pattern of acetone). In addition, when the reaction was carried out below 0°, a small amount of 4,5-dimethyl-1,2-dithiole-3-thione (XII) could be isolated. This compound was more readily prepared by adding hydrogen sulfide to the reaction mixture (see Experimental Section).

The structures of X, XI, and XII were inferred mainly from the infrared and ultraviolet spectra. The features of infrared and ultraviolet spectra of X was quite identical with those of 4(1H)-thiono-5,6,7,8-tetrahydro-2H-3,1-benzothiazine-2-spirocyclohexane.[2] Likewise, the spectrum of XI was similar to that of V. The features of the ultraviolet spectrum of XII were identical with those of 5-phenyl-1,2-dithiole-3-thione.[5]



Experimental Section

6-Hydroxy-4,4,6-trimethyltetrahydro-2H-1,3-thiazine-2-thione (I).—To a mixture of acetone (58 g, 1 mol) and carbon disulfide (152 g, 2 mol) was gently passed dry ammonia gas for *ca.* 30 hr with shaking at room temperature (*ca.* 17°), and the mixture was allowed to stand overnight. Water (50 ml) was added to this reaction mixture to dissolve ammonium dithiocarbamate produced. The solid product was collected, washed with water, and dried: yield 32 g (34%). The crude crop (I) was recrystallized from acetone or methanol or DMF. The recrystallization also was effected by adding twice the volume of water to a saturated solution of the crude substance in pyridine: colorless prisms (20 g); mp 114–115° dec (slow heating) and 122–126° dec (rapid heating); the compound produced yellowish green or light green coloration toward Grote reagent;[6] uv max (99% EtOH) 241 mμ (log ε 3.85), 286 (4.11); ir (KBr) 3350 (m), 3174 (m), 1536 (s), 1012 (s), 958 cm^{-1} (s).

Anal. Calcd for $C_7H_{13}NOS_2$: C, 43.94; H, 6.85; N, 7.32; S, 33.52; mol wt (vapor pressure osmometer), 191.3. Found: C, 44.35; H, 6.82; N, 7.39; S, 33.08; mol wt, 214 (in acetone).

The melting point and the infrared spectrum of this compound were in good agreement with the ones reported by Jansen and Mathes[3] (reported mp 114° dec).

Conversion of 6-Amino-4,4,6-trimethyltetrahydro-2H-1,3-thiazine-2-thione (II) into I.—Compound II (1 g), which is described below, was dissolved in 6 *N* aqueous sodium hydroxide and kept for 10 hr. The solution was acidified by adding 7 ml of 6 *N* hydrochloric acid while cooling with ice. The white precipitate produced was collected, washed with water, dried, and recrystallized as above: yield 0.86 g. The substance was identified with I by mixture melting point and infrared and ultraviolet spectra.

In accordance with Jansen and Mathes,[3] I upon treatment with 70% sulfuric acid at 85° was dehydrated to give VII, mp 121–122°.

Compound I (3.5 g) was dissolved in 10 ml of 14% aqueous sodium hydroxide and kept for several hours at *ca.* 25°, and then made acidic with 2 *N* hydrochloric acid. The original compound could be nearly quantitatively recovered. The compound thus seemed to be considerably stable toward caustic alkali. Compound I was indifferent toward sodium nitroprusside.

6-Amino-4,4,6-trimethyltetrahydro-2H-1,3-thiazine-2-thione (II).—A mixture of acetone (20.3 g, 0.35 mol), carbon disulfide (100 g, 1.3 mol), and 73 ml of aqueous ammonia (28%) was reacted in a manner similar to that described.[2] The yellow needles produced were collected, washed with water and ether, and dried to yield 14 g (42%).

The crude crop was dissolved in a minimal amount of cold DMF until saturation. To this was added an equal volume of water, and the crystals which separated were collected: yield 9.5 g. Recrystallization also was carried out from ethanol or,

(4) Refer to the paper (p 980) cited in ref 2.

(5) H. Behringer and D. Deichmann, *Tetrahedron Lett.*, No. 11, 1013 (1967).

(6) The color was observed within several minutes after the reagent was applied. It was used merely for reference purpose (test for SH, CS, and CSSH).

better, from acetone below 55°; higher temperature caused partial conversion of II into V and another substance. The compound formed colorless prisms: mp 146–147° dec (slow heating) and 150–157° dec (rapid heating); Grote test, light green tinged with ochre; uv max (99% EtOH) 245 mμ (log ε 3.81), 289 (4.11); ir (KBr) 3372 (m), 3300 (m), 3150 (s), 1620 (m), 1524 (s), 1008 (s), 964 cm^{-1} (s); ir ($CHCl_3$) 3400 (w), 3340 (s), 3150 (m), 1620 (m), 1485 (s), 1004 (s), 965 cm^{-1} (s).

Anal. Calcd for $C_7H_{14}N_2S_2$: C, 44.17; H, 7.42; N, 14.72; S, 33.69; mol wt (vapor pressure osmometer), 190.3. Found: C, 44.22; H, 7.23; N, 14.37; S, 33.59; mol wt, 187 (in acetone).

Conversion of I into II.—A suspension of I (7 g, 0.037 mol) in 15 ml of aqueous ammonia (28%) was shaken at room temperature for 8 hr. The crystals (needles) which separated were collected, washed with water, and dried to yield 4.1 g (59%). Recrystallization gave colorless prisms (*ca.* 3 g) which agreed with II in all respects.

The hydrochloride of II was prepared as follows. Compound II (1 g) was dissolved in 5 ml of 6 *N* hydrochloric acid. The white precipitate produced was collected and recrystallized from aqueous acetone to give colorless crystals, melting above 250°.

Anal. Calcd for $C_7H_{15}N_2S_2Cl$: C, 37.07; H, 6.67; N, 12.35; Cl, 15.63. Found: C, 36.68; H, 6.31; N, 12.31; Cl, 15.41.

Upon refluxing in ethanol or recrystallization from acetic acid or DMF, II was converted into V.

Upon treatment with aqueous ammonia (28%) at room temperature for 3 to 4 days or at 55° for 1 hr, II was converted into III.

Compound II, added to ammoniacal sodium nitroprusside, produced at first yellow coloration and the whole then gradually turned pink-purple.

When refluxed with methanol II yield IV in addition to V (see below). A saturated solution of II in methanol on standing at room temperature for 3 to 4 days afforded IV.

Treatment of II with sodium methoxide in methanol at room temperature likewise gave IV and V.

6-Amino-4,4,6-trimethyltetrahydro-2(1H)-pyrimidinethione (III).—A solution of I (15 g) in 150 ml of aqueous ammonia (28%) was warmed at 55–60° for 1 hr. Colorless prisms separated from the solution. After the mixture cooled, the crystals were collected, washed with 10% aqueous ammonia, and dried: yield 9.8 g (72%). The compound (III) formed colorless prisms, mp 256–258° dec and 251–252° dec (in sealed tube), which cracked near 200° especially when the measurement of melting point was conducted in an open tube. Recrystallization from methanol was not achieved. Upon recrystallization III converted partly into IV and V thereby lowering the purity: Grote test, greenish blue; uv max (99% EtOH) 248 mμ (log ε 4.15); ir (KBr) 3335 (m), 3200 (s, br), 1568 (s), 1535 (s), 1012 cm^{-1} (m); ir ($CHCl_3$) 3404 (s), 3200 (m, br), 1565 (m), 1525 (m), 1002 cm^{-1} (m).

Anal. Calcd for $C_7H_{15}N_3S$: C, 48.52; H, 8.73; N, 24.25; S, 18.51. Found: C, 48.51; H, 8.60; N, 22.79; S, 18.63. The analysis was repeated several times, but the nitrogen content measured was always lower than the calculated value. This may be due to the nature of the compound which was likely to liberate ammonia.

Compound III upon recrystallization from acetic acid, DMF, or morpholine was converted into V. When refluxed with methanol for 1 hr III yielded IV in addition to V (see below).

Compound III, on standing, gradually liberated ammonia and was converted into V. The abortive attempt to prepare the hydrochloride of III may be due to this nature of the compound.

Conversion of II into 6-Methoxy-4,4,6-trimethyltetrahydro-2(1H)-pyrimidinethione (IV).—Compound II (4 g) was dissolved in 40 ml of hot methanol and refluxed for 1 hr. After being cooled, colorless prisms which separated were collected, washed with methanol, and dried: yield 1.8 g (51%). The crude crop was dissolved in a minimal quantity of cold DMF, and to this was added an equal volume of water. The crystals which separated were collected: colorless prisms or cubes (yield, 1.2 g); mp 267° dec and 241–242° dec (in sealed tube); the crystal cracked near 200° before it had melted; Grote test, light green tinged with ochre; uv max (99% EtOH) 249 mμ (log ε 4.08); ir (KBr) 3200 (s, br), 1565 (s), 1510 (s), 1182 (s), 1086 cm^{-1} (m); ir ($CHCl_3$) 3400 (s), 1530 (s, br), 1495 (s), 1152 (s), 1084 cm^{-1} (m).

Anal. Calcd for $C_8H_{18}N_2OS$: C, 51.05; H, 8.57; N, 14.88; S, 17.00; mol wt (Rast), 188.2. Found: C, 51.30; H, 8.27; N, 15.25; S, 17.41; mol wt, 180.

Conversion of III into IV.—Compound III (0.5 g) was suspended in 5 ml of methanol and refluxed for 1 hr. The crystalline product was collected, washed with methanol, and dried to yield 0.4 g (74%).

The product obtained by this or preceding method was contaminated by V.

Conversion of II into IV.—Compound IV also was obtained from II by treating the latter with sodium methoxide in methanol at *ca.* 25° for several hours. In this case contamination by V also was inevitable.

When a saturated solution of II in methanol was allowed to stand at room temperature for 2 to 3 days, a small amount of IV separated from the solution. This specimen consisted of almost pure IV.

Upon recrystallization from DMF or morpholine IV was converted into V.

Conversion of III into 3,4-Dihydro-4,4,6-trimethyl-2(1H)-pyrimidinethione (V).—Compound III (2 g) was refluxed with 4 ml of DMF for 10 min (considerable amount of ammonia gas evolved) and then allowed to stand. Long needles separated from the solution, and at the same time, the color of the solution turned greenish blue. When the whole was cooled to room temperature, the color turned ochre yellow. To the reaction mixture was added 10 ml of water and the whole then was filtered. The crystalline product obtained was washed with water and dried: yield 1.75 g (97%). Recrystallization from ethanol gave colorless needles (*ca.* 1 g): mp 266–267° dec (slow heating) and 274–276° dec (rapid heating); Grote test, light green tinged with ochre; uv max (99% EtOH) 269 mμ (log ε 4.08); ir (KBr) ~3200 (s, br), 1704 (m), 1658 (m), 1578 (s), 1493 cm^{-1} (m); ir ($CHCl_3$) 3428 (s), 3400 (s), 1700 (m), 1650 (w), 1535 cm^{-1} (s); nmr (CF_3CO_2H) δ 8.89 [s, 1, N(3)H], 8.07 [s, 1, N(1)H], 4.95 (s, 1, CH), 1.94 (s, 3, CH_3), 1.49 (s, 6, $2CH_3$).

Anal. Calcd for $C_7H_{12}N_2S$: C, 53.81; H, 7.74; N, 17.93; S, 20.52; mol wt (Rast), 156.2. Found: C, 53.75; H, 7.66; N, 17.57; S, 20.44; mol wt, 180.

3,4-Dihydro-4,4,6-trimethyl-2(1H)-pyrimidinethione (V).—A mixture of acetone (29 g, 0.5 mol), carbon disulfide (76 g, 1 mol), and 240 ml of aqueous ammonia (28%) was treated as above: crude crop yield 7 g (18%). Recrystallization from ethanol gave colorless needles (*ca.* 5 g) which were identified with V by mixture melting point, infrared spectrum, and elemental analysis.

Compound V also was prepared as follows. A mixture of thiourea (2 g, 0.026 mol) and mesityl oxide (10 g, 0.1 mol) was refluxed for 8 hr. After the mixture cooled, the crystalline product was collected, washed with ethanol, and dried to yield 2 g (48%). Recrystallization from ethanol gave colorless needles (*ca.* 1.1 g) which were identified with V by the same method as above.

Compound V was rather stable toward acid and alkali. When refluxed with 6 *N* hydrochloric acid for 3 hr or with 12 *N* sulfuric acid for the same period, the compound afforded acetone which was identified by the 2,4-dinitrophenylhydrazone. Compound V was indifferent toward sodium nitroprusside.

6-Hydroxy-4,4,6-trimethyltetrahydro-2H-3,1-thiazine-2-thione (VI).—The preparation followed the method described by Jansen and Mathes.[7]

A small amount of the compound was formed in the following reaction in an alkaline medium. A mixture of mesityl oxide (24.5 g, 0.25 mol), carbon disulfide (19 g, 0.25 mol), and 17 ml of aqueous ammonia (28%) was shaken at room temperature for 1 day and then allowed to stand for 10 days. The pasty product which separated was collected, washed with water and ethanol, and dried: yield 2.5 g (5.2%). Recrystallization from benzene gave colorless needles (*ca.* 1.5 g): mp 126–127° (slow heating) and 154–156° (rapid heating) (reported[3] mp 128–129°); ir (KBr) 3320 (s), 3162 (s), 1525 (s), 1008 cm^{-1} (s); ir ($CHCl_3$) 3578 (m), 3340 (m), 1483 (m), 1010 cm^{-1} (s).

Anal. Calcd for $C_7H_{13}NOS_2$: C, 43.95; H, 6.85; N, 7.32; S, 33.52. Found: C, 43.85; H, 6.69; N, 7.35; S, 33.47.

The infrared spectrum of this specimen was in good agreement with that of the specimen prepared by the method of Jansen and Mathes.[3]

Compound VI, on treatment with an acid, was easily dehydrated to give 4,4,6-trimethyldihydro-2H-3,1-thiazine-2-thione (VIII) which melted at 95–97° and was considered to be identical with the compound obtained by Jansen and Mathes.[7]

(7) J. E. Jansen and R. A. Mathes, *J. Amer. Chem. Soc.*, **77**, 2866 (1955).

Elimination of Dithiocarboxyl Group from I and VI.—Compound I (2 g) was refluxed with 8 ml of morpholine for several minutes. After being cooled, the separated crystals were collected, washed with ether, and dried to yield 1.9 g (73%). Recrystallization from morpholine gave colorless needles (1.2 g) which were identified with IX by mixture melting point and infrared spectrum.

Compound VI was treated in the same way as above to give IX in 65% yield. It seemed that the reaction of VI was somewhat slow. Further, I, on treatment with piperidine, gave only an oily product.

Reaction of 3,4-Dihydro-4,4,6-trimethyl-2H-1,3-thiazine-2-thione (VII) and 4,4,6-Trimethyldihydro-2H-3,1-thiazine-2-thione (VIII) with Morpholine.—Compound VII which was prepared by the method of Jansen and Mathes,[3] on the same treatment as above, yielded an oily product, which was not studied further.

Compound VIII (2 g) was refluxed with 8 ml of morpholine for 15 min; upon heating the solution turned in the sequence of yellow, yellowish green, yellow, and finally red. After being cooled, the whole was poured in 30 ml of ice–water and stirred thoroughly. The solid product was collected, washed with water and ether, and dried: yield 0.4 g. Recrystallization from ethanol gave colorless plates (*ca.* 0.2 g), mp 175–176°.

Anal. Found: C, 41.14; H, 6.29; N, 19.02; S, 22.19.

The compound was not investigated further.

2-Ethyldihydro-2,5,6-trimethyl-4H-3,1-thiazine-4-thione (X).—A mixture of methyl ethyl ketone (50 g, 0.69 mol), carbon disulfide (53 g, 0.63 mol), and 145 ml of aqueous ammonia (28%) was reacted as mentioned already below 0°. When the crude product was recrystallized from methanol, *ca.* 12 g of yellow plates (X) was obtained: mp 145–146°; Grote test, yellow ochre; color reaction toward cupric ion, deep red; uv max (99% EtOH) 334 mμ (log ε 3.65), 406 (ε 3.35); ir (KBr) 3165 (s), 1548 (s), 1516 (vs), 1452 cm^{-1} (m); ir ($CHCl_3$) 3396 (s), 1525 (s), 1455 cm^{-1} (m).

Anal. Calcd for $C_9H_{15}NS_2$: C, 53.72; H, 7.51; N, 6.96; S, 31.81; mol wt (vapor pressure osmometer), 201.22. Found: C, 53.87; H, 7.44; N, 6.82; S, 31.88; mol wt, 200 (in acetone).

In this case, XI (mentioned below) could not be isolated, and XII (also mentioned below) was isolated in poor yield (0.5 g).

4-Ethyl-3,4-dihydro-4,5,6-trimethyl-2(1H)-pyrimidinethione (XI).—The proceding reaction was carried out at 25–30° for *ca.* 70 hr and then kept overnight. The reaction mixture was concentrated, and the yellow pasty mass which separated from the solution was collected and washed with water and ether. The crude product, which weighed *ca.* 16 g, was washed with methanol and recrystallized from ethanol to give *ca.* 12 g of colorless short prisms (XI): mp 246–247°; Grote test, light yellowish green tinged with ochre; uv max (99% EtOH) 265 mμ (log ε 4.08); ir (KBr) 3210 (s), 1702 (m), 1575 cm^{-1} (s).

Anal. Calcd for $C_9H_{16}N_2S$: C, 58.67; H, 8.75; N, 15.21; S, 17.37; mol wt (vapor pressure osmometer), 184.23. Found: C, 58.64; H, 8.48; N, 15.14; S, 17.33; mol wt, 189 (in chloroform).

An additional amount (*ca.* 0.5 g) of X was isolated by concentrating the above methanol washings.

4,5-Dimethyl-1,2-dithiole-3-thione (XII).—To a mixture of methyl ethyl ketone (50 g, 0.69 mol), carbon disulfide (53 g, 0.63 mol), and 300 ml of aqueous ammonia (28%) was gently passed hydrogen sulfide for *ca.* 8 hr with stirring at 25–33° and then kept overnight. When the reaction mixture was concentrated, an yellow-orange pasty mass was obtained, washed with water, and dried; yield *ca.* 2 g. The crude product was shaken with carbon tetrachloride and filtered. The filtrate was concentrated to give *ca.* 1 g of yellow needles (XII): mp 96°; Grote test, dark green; uv max (99% EtOH) 225 mμ (log ε 4.00), 243 (sh) (3.77), 275 (3.81), 310 (3.73), 409 (4.01).

Anal. Calcd for $C_5H_6S_3$: C, 37.05; H, 3.73; S, 59.22; mol wt (vapor pressure osmometer), 162.10. Found: C, 37.05; H, 3.78; S, 59.27; mol wt, 161.2 (in chloroform).

The above crude product from which XII was removed was recrystallized from methanol to give *ca.* 1 g of X.

Registry No.—I, 16504-29-3; II, 16504-30-6; III, 16504-31-7; IV, 16504-32-8; V, 5778-17-6; VI, 16504-34-0; X, 16504-35-1; XI, 16504-36-2; XII, 3354-39-0; carbon disulfide, 75-15-0; ammonia, 7664-41-7; acetone, 67-64-1; methyl ethyl ketone, 78-93-3.

Acknowledgment.—The authors are grateful to Dr. Hiroshi Midorikawa (The Institute of Physical and Chemical Research) for his generous aid in many respects. Heartfelt thanks are also owed to Dr. Heinosuke Yasuda and Miss Hiroe Asaba for their useful advice and help.

The Rearrangement of Methoxylated Phenylanthranils

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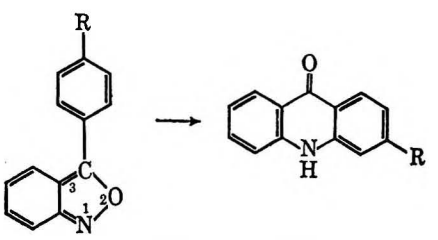
Received February 26, 1968

Methoxylated phenylanthranils rearrange under pyrolytic conditions to acridones in which the nitrogen is *para* instead of *meta* to the methoxyl function. In the presence of nitrous acid, these methoxylated anthranils yield substituted azoxybenzoic acids instead of the anticipated acridones. This new rearrangement and reaction of methoxylated phenylanthranils may be explained by the activating effect of the methoxyl function on the position *para* to it. A nitrene has been proposed as the intermediate in the rearrangement. The application of these new reactions to the synthesis of compounds related to the anticancer alkaloid, acronycine, is reported.

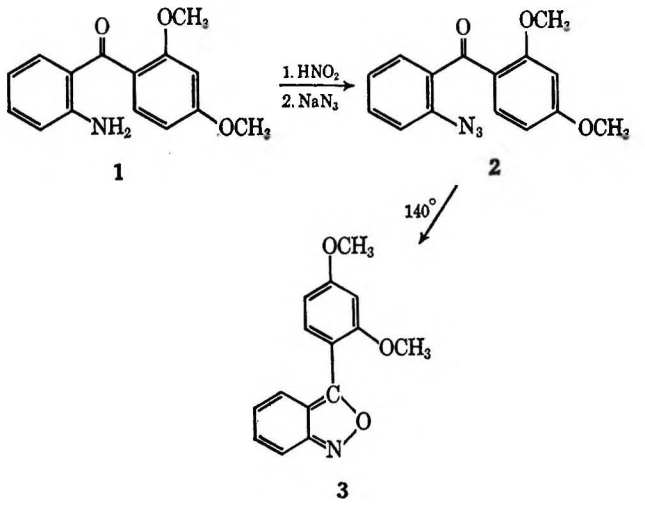
Acridones are often synthesized by the rearrangement of phenylanthranil and *para*-substituted phenylanthranils[1-6] catalyzed by nitrous acid or heat. The yields are generally high and the *para* relationship of the substituent R of the phenyl ring to the carbon 3 of the anthranil ring system has been shown to remain after the rearrangement.[5] The lack of information concerning the rearrangement of alkoxyphenylanthranils and the need for methoxyacridones prompted us to investigate this rearrangement. These methoxyacridones were necessary as starting materials for our work



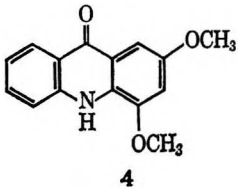
R = alkyl or halogen

(1) A. Kliegl, *Ber.*, **42**, 591 (1909).
(2) E. Bamberger, *ibid.*, **42**, 1707 (1909).
(3) I. Tanasescu and M. Suciu, *Bull. Soc. Chim. Fr.*, **4**, 245 (1937).
(4) R. B. Davis and L. C. Pizzini, *J. Org. Chem.*, **25**, 1884 (1960).
(5) I. Tanasescu, C. Anghel, and A. Popescu, *Studia Univ. Babes-Bolyai, Ser. I*, **8**, 141 (1963); *Chem. Abstr.*, **61**, 13279d (1964).
(6) P. L. Coe, A. E. Jukes, and J. C. Tatlow, *J. Chem. Soc., Sect. C*, 2020 (1966).

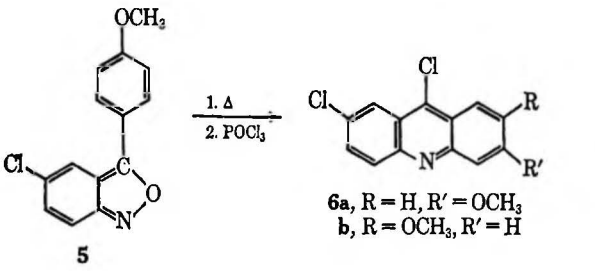
in the synthesis of acronycine.[7,8] The study of the rearrangement of 3-(2,4-dimethoxyphenyl)anthranil (3) was therefore undertaken.



Phenylanthranil has been reported as the product from the pyrolysis of 2-azidobenzophenone.[9] Accordingly, conversion of 2,4-dimethoxy-2′-aminobenzophenone[10] (1) into 2,4-dimethoxy-2′-azidobenzophenone (2) followed by pyrolysis at 140° gave 3. Pyrolysis of 3 at 260° gave a dimethoxyacridone in 50% yield which was not the expected 1,3-dimethoxyacridone.[11] There was no evidence of any of the expected product. Based on nmr data the product was assigned the structure 2,4-dimethoxyacridone (4). H-2 and H-4 of 1,3-dimethoxyacridone in DMSO-d_6 appear as two doublets at 6.26 and 6.51 ppm (J = 2 cps). H-3 of 4 in $CDCl_3$ can be observed as a doublet at 6.67 ppm (J = 2.5 cps). H-1 is deshielded by the carbonyl function and can not be distinguished from the rest of the aromatic protons.



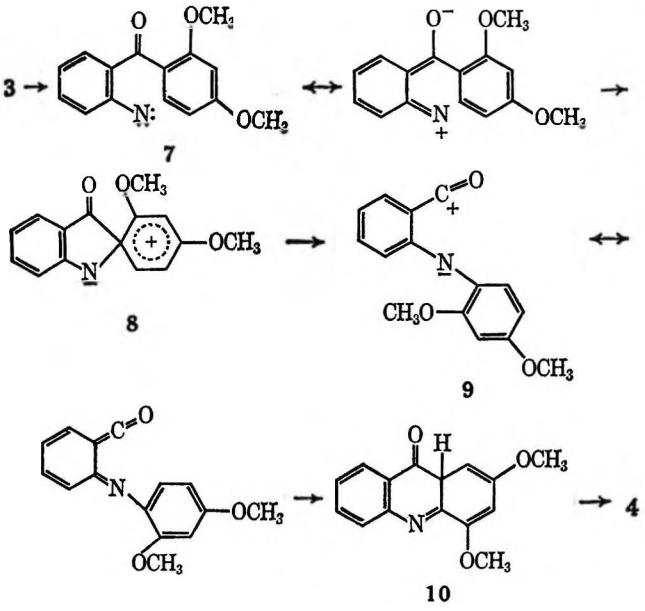
The formation of this unexpected product indicated that the methoxy groups may have a strong directing effect on the rearrangement. 3-(*p*-Methoxyphenyl)-5-chloroanthranil[4] (5) was pyrolyzed in the same manner in order to assess the influence of the methoxy function on this novel rearrangement. The crude product was very insoluble and was converted into the corresponding 9-chloroacridine by treatment with phosphorous oxychloride.[5] Purification by column chromatography led to the separation of two isomeric 9-chloroacridines in the ratio of 3:1. The major component, mp 192–195°, was assigned the 3-methoxy-7,9-di-



chloroacridine (6a) structure (lit.[12] mp 194–195°) and the minor component, mp 200–203, was assigned the 2-methoxy-7,9-dichloroacridine (6b) structure (lit.[13] mp 204–205°).

The above observations clearly indicate that the methoxy function is changing the course of the rearrangement by activating the position *ortho* and *para* to it. The probable mechanism is outlined in Scheme I. Presumably, a nitrene 7 is initially formed, followed by the formation of a five-membered intermediate 8. This intermediate 8 is a result of the attack of the positively charged nitrogen at the activated position. In the absence of an activating group, a six-membered intermediate will be formed, leading to the normal rearrangement product, without breaking any C–C bond. Cleavage of the C–C bond of the five-membered ring gives 9, followed by ring closure to give 10, which gives the product 4 by a proton shift.

SCHEME I



The nitrous acid catalyzed rearrangement of these substituted phenylanthranils was also investigated. When 5 was treated with sodium nitrite in 5% sulfuric acid in acetic acid, instead of an acridone, a yellow crystalline product was obtained in good yield. Physical and spectral informations pointed to an azoxy function. Even though no satisfactory elemental analysis was obtained, the product, which was probably contaminated with some azo compound was assigned structure 11. Further support for this structural assignment came

(7) J. R. Beck, R. N. Booher, A. C. Brown, R. Kowk, and A. Pohland, *J. Amer. Chem. Soc.*, **89**, 3934 (1967).

(8) J. R. Beck, R. Kowk, A. Pohland, R. N. Booher, A. C. Brown, L. E. Patterson, P. Pranc, and B. K. Rockey, *ibid.*, in press.

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(11) L. J. Drummond and F. N. Tehey, *Aust. J. Sci. Res.*, **A2**, 630 (1949).

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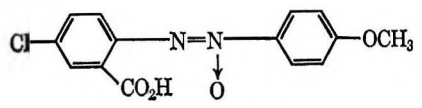
(13) I. K. H. Feldman and E. L. Kopeliovich, *Arch. Pharm.* (Weinheim), 488 (1935).



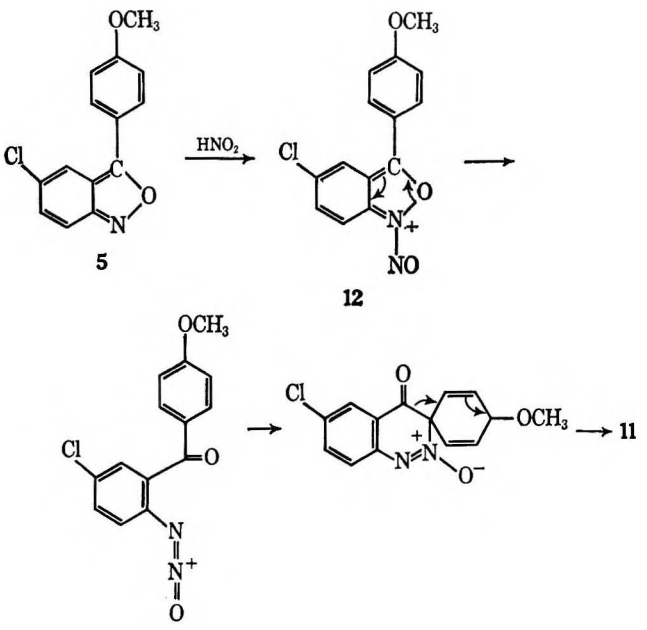
11

from the cleavage of **11** with sodium hydrosulfite to give 5-chloroanthranolic acid and *p*-anisidine.

Similarily, **3** was treated successively with nitrous acid and sodium hydrosulfite. The expected product, 2,4-dimethoxyaniline was isolated and identified by thin-layer chromatography. The position of the azoxy oxygen has not been definitely determined. The assignment is based on mechanistic grounds only.

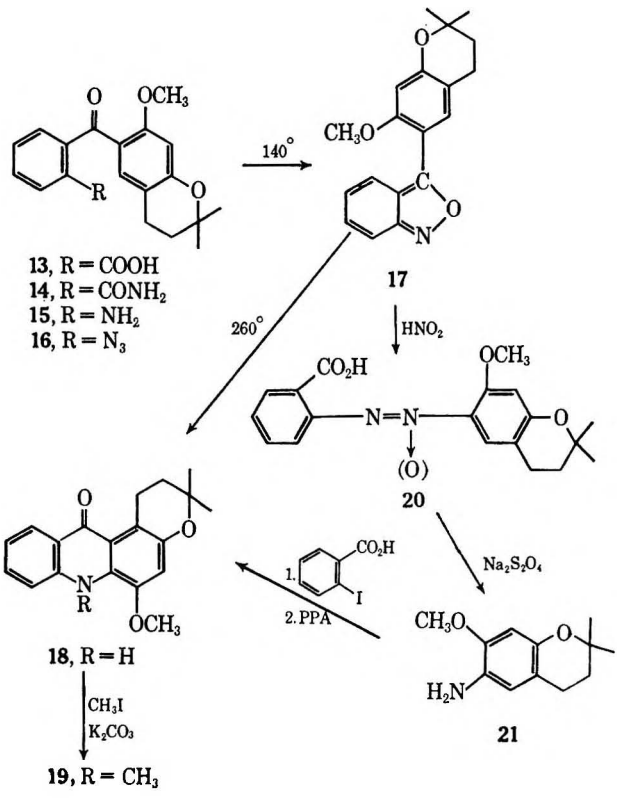
As in the case of the thermal rearrangement, the position *para* to the methoxy function is activated leading to the attack by the nitroso intermediate as shown in the reaction mechanism outlined in Scheme II.

SCHEME II



The utility of this novel rearrangement was applied to the synthesis of compounds related to acronycin.[7] The reaction sequence is shown in Scheme III. Friedel–Crafts reaction between phthalic anhydride and 7-methoxy-2,2-dimethylchroman[8] gave the keto acid **13**, which was converted into the amide **14**. Hofmann rearrangement of **14** gave the amine **15**. Conversion of the amine **15** into the azide **16** followed by pyrolysis gave the anthranil **17**. Heating the anthranil **17** at 260° gave the acridone **18** which was methylated with methyl iodide and potassium carbonate to give **19**. Compound **19** is isomeric to dihydroacronycine.[7] The anthranil **17** reacted with nitrous acid to give a mixture of azo and azoxy compounds **20** which were cleaved with sodium hydrosulfite to give 6-amino-7-methoxy-2,2-dimethylchroman (**21**). Compound **21** was treated with *o*-iodobenzoic acid followed by cyclization in polyphosphoric acid to give **18** (Scheme III).

SCHEME III



Experimental Section

Melting points were determined on a Thomas–Hoover apparatus and are corrected. Nuclear magnetic resonance spectra were recorded using a Varian HA-60 spectrometer. Tetramethylsilane was used as internal reference.

2-Azido-2′,4′-dimethoxybenzophenone (2).—A solution of 3 g of 2,4-dimethoxy-2′-aminobenzophenone[11] (**1**) in 30 ml of acetic acid and 15 ml of 1 *M* sulfuric acid was cooled to −20° (Dry Ice, acetone) with stirring. To this solution was added 0.7 g of sodium nitrite in 6 ml of water. After 5 min 1.3 g of sodium azide in 6 ml of water was added as fast as the evolution of nitrogen would allow. The mixture was stirred for another 30 min, and temperature was allowed to go up slowly. It was diluted with 100 ml of water and extracted with ether. The ether solution was washed with water, dilute sodium bicarbonate, and water, and was dried. Removal of solvent under reduced pressure gave an oily residue which crystallized when washed with ether. The product was recrystallized from ether to give 2 g of colorless crystals, mp 96–98°.

Anal. Calcd for $C_{15}H_{13}N_3O_3$: N, 14.83. Found: N, 14.88.

3-(2,4-Dimethoxyphenyl)anthranil (3).—The azide **2** (2 g) in a 50-ml round-bottom flask was heated in an oil bath at 140° for 5 min. (Large runs led to uncontrollable exothermic reaction.) The products from seven such runs were combined and recrystallized from hexane to give 13 g of greenish yellow needles, mp 93–95°. Further recrystallization from the same solvent gave the analytical sample, mp 94–95°.

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.87; H, 5.22; N, 5.28.

2,4-Dimethoxyacridone (4).—A 100-ml, round-bottom flask containing 5 g of 3-(2,4-dimethoxyphenyl)anthranil (**3**) was heated at 255–260° in a Wood's metal bath for 10 min. The crude product was chromatographed on 700 g of Woelm silica gel and was eluted with benzene–ethyl acetate mixture (4:1). The product isolated was recrystallized from benzene–hexane, to give 2.5 g of yellow crystals, mp 185–187°.

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.34; H, 5.01; N, 5.29.

Pyrolysis of 3-(*p*-Methoxyphenyl)-5-chloroanthranil[4] (5).—A 50-ml round-bottom flask containing 7 g of **5** was heated at 260° for 10 min. The crude product was refluxed in 50 ml of phosphorous oxychloride for 1 hr. The excess phosphorous oxychloride was removed under reduced pressure. The residue was poured into ice-cold ammonium hydroxide. After 2 hr at room temperature the mixture was extracted with chloroform and dried. After removal of solvent, the residue was chromatographed on 1 kg of Woelm silica gel and eluted with 2% ethyl acetate in benzene. The first compound to come out was **6b**. It was recrystallized from hexane to give 0.53 g, mp 200–203°.

Compound **6a** was recrystallized from chloroform–hexane to give 1.5 g, mp 194–195°.

5-Chloro-2-(4-methoxyphenylazoxy)benzoic Acid (11).—A solution of 12 g of the anthranil **5** in 500 ml of 5% sulfuric acid in acetic acid was cooled slightly on ice. To it was added 24 g of finely powdered sodium nitrite in small portions in about 15 min. It was removed from the ice, kept at room temperature for 10 min, and then poured into 1200 ml of water. The precipitate was filtered and recrystallized from acetonitrile to give 10 g of yellow needles, mp 195–197°. The product was cleaved with sodium hydrosulfite in a manner similar to that used in the preparation of **21** to give 5-chloroanthranilic acid and *p*-anisidine, both of which were identical with authentic samples.

Reaction of 3-(2,4-Dimethoxyphenyl)anthranil (3) with Nitrous Acid.—In a manner similar to that of the preparation of **11**, 2 g of **3** was treated with 4 g of sodium nitrite. The crude product (0.5 g) could not be recrystallized. It was treated with sodium hydrosulfite as described in the preparation of **21**. The basic material was extracted with ether, and the product, 2,4-dimethoxyaniline, was identified by thin layer chromatography.

6-(2-Carboxybenzoyl)-7-methoxy-2,2-dimethylchroman (13).—A mixture of 15 g (0.078 *M*) of 7-methoxy-2,2-dimethylchroman[8] and 11.6 g (0.078 *M*) of phthalic anhydride in 100 ml of tetrachloroethane and 20 ml of nitrobenzene was stirred in ice bath until temperature was below 5°. To the mixture was added 21 g (0.156 *M*) of aluminum chloride in small portions. The mixture was kept in the refrigerator for 2 days. It was poured into ice and treated with excess dilute HCl. The organic solvent was removed by steam distillation. The gummy residue from the aqueous layer was cooled and triturated with acetonitrile to give a light brown solid which was recrystallized once from acetonitrile to give 10 g of colorless crystals, mp 180–182°. A further recrystallization from the same solvent gave the analytical sample, mp 181–182°.

Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.49; H, 6.01.

6-(2-Carboxyamidobenzoyl)-7-methoxy-2,2-dimethylchroman (14).—To a solution of 8 g of the acid **13** in 60 ml of pyridine cooled in ice bath was added 10 ml of thionyl chloride in small portions. The solution was kept at room temperature for another 2 hr and was then added to ice-cold ammonium hydroxide slowly with stirring. Excess ammonia was removed under reduced pressure. The mixture was further diluted with water, and the precipitate was filtered and washed with water. Recrystallization from acetonitrile gave 5.6 g of colorless crystals, mp 185–188°. The analytical sample from the same solvent had mp 193–195°.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 71.04; H, 6.45; N, 4.16.

6-(2-Aminobenzoyl)-7-methoxy-2,2-dimethylchroman (15).—To a suspension of 10 g of amide **14** in 30 ml of water containing 2.8 g of sodium hydroxide was added 60 ml of 5% sodium hypochlorite solution. The mixture was stirred at room temperature for 45 min and filtered, and the clear filtrate was heated on a steam bath for 40 min. It was diluted with 150 ml of water and kept in the refrigerator overnight. The yellow precipitate was collected and washed with water and recrystallized once from chloroform–hexane to give 6.6 g of yellow crystals, mp 75–77°. Further recrystallization from hexane gave the analytical sample, mp 77–79°.

Anal. Calcd for $C_{19}H_{21}NO_3$: N, 4.50. Found: N, 4.58.

6-(2-Azidobenzoyl)-7-methoxy-2,2-dimethylchroman (16).—Similar to the preparation of **2**, 6 g of the amine **15** was treated with 2 g of sodium azide. The crude product was recrystallized from hexane to give 4.3 g of colorless crystals, mp 80–83°. The analytical sample from the same solvent had mp 82–83°.

Anal. Calcd for $C_{19}H_{19}N_3O_3$: N, 12.45. Found: N, 12.30.

3-(7-Methoxy-2,2-dimethyl-6-chromanyl)anthranil (17).—The azide **16** (4.5 g) was placed in a test tube and heated to 140° in an oil bath for about 6 min until evolution of nitrogen stopped. The dark brown crude product was chromatographed on 200 g of Woelm silica gel and was eluted with 1% ethyl acetate in benzene. The product failed to crystallize and had uv bands at λ_{max} 260 and 362 mμ.

6-Methoxy-3,3-dimethyl-2,3-dihydro-12(7H)-1H-pyrano[3,2-*a*]-acridone (18).—The anthranil **17** (4 g) was heated to 250–260° for 10 min in a Wood's metal bath. The dark brown crude product was chromatographed on 200 g of Woelm silica gel and was eluted with 10% ethyl acetate in benzene. The isolated product was recrystallized from acetone–hexane to give 2.25 g of yellow crystals, mp 200–202°. Further recrystallizations from the same solvents gave the analytical sample, mp 205–207°.

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.16; N, 4.53. Found: C, 73.65; H, 6.37; N, 4.30.

6-Methoxy-3,3,7-trimethyl-2,3-dihydro-12(7H)-1H-pyrano-[3,2-*a*]acridone (19).—A mixture of 2 g of the acridone **18**, 40 g of anhydrous potassium carbonate, and 50 ml of methyl iodide in 250 ml of acetone was refluxed for 3 days. Solvent was removed under reduced pressure and the residue, diluted with water, was extracted with chloroform, and the chloroform layer was dried. Removal of solvent gave a yellow residue which was chromatographed on 100 g of Woelm silica gel eluted with 1% ethyl acetate in benzene. The product was isolated and recrystallized from hexane to give 1.25 g of yellow crystals, mp 119–121°.

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.54; N, 4.33. Found: C, 73.99; H, 6.57; N, 4.42.

2-(7-Methoxy-2,2-dimethyl-2-chromanylazoxy)benzoic Acid (20).—A solution of 4 g of anthranil **17** in 120 ml of 5% sulfuric acid in acetic acid was treated with 12 g of sodium nitrite in a manner similar to that of the preparation of **11**. The orange-colored product was recrystallized from methanol, mp 170–171°.

6-Amino-7-methoxy-2,2-dimethylchroman[3] (21).—A suspension of 0.9 g of the azoxy compound **20** in 20 ml of water was treated with dilute sodium hydroxide solution until a clear solution was obtained. It was warmed to 45–50° in a water bath with stirring. To this solution was added 1.5 g of sodium hydrosulfite. Stirring was continued for 20 min. After heating on a steam bath for 10 min, the solution became cloudy, and upon cooling a white precipitate was formed. The precipitate was filtered, washed with water, and dried to give 300 mg of material which was recrystallized from hexane twice to give small crystals, mp 89–90°.

6-Methoxy-3,3-dimethyl-2,3-dihydro-12(7H)-1H-pyrano[3,2-*a*]-acridone (18) from 21.—A mixture of 0.4 g of *o*-iodobenzoic acid, 0.11 g of copper, 0.35 g of cupric carbonate and 0.14 g of potassium carbonate in 20 ml of *n*-amyl alcohol was refluxed with stirring for 52 hr. The alcohol was removed by steam distillation. The aqueous portion was filtered and extracted with chloroform to remove unreacted starting material. The aqueous solution was acidified with concentrated HCl, extracted with chloroform, and dried. Solvent was removed under reduced pressure, and the residue was heated on a steam bath with 40 ml of polyphosphoric acid for 2 hr. It was diluted with ice water. The brownish precipitate was extracted with chloroform, washed with sodium bicarbonate solution and water, and dried. After removing the solvent under reduced pressure, the residue was chromatographed on 50 g of Woelm silica gel eluted with 2% ethyl acetate in benzene to give 40 mg of **18**, mp 200–202°.

Registry No.—**2**, 16710-28-4; **3**, 16710-29-5; **4**, 16710-30-8; **6a**, 16710-31-9; **6b**, 16710-32-0; **13**, 16710-33-1; **14**, 16710-34-2; **15**, 16710-35-3; **16**, 16710-36-4; **18**, 16710-38-6; **19**, 16710-37-5; **20**, 16720-15-3.

Acknowledgment.—The authors wish to thank Drs. Jack Baldwin, Nelson Leonard, and Ernest Wenkert for helpful discussions.

Reactions of 3,4-Disubstituted 4-Oxazolin-2-ones. III.[1] The Reaction of 3,4-Diphenyl-4-oxazolin-2-one with Organic Nitrites

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Received February 19, 1968

The reaction of 3,4-diphenyl-4-oxazolin-2-one (**4**) with benzyl, *n*-butyl, or *n*-amyl nitrite under acidic conditions leads to 4-alkoxy-3,4-diphenyl-5-oximinooxazolidin-2-ones (**6a**, **6b**, and **6c**, respectively), *via* addition of the nitrite ester to the double bond and rearrangement of the unstable intermediate 5-nitroso-2-oxazolidinone **5**. Compound **6a** was chosen for further chemical investigation; it rearranged in the presence of bases to 5-benzyloxy-4,5-diphenyl-3-hydroxyhydantoin (**8**), which was converted into 4,5-diphenyl-5-hydroxyhydantoin (**10**). The latter compound was independently synthesized through a novel route.

Previous work[1] from this laboratory has dealt with some unusual reactions of 3,4-disubstituted 4-oxazolin-2-ones (such as **1**), whose unexpected reactivity has been correlated with the lack of a substituent at position 5. In the course of our study, we investigated the reaction of 3,4-diphenyl-4-oxazolin-2-one (**4**, Scheme I) with alkyl nitrites under acidic conditions. By analogy with the behavior of compound **4** toward bromine,[1a] and of other heterocycles, *e.g.*, pyrazolin-5-ones, toward bromine or alkyl nitrites,[3] a substitution with formation of the 5-nitroso derivative **2** was anticipated. However, the analytical data for the products of the reactions between **4** and benzyl, *n*-butyl, or *n*-amyl nitrite (50–75% yield) indicated that *addition* of the reagents to the oxazolone had taken place. Structures **3** or **5**, which could be expected from these additions, were not in agreement with the ir spectra, which showed absorption in the 3-μ region (hydroxyl), and two strong bands in the 5.5–5.8-μ region (C=O and possibly C=N). These data rather pointed to the oximino structures **6a**, **b**, and **c**, which are tautomeric with those of type **5**. No evidence was found for the presence of even small amounts of the latter forms, which certainly are intermediates of the reaction.

Compound **6a** (R = benzyl) was selected for further chemical investigation, in view of the greater reactivity and ease of characterization shown by benzyl derivatives. Acetylation and benzoylation of **6a** gave the acetate and benzoate **7a** and **b**, respectively, thus providing further evidence for the presence of the oximino group. Treatment of **6a** with bases (KOH in ethanol, pyridine, etc.) produced an alkali-soluble compound, which gave a positive ferric chloride test for hydroxamic acid, and showed in its ir spectrum the typical hydantoin carbonyl absorption[4] (λ_{CO} 5.58, 5.72 μ). These data, and the reported similar case of the facile isomerization of phthaloxime to N-hydroxyphthalimide,[5] led us to formulate this compound as 5-benzyloxy-1,5-diphenyl-3-hydroxyhydantoin (**8**, Scheme II). Further structural proofs were obtained as follows. Attempts to remove the 3-hydroxy group by reduction with zinc in acetic acid, according to a procedure which has proven useful in a similar case,[6] gave, besides the expected benzyloxyhydantoin **9**, benzyl acetate and a product clearly originating from debenzylation of **9**, which was identified as 1,5-diphenyl-5-hydroxyhydantoin (**10**). The latter compound could also be obtained on treatment of **9** with zinc chloride in acetic acid. 1,5-Diphenyl-5-hydroxyhydantoin has been prepared[7,8] by chromic acid oxidation of 1,5-diphenylhydantoin. However, for an independent preparation of compound **10** the procedure outlined in the sequence **14** → **17** was preferred. Treatment of 2-aminoacetophenone hydrochloride (**14**) with phenyl isocyanate (**15**) according to an usual procedure for the preparation of imidazolones,[9] gave 3,4-diphenyl-4-imidazolin-2-one (**16**). Treatment of **16** with bromine in acetic acid in the presence of sodium acetate gave 5-acetoxy-1,5-diphenylhydantoin[10] (**17**), whose deacetylation afforded a product which was identical with **10**. On the other hand, **17** could be obtained on treatment of **10** with acetic anhydride.

Debenzylation of **8** with zinc chloride in acetic acid gave the desired 3,5-dihydroxyhydantoin **11** (λ_{OH} 3.0; λ_{CO} 5.62, 5.85 μ) in good yield. However, attempts to reduce **11** to **10** with zinc in acetic acid constantly gave a different compound, also obtained in minute yield as a by-product in the reduction of **8** with the same reagent. The compound could also be obtained in good yield on treatment of **10** with zinc in acetic acid and *was reconverted into* **10** *by chromic acid oxidation.* These data, together with analytical and spectral evidence, led us to formulate the compound as N-mandelyl-N′-phenylurea (**12**). Indeed, elemental analysis indicated the formula $C_{15}H_{14}N_2O_3$, the ir spectrum showed bands at 2.97, 3.05 μ (OH and/or NH) and a strong carbonyl band at 5.85 μ, and the nmr spectrum showed, besides the aromatic protons, three broad signals at δ 10.3, 9.2, and 4.25 (1 H each), attributable to different types of active hydrogen, and a singlet at 5.16 (1 H, benzyl proton).

It may be assumed that small amounts of the open-chain tautomers **18** exist at equilibrium in solutions of **10**

(1) For parts I and II of the series, *cf.* (a) M. F. Saettone, *J. Org. Chem.*, **31**, 1959 (1966); (b) M. F. Saettone and A. Marsili, *Tetrahedron Lett.*, 6009 (1966).

(2) Taken in part from the doctoral thesis of E. Bucci.

(3) See, *e.g.*, "The Chemistry of Heterocyclic Compounds," Vol. 20, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1964, pp 81, 85.

(4) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1959, p 221.

(5) L. A. Carpino, *J. Amer. Chem. Soc.*, **79**, 98 (1957).

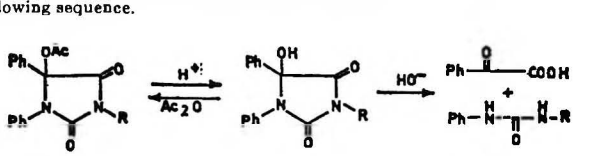
(6) J. A. Moore and J. Binkert, *ibid.*, **81**, 6038 (1959).

(7) H. Aspelund, *Acta Acad. Aboensis, Math. Phys.*, **23**, 11 (1962).

(8) G. A. Holmberg, *Acta Chem. Scand.*, **4**, 821 (1950).

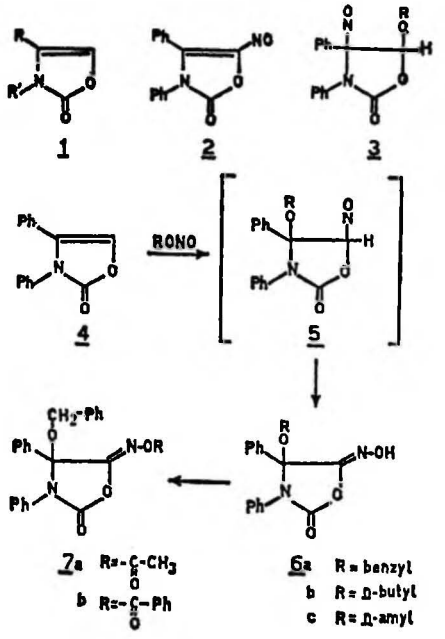
(9) See, *e.g.*, P. Fritsch, *Ber.*, **26**, 427 (1893).

(10) This synthesis is the outcome of independent work on the bromination of 5-unsubstituted 4-imidazolin-2-ones, which will be published at a later date. The structure of compounds of type **17** was proven through the following sequence.

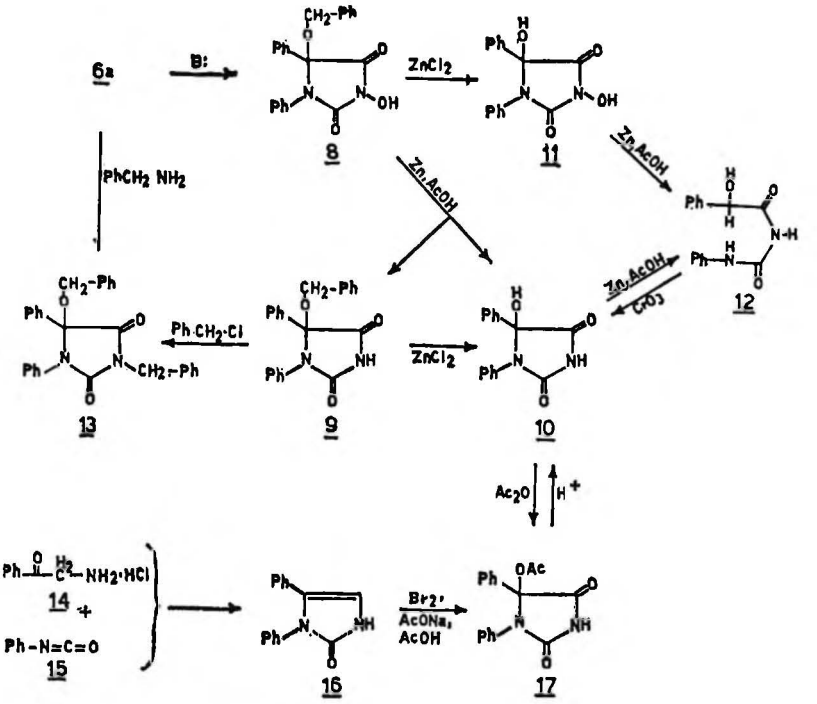


For an analogous reaction, *cf.* H. Greenberg, T. Van Es, and O. G. Backeberg, *J. Org. Chem.*, **31**, 3951 (1966).

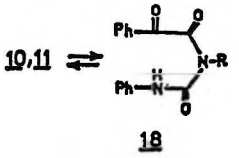
Scheme I



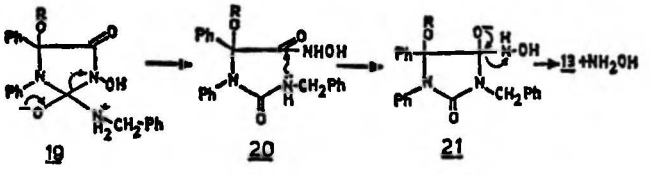
Scheme II



and **11**, so that reduction of the phenylglyoxylyl derivative **18** may occur to give the mandelyl derivative **12**. On the other hand, oxydation of **12** would reconvert the product into **18** (R = H), and hence into **10**. These data are in agreement with the known facile interconversion of mandelic and phenylglyoxylic acid.[11]



A further transformation of **6a** follows. Treatment of the compound with benzylamine in the absence of solvent gave 3-benzyl-5-benzyloxy-1,5-diphenylhydantoin (**13**). The structure of **13** was proved through its preparation from the sodium salt of **9** and benzyl chloride. Since a treatment of **6a** with benzylamine in benzene solution had given the benzylamine salt of **8**, the formation of **13** should involve rearrangement of **6a** to **8** and further interaction of benzylamine with the latter. The reaction probably involves attack by the amine on one of the carbonyl groups of **8** to yield **13** through the intermediates **19**, **20**, and **21** (or the analogous ones deriving from attack on the 4-oxo group).



The interest of the presently reported reaction of **4** with organic nitrites lies mainly in the fact that the products result, at least formally, from an *addition* of the reagent to the substrate, rather than from the usual substitution. To our knowledge, similar cases of addition of organic nitrites to double bonds have not yet been reported. Three factors appear to play an important role in this reaction: (1) the particular enamide enol ester structure of compound **4** (no similar addition takes place when compounds possessing normal olefinic double bonds are used as substrates); (2) lack of substituents at the 5 position of the oxazolinone (5-substituted oxazolinones, *e.g.*, 3,4-diphenyl-5-methyl-4-oxazolin-2-one, where transformation of a nitroso derivative of type **5** into the tautomeric oximino derivative **6** is impossible, *do not* undergo nitrite addition); (3) presence of hydrogen chloride (compound **4** is recovered unchanged when the reaction is carried out in the absence of acid). However, the data gathered so far do not allow formulation of a definite mechanism for the reaction under discussion. The role of hydrogen chloride could be tentatively explained in terms of an activation, through protonation, of the organic nitrite. Clearly, a two-stage ionic mechanism should be rejected because it cannot be seen why a carbonium ion, formed by interaction of NO^+ with the substrate, should react only with the alcohol and not with the chloride ion. Furthermore, if free alcohol were formed, it should, at least in the case of the reaction with benzyl nitrite, be very rapidly transformed into alkyl chloride. An alternative mechanism, involving addition of nitrosyl chloride (formed by interaction of the organic nitrite with hydrogen chloride[12]) to **4**, and reaction of the intermediate chloro oxime with the alcohol seems even less likely. Indeed, such a chloro oxime, once formed, should be rather stable in the presence of a high concentration of chloride ions. Anyway, no chlorinated products were isolated from the reactions. We resist the temptation of proposing any definite representation of the transition state of the reaction; however, we think that a four-center mechanism, basically similar to that proposed by

(11) See, *e.g.*, L. Claisen, *Ber.*, **10**, 844 (1877); R. Meyer and A. Baur, *ibid.*, **13**, 1495 (1880).

(12) L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 324 (1951).

Meinwald, *et al.*,[13] for the addition of nitrosyl chloride to norbornene, might be operative in the present case.

Further work on this and related reactions is underway in order to clarify their mechanism.

Experimental Section[14]

Reactions of 3,4-Diphenyl-4-oxazolin-2-one with Nitrites. A. Reaction with Benzyl Nitrite.—A solution of 4[15a] (15.0 g) in anhydrous tetrahydrofurane (15 ml) was saturated with dry hydrogen chloride, while cooling at 0–5°. To the stirred and cooled solution, freshly prepared benzyl nitrite[15b] (9.0 g) was added dropwise. Each addition caused the solution to assume a dark-red color, which disappeared on stirring. Evaporation of the solvent under reduced pressure gave an oily residue, which solidified on trituration with petroleum ether. Recrystallization of the crude product (14.2 g) from benzene–petroleum ether gave pure 4-benzyloxy-3,4-diphenyl-5-oximinooxazolidin-2-one (6a): mp 205–208° dec; ir, λ_{max} 3.0, 5.50, 5.80, 6.90, 7.35, 8.90, 9.80, 10.0, 11.28, 12.35, and 14.0 μ.

Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.77; H, 4.96; N, 7.44.

B. Reaction with *n*-Butyl Nitrite.—The reaction was carried out as indicated under A, using freshly prepared *n*-butyl nitrite.[16] The crude 4-*n*-butyloxy-3,4-diphenyl-5-oximinooxazolidin-2-one (6b, 76% yield) melted at 178–181° dec after recrystallization from benzene–petroleum ether: ir, λ_{OH} 3.0, λ_{CO} 5.51, 5.83 μ.

Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 66.81; H, 5.95; N, 8.38.

C. Reaction with *n*-Amyl Nitrite.—This reaction was also carried out as described under A, using freshly prepared *n*-amyl nitrite,[16] to give 4-*n*-amyloxy-3,4-diphenyl-5-oximinooxazolidin-2-one (6c, 49% yield): mp 151–153° from benzene–petroleum ether; ir, λ_{OH} 2.98, λ_{CO} 5.50, 5.82 μ.

Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.64; H, 6.32; N, 7.96.

Acetylation and Benzoylation of 6a.—Treatment of 6a with acetic anhydride in pyridine at 100° for 6 hr gave, after the usual work-up, the acetyl derivative **7a** in 89% yield: mp 139–141° after crystallization from benzene–petroleum ether; ir, λ_{CO} 5.50, 5.59 (sh), 5.90 μ.

Anal. Calcd for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 68.97; H, 4.92; N, 6.91.

The benzoylation of 6a was carried out as follows. To a solution of 6a (0.5 g) in anhydrous pyridine (5.0 ml) was added 0.3 g benzoyl chloride. The mixture was heated at 100° for 4.5 hr, then was poured into water (50 ml). The solid which separated was collected, washed with 10% HCl, and extracted with ether. The ethereal solution was washed with 10% Na_2CO_3 and water, dried ($MgSO_4$), and evaporated to yield the benzoyl derivative **7b** (0.52 g): mp 131–133° from benzene–petroleum ether; ir, λ_{CO} 5.50, 5.69, 5.95 μ.

Anal. Calcd for $C_{29}H_{22}N_2O_5$: C, 72.79; H, 4.63; N, 5.86. Found: C, 72.80; H, 4.83; N, 5.83.

5-Benzyloxy-1,5-diphenyl-3-hydroxyhydantoin (8).—A solution of 6a (0.5 g) in ethanolic 2% KOH (37.5 g) was refluxed 30 min, then diluted with water, and acidified with dilute HCl. The precipitate was collected, dried (0.49 g), and crystallized from benzene–petroleum ether to afford pure **8**: mp 166–168°; ir, λ_{max} 3.10, 5.58, 5.75, 6.89, 7.40, 8.55, 9.50, 13.35, 14.15 μ.

Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.71; H, 5.01; N, 7.25.

An ethanolic solution of **8** turned red on addition of a few drops of $FeCl_3$ solution (hydroxamic acid).[17]

Treatment of 6a at reflux temperature with tertiary aromatic or aliphatic amines (pyridine, triethylamine, etc) produced **8** in lesser (50–70%) yield.

Reaction of 8 with Zinc in Acetic Acid.—To a solution of **8** (1.5 g) in glacial acetic acid (25 ml) was added 1.5 g of finely powdered zinc. The mixture was refluxed 3 hr, then the excess zinc was filtered off, and the filtrate was evaporated at reduced pressure. The oily residue (A) was washed several times with water, and solidified on trituration. Crystallization of this material from ethanol afforded 0.46 g of **5-benzyloxy-1,5-diphenylhydantoin (9)**: mp 176–178° after crystallization from benzene–petroleum ether; ir, λ_{NH} 3.15, 3.28, λ_{CO} 5.61, 5.85 μ.

Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.98; H, 5.16; N, 7.56.

Extraction with ether of the aqueous washings of the residue (A), followed by evaporation of the dried ($MgSO_4$) ethereal extract, afforded 90 mg of a compound, mp 146–148°, identified as **N-mandelyl-N′-phenylurea (12**, see below).

The mother liquors from **9** were diluted with water and extracted with ether. Evaporation of the dried ($MgSO_4$) ethereal extract gave an oily residue (B), which solidified on washing and trituration with petroleum ether to afford **1,5-diphenyl-5-hydroxyhydantoin (10**, 0.34 g): mp 185–187° (lit.[7,8] mp 182–183°) after crystallization from benzene; ir, λ_{OH} 3.0, λ_{CO} 5.62, 5.85 μ.

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44. Found: C, 66.96; H, 4.54; N, 10.35.

Evaporation of the petroleum ether washings of the residue (B) gave a small amount of an oil which was identified as **benzyl acetate** by comparison with an authentic sample.

Reaction of 9 with Zinc Chloride.—A solution of **9** (0.2 g) in glacial acetic acid (12 ml) containing 0.2 g of recently fused zinc chloride was refluxed 2.5 hr and then was poured into water (200 ml). The mixture was extracted with ether; the ethereal extract was washed with 10% Na_2CO_3 and water, dried ($MgSO_4$), and evaporated to yield an oil which solidified on treatment with petroleum ether. The solid (0.12 g) was identified as **10**. Evaporation of the petroleum ether washings from **10** gave benzyl acetate.

Structure Proof of 10. A. 3,4-Diphenyl-4-imidazolin-2-one (16).—A mixture of 2-aminoacetophenone hydrochloride[18] (6.0 g), phenyl isocyanate (4.4 g), and anhydrous pyridine (15 ml) was heated 3 hr at 120°. A solid began to separate from the hot mixture after 1–2 hr. This was collected and crystallized from chloroform, then from ethanol, to afford 5.0 g of pure **3,4-diphenyl-4-imidazolin-2-one (16)**: mp 241–244°; ir, λ_{NH} 3.15, 3.30 (sh), λ_{CO} 5.95 μ.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.26; H, 5.31; N, 11.98.

B. 5-Acetoxy-1,5-diphenylhydantoin (17).—To a solution of **16** (1.5 g) and freshly fused sodium acetate (1.5 g) in glacial acetic acid (30 ml) was slowly added, at room temperature, a 0.4 *M* solution of bromine in glacial acetic acid (32.5 ml). The mixture was then poured into cold water (500 ml), and the product which separated was collected, dried (0.9 g), and crystallized from ethanol–benzene to afford pure **17**: mp 196–198°; ir, λ_{NH} 3.18, 3.29, λ_{CO} 5.59, 5.70 (sh), 5.80 μ.

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 66.01; H, 4.65; N, 8.96.

C. Conversion of 17 into 10, and Vice Versa.—Compound **17** (0.1 g) was added, with stirring, to cold concentrated H_2SO_4 (5 ml). The solution, which had an intense red color, was then poured onto cracked ice. The white solid which separated was collected, washed with water, dried (83 mg), and identified as **10**.

A solution of **10** (1.0 g) in a mixture of acetic anhydride (10 ml) and pyridine (1.0 ml) was heated 3 hr at 100°. Evaporation of the solvents under reduced pressure gave a solid residue which was crystallized from benzene–ethanol to yield 0.9 g of pure **17**.

Reaction of 8 with Zinc Chloride. 3,5-Dihydroxy-1,5-diphenylhydantoin (11).—A solution of **8** (0.50 g) and freshly fused zinc chloride (0.24 g) in glacial acetic acid (5.0 ml) was refluxed 2.5 hr, then was poured into water (50 ml). The aqueous solution was extracted with ether; the dried ($MgSO_4$) ethereal extract was evaporated to give a residue which solidified on trituration with petroleum ether. Crystallization of this material from benzene gave pure **11** (0.3 g): mp 101–103°; ir, λ_{OH} 3.0; λ_{CO} 5.61, 5.81 μ.

Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.26; N, 9.86. Found: C, 63.22; H, 4.31; N, 9.72.

N-Mandelyl-N′-phenylurea (12). A. From 11.—Powdered zinc (0.5 g) was added to a solution of **11** (0.28 g) in glacial acetic acid (5.0 ml); the mixture was refluxed 15 min and then poured

(13) J. Meinwald, Y. C. Meinwald, and T. N. Baker, III, *J. Amer. Chem. Soc.*, **85**, 2513 (1963); **86**, 4074 (1964).

(14) Melting points were determined on a Kofler apparatus, and are not corrected; ir spectra were recorded on Nujol mulls and the nmr spectrum on a deuteriochloroform solution with tetramethylsilane as internal standard. Identity of compounds was verified by mixture melting point and comparison of ir spectra. Petroleum ether refers to the fraction of boiling range 60–80°.

(15) A. Bayer and V. Villiger, *Ber.*, **34**, 755 (1901).

(16) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co. Ltd., London, 1956, p 306.

(17) See ref 16, p 1062.

(18) C. Mannich and F. L. Hahn, *Ber.*, **44**, 1542 (1911).

into water. The solid which separated was collected and crystallized from benzene–petroleum ether to give pure **12** (0.2 g): mp 146–148°; ir, λ_{max} 2.97, 3.05, 5.85, 5.90 (sh), 6.41, 6.75, 8.10, 8.51, 9.39, 13.16 μ; for nmr, see text.

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.63; H, 5.27; N, 10.54.

B. From 10.—Treatment of **10** with zinc in acetic acid as described for **11** gave N-mandelyl-N′-phenylurea (**12**) in 75% yield.

Oxidation of 12 to 10.—To a cooled solution of **12** (0.27 g) in acetone (10 ml) was slowly added an 8 *N* solution of CrO_3[19] (2.0 ml). The mixture was heated 5 min at 50°, then was poured into cold water. The solid which separated (0.15 g) was identified as **10**.

3-Benzyl-5-benzyloxy-1,5-diphenylhydantoin (13). A. From 6a.—A solution of **6a** (0.5 g) in benzylamine (10 ml) was heated 6 hr at 175°, then was poured into water (50 ml). The yellow oil which separated was extracted several times with hot petroleum ether. The combined extracts were washed with dilute HCl and water, dried ($MgSO_4$), and evaporated to yield 0.3 g of **13**: mp 121–123° after crystallization from benzene–petroleum ether; ir, λ_{CO} 5.62, 5.81 μ.

Anal. Calcd for $C_{29}H_{24}N_2O_3$: C, 77.66; H, 5.39; N, 6.25. Found: C, 77.51; H, 5.52; N, 6.41.

B. From 9.—To a solution of **9** (0.1 g) and benzyl chloride (0.1 g) in 95% ethanol (7.0 ml) was added a 0.11 *N* solution of KOH in ethanol (2.7 ml). The mixture was refluxed 2 hr; then it was diluted with water and extracted with ether. The dried ($MgSO_4$) ethereal extract was evaporated to give a residue which solidified on trituration with ethanol. This product (80 mg) was crystallized from benzene–petroleum ether to give pure **13**.

(19) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

Registry No.—**6a**, 16710-18-2; **6b**, 16710-19-3; **6c**, 16710-20-6; **7a**, 16710-21-7; **7b**, 16710-22-8; **8**, 16710-23-9; **9**, 16710-24-0; **10**, 15903-38-5; **11**, 16710-26-2; **12**, 16710-27-3; **13**, 16709-72-1; **16**, 16709-73-2; **17**, 16709-74-3.

Synthesis and Reactions of "Anhydrochloralurethans"

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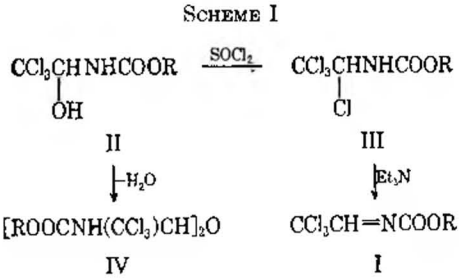
Received February 13, 1968

The previously unreported anhydrochloralurethans (I) are obtained by dehydrochlorination of alkyl 1,2,2,2-tetrachloroethylcarbamates (III). Reaction of I with water, alcohols, and amines affords chloral O,N- and N,N-acetals. The latter compounds are also produced in the reaction of chloralurethans (II) with alkyl and aryl isocyanates. Treatment of II and III with carbonyl chloride in the presence of N,N-dimethylformamide as the catalyst gives rise to the formation of 1,2,2,2-tetrachloroethyl isocyanate (XI), which undergoes the Michalis–Arbuzov reaction with triethyl phosphite to afford diethyl 1-isocyanato-2,2,2-trichloroethylphosphonate (XII).

The synthesis of "anhydrochloralurethans" (I) was reported in 1891 by Moscheles.[1] However, Feist[2] had shown later that the compounds, isolated by Moscheles, had structure IV rather than I. In view of the anticipated reactivity of the imines I with regard to addition to the activated double bond, we attempted their synthesis from chloralurethans (II).[3] Since dehydration led to the formation of IV,[1,2] most likely *via* addition of unreacted II to the generated I, we selected a dehydrochlorination procedure.

Heating of chloralurethans (II) with thionyl chloride affords alkyl 1,2,2,2-tetrachloroethylcarbamates (III) in high yield (Scheme I). The dehydrochlorination of III in benzene, using triethylamine as the hydrogen chloride acceptor, proceeds at room temperature, and the previously unreported "anhydrochloralurethans" I are thus obtained in 40–50% yield of distilled product.

SCHEME I



(1) R. Moscheles, *Ber.*, **24**, 1803 (1891).
(2) F. Feist, *ibid.*, **45**, 945 (1912).
(3) C. Bischoff, *ibid.*, **7**, 628 (1874).

The imines I are colorless liquids which darken on standing. Their structure was verified by elementary analysis, infrared ($\nu_{C=O}$ 1745 cm^{-1}, $\nu_{C=N}$ 1669 cm^{-1}) and nmr spectroscopy. For example, I (R = C_2H_5) shows the following signals (50% CCl_4, relative to TMS): singlet at 8.2 ppm, quartet at 4.3 ppm, and triplet at 1.38 ppm, with a relative intensity ratio of 1:2:3.

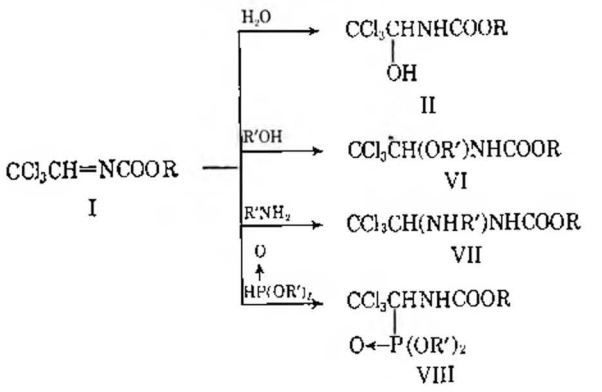
Likewise, ethyl 1-chloro-2,2,2-tribromoethylcarbamates obtained from ethyl 1-hydroxy-2,2,2-tribromoethylcarbamate[3] and thionyl chloride can be dehydrochlorinated to C-tribromomethyl-N-carboethoxyazomethine (V), as evidenced by infrared and nmr spectroscopy. However, the imine V is heat sensitive, and purification by vacuum distillation is not possible.[4,5]

The reactivity of the C=N double bond in I is evidenced by rapid and exothermic addition of water, alcohols, and amines to yield the corresponding hemiacetals II, O,N-acetals VI, and N,N-acetals VII (Scheme II). However, addition of hydrogen phosphite to afford the 1:1 adduct VIII is quite sluggish and requires the use of a base catalyst. For N-aroyl imines a similar activation of the C=N double bond toward addition of nucleophiles has been observed recently.[6]

The chloro group adjacent to nitrogen in alkyl 1,2,2,2-

(4) After completion of our investigation the *in situ* generation of I (R = $CH_2C_6H_5$) has been described, but purification by vacuum distillation was not possible because of heat sensitivity.[5]
(5) F. Weygand, W. Steglich, I. Lengyel, F. Fraunberger, A. Maierhofer, and W. Oettmeier, *Chem. Ber.*, **99**, 1944 (1966).
(6) S. W. Breuer, T. Bernath, and D. Ben-Ishai, *Tetrahedron Lett.*, 4569 (1966).

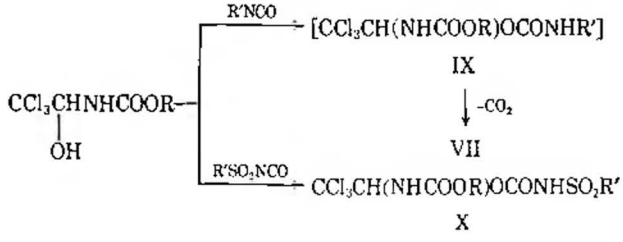
SCHEME II



tetrachloroethylcarbamates (III) undergoes rapid nucleophilic substitution and participates readily in the Michaelis–Arbuzov reaction. Therefore compounds II, VI, VII, and VIII can also be obtained from III. However, the reactions of III with water, alcohols, and amines may proceed by an elimination–addition sequence, involving I as the intermediate.

The N,N-acetals VII are also obtained in the base-catalyzed reaction of II with alkyl and aryl isocyanates. The initially formed 1:1 adducts IX undergo rapid elimination of carbon dioxide with formation of VII. In contrast, reaction of II with tosyl isocyanate results in the formation of the expected carbamate X (Scheme III).

SCHEME III



The elimination of carbon dioxide in the reaction of chloralamides with alkyl and aryl isocyanates has been observed recently,[7] while chlorosulfonyl isocyanate undergoes reaction with dialkyl 1-hydroxy-2,2,2-trichloroethylphosphonates to afford the expected 1:1 adducts.[8] Thus, a general trend is observed in the reaction of the chloral hemiacetalic hydroxy groups with alkyl, aryl, and sulfonyl isocyanates.

Since chloralurethans are readily available, we attempted conversion of the carbamate group into an isocyanate function, using carbonyl chloride as the attacking species. In the case of II simultaneous conversion of the hydroxy group into a chloro group was anticipated. While previously phosphorus pentachloride[9] and pyrocatechol–phosphorus trichloride[10] have been used to convert carbamates into isocyanates, carbonyl chloride does not undergo reaction with carbamates even at temperatures above 100°. However, addition of a catalytic amount of N,N-dimethylformamide achieves rapid conversion.[11]

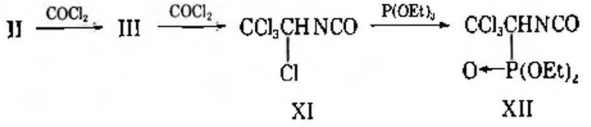
(7) A. Doerken and G. Schrader, German Patent 1,186,467 (1965); *Chem. Abstr.*, **62**, 16,149 (1965).

(8) H. Timmler, R. Wegler, and G. Unterstenhöfer, French Patent 1,403,523 (1965); *Chem. Abstr.*, **64**, 15,925 (1966).

(9) O. Folin, *Amer. Chem. J.*, **19**, 323 (1897).

(10) H. Gross and J. Gloede, *Chem. Ber.*, **96**, 1387 (1963).

Thus, simultaneous addition of carbonyl chloride and DMF to II or III in toluene or chlorobenzene affords 1,2,2,2-tetrachloroethyl isocyanate (XI), which



had been previously obtained in the reaction of 1-hydroxy-2,2,2-trichloroethyl isocyanate and thionyl chloride.[12] The chloro group adjacent to nitrogen is quite mobile and treatment of XI with triethyl phosphite results in the formation of the isocyanatophosphonate XII. Addition of alcohol to isocyanatophosphonates affords the carbamates VIII, identical with the compounds obtained from I and dialkylhydrogen phosphite and III and trialkyl phosphite.

The mechanism of formation of XI in the reaction of the carbamates II and III with carbonyl chloride involves the corresponding chloroformimidate as the intermediate.[11]

Experimental Section[13]

Methyl 1,2,2,2-Tetrachloroethylcarbamate (III, R = CH_3).—To a suspension of 222.5 g (1 mol) of methyl 1-hydroxy-2,2,2-trichloroethylcarbamate in 1200 ml of methylene chloride 119 g (1 mol) of thionyl chloride, containing 2.2 g of pyridine, is added. After refluxing for 60 min a clear solution is obtained and evaporation of the solvent affords 240 g (99.5%) of methyl 1,2,2,2-tetrachloroethylcarbamate, mp 91–92° (lit.[14] mp 90–91°) after recrystallization from carbon tetrachloride.

Anal. Calcd for $C_4H_5Cl_4NO_2$: C, 19.94; H, 2.09; N, 5.81. Found: C, 20.13; H, 1.97; N, 5.65.

In a similar manner **ethyl 1,2,2,2-tetrachloroethylcarbamate (III, R = C_2H_5** [mp 60–62° (lit.[14] mp 62–63°)], yield 97.3%], and **ethyl 1-chloro-2,2,2-tribromoethylcarbamate** (mp 77–78°, yield 96.4%) was obtained.

Anal. Calcd for $C_5H_7Br_3ClNO_2$: N, 3.60. Found: N, 3.60.

C-Trichloromethyl-N-carbomethoxyazomethine (I, R = CH_3).—To a solution of 20.2 g (0.02 mol) of triethylamine in 200 ml of benzene dropwise and with stirring 48.2 g (0.2 mol) of methyl 1,2,2,2-tetrachloroethylcarbamate in 200 ml of benzene is added over a period of 20 min at 25–40°. After cooling and removal of triethylamine hydrochloride by filtration the benzene is evaporated and vacuum distillation of the residue affords 16.7 g (40.7%) of C-trichloromethyl-N-carbomethoxyazomethine, bp 41–42° (0.1 mm).

Anal. Calcd for $C_4H_4Cl_3NO_2$: C, 23.50; H, 1.97; N, 6.85. Found: C, 23.62; H, 2.03; N, 7.02.

In a similar manner **C-trichloromethyl-N-carbethoxyazomethine (I, R = C_2H_5** [bp 70° (1.1 mm), yield 47.7%] was obtained.

Anal. Calcd for $C_5H_6Cl_3NO_2$: C, 27.73; H, 2.78; N, 6.56. Found: C, 27.92; H, 2.75; N, 6.83.

Reaction with Water.—Addition of I, R = C_2H_5, to aqueous acetone and evaporation of the acetone affords **ethyl 1-hydroxy-2,2,2-trichloroethylcarbamate (II, R = C_2H_5)**, mp 103° (lit.[3] mp 103°), in quantitative yield.

Reaction with Methanol.—The amount of 1.09 g (0.005 mol) of C-trichloromethyl-N-carbethoxyazomethine is added to excess methanol (5 ml). An immediate exothermic reaction occurs and evaporation of the methanol affords 1.12 g (90%)

(11) H. Ulrich, B. Tucker, and A. A. R. Sayigh, *Angew. Chem. Intern. Ed. Engl.*, **6**, 836 (1967).

(12) F. W. Hoover, H. B. Stevenson, and H. S. Rothrock, *J. Org. Chem.*, **28**, 1825 (1963).

(13) Analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared spectra were determined in chloroform solution, using a Beckman IR-8 spectrophotometer. Nmr spectra were obtained from samples in deuteriochloroform solution on a Varian A-60 instrument using tetramethylsilane as the internal standard.

(14) M. Pianka and J. D. Edwards, British Patent 993,051 (1965); *Chem. Abstr.*, **63**, 9822 (1965).

of ethyl 1-methoxy-2,2,2-trichloroethylcarbamate (**VI**, R = C_2H_5, R′ = CH_3O), mp 59–61° (lit.[12] mp 64–65°).

Reaction with Aniline.—To 1.09 g (0.005 mol) of C-trichloromethyl-N-carbethoxyazomethine in 15 ml of carbon tetrachloride 0.465 g (0.005 mol) of aniline is added. An immediate exothermic reaction occurs and evaporation of the solvent affords 1.56 g (100%) of ethyl 1-phenylamino-2,2,2-trichloroethylcarbamate (**VII**, R = C_2H_5, R′ = C_6H_5), mp 85–87° after recrystallization from aqueous methanol.

Anal. Calcd for $C_{11}H_{13}Cl_3N_2O_2$: C, 42.41; H, 4.20; N, 8.99. Found: C, 42.40; H, 4.13; N, 9.14.

C-Tribromoethyl-N-carbethoxyazomethine (V).—To a solution of 7.7 g (0.02 mol) of ethyl 1-chloro-2,2,2-tribromoethylcarbamate in 70 ml of benzene with stirring and dropwise 2.22 g (0.022 mol) of triethylamine is added over a period of 3 min at 25–33°. After stirring for 30 min the precipitate triethylamine hydrochloride is removed by filtration and evaporation of the benzene affords a quantitative yield (7.05 g) of C-tribromomethyl-N-carbethoxyazomethine as a yellow oil, $\lambda_{max}^{CCl_4}$ (infrared), 1739 (C=O) and 1669 cm^{-1} (C=N). The compound decomposed on attempted vacuum distillation.

Addition of a sample of V to aqueous acetone and evaporation of the acetone affords ethyl 1-hydroxy-2,2,2-tribromoethylcarbamate, mp 137–138° (lit.[3] mp 132°).

Reaction of Ethyl 1-Hydroxy-2,2,2-trichloroethylcarbamate (II, R = C_2H_5) with Phenyl Isocyanate.—To a solution of 9.5 g (0.04 mol) of ethyl 1-hydroxy-2,2,2-trichloroethylcarbamate in 95 ml of benzene, containing 0.095 g of triethylenediamine (DABCO), 4.8 g (0.04 mol) of phenyl isocyanate is added and after refluxing for 100 min the solvent is evaporated to afford 12.2 g (86%) of ethyl 1-phenylamino-2,2,2-trichloroethylcarbamate (**VII**, R = C_2H_5, R′ = C_6H_5), mp 87–88° after recrystallization from aqueous methanol.

The mixture melting point with a sample of VII (R = C_2H_5, R′ = C_6H_5) obtained from I (R = C_2H_5) and aniline was not depressed.

Reaction of Methyl 1-Hydroxy-2,2,2-trichloroethylcarbamate (II, R = CH_3) with Isocyanates. A. Methyl Isocyanate.—To a solution of 11.1 g (0.05 mol) of methyl 1-hydroxy-2,2,2-trichloroethylcarbamate in 110 ml of chlorobenzene 0.11 g (1% by weight) of potassium *t*-butoxide and 3.13 g (0.055 mol) of methyl isocyanate is added. The temperature rose to 32° and after short refluxing at 132° the solvent is evaporated under vacuum affording 10.75 g (88%) of methyl 1-methylamino-2,2,2-trichloroethylcarbamate (**VII**, R = CH_3, R′ = CH_3): mp 109° after recrystallization from acetone; nmr ($CDCl_3$), singlet at 1.9 ppm (NH attached to CH_3 group), singlet at 2.57 ppm (N–CH_3), singlet at 3.75 ppm (O–CH_3), doublet at approximately 5.0 ppm (NH attached to the carbomethoxy group), and doublet at 5.8 ppm (CH group); intensity ratio, 1:3:3:1:1.

Anal. Calcd for $C_5H_9Cl_3N_2O_2$: C, 25.50; H, 3.85; N, 11.89. Found: C, 25.68; H, 3.94; N, 11.96.

B. Cyclohexyl Isocyanate.—The reaction is conducted analogously to A and a 76% yield of methyl 1-cyclohexylamino-2,2,2-trichloroethylcarbamate (**VII**, R = CH_3, R′ = C_6H_{11}), mp 110–111° after recrystallization from ethyl acetate, is obtained.

Anal. Calcd for $C_{10}H_{17}Cl_3N_2O_2$: C, 39.55; H, 5.64; N, 9.22. Found: C, 39.73; H, 5.80; N, 9.15.

C. *p*-Toluenesulfonyl Isocyanate.—To a solution of 2.2 g (0.01 mol) of methyl 1-hydroxy-2,2,2-trichloroethylcarbamate in 25 ml of chloroform 1.97 g (0.01 mol) of *p*-toluenesulfonyl isocyanate is added. After refluxing for 30 min the solvent is evaporated and the residue is dissolved in glacial acetic acid. Addition of water causes precipitation of 2.15 g (51.5%) of 1-aminocarbethoxy-2,2,2-trichloroethyl *p*-toluenesulfonylcarbamate (**X**, R = CH_3, R′ = $CH_3C_6H_4$), mp 137–140°.

Anal. Calcd for $C_{12}H_{13}Cl_3N_2O_6S$: C, 34.34; H, 3.12; N, 6.67. Found: C, 34.14; H, 3.18; N, 6.41.

1,2,2,2-Tetrachloroethyl Isocyanate (XI). A. From II, R = C_2H_5.—To a solution of 18.8 g (0.08 mol) of II, R = C_2H_5, in chlorobenzene at reflux temperature simultaneously phosgene and a solution of 0.94 g of DMF in 25 ml of chlorobenzene are added over a period of 288 min. Distillation of the solvent and vacuum distillation of the residue affords 2.2 g (13.1%) of 1,2,2,2-tetrachloroethyl isocyanate, bp 41–45° (7.5 mm). Addition to excess methanol and evaporation affords methyl 1-methoxy-2,2,2-trichloroethylcarbamate, mp 64–65° (lit.[12] mp 64–65°).

B. From III, R = CH_3.—To a solution of 24.1 g (0.1 mol) of methyl 1,2,2,2-tetrachloroethylcarbamate in 100 ml of toluene carbonyl chloride and a solution of 2.4 g of DMF in 20 ml of toluene is added simultaneously at 110–115° over a period of 90 min. After removal of excess carbonyl chloride with nitrogen, evaporation of the solvent, and vacuum distillation of the residue, 10.05 g (48.2%) of 1,2,2,2-tetrachloroethyl isocyanate, bp 68–72° (20 mm), is obtained. Similarly a 40.2% yield of 1,2,2,2-tetrachloroethyl isocyanate can be obtained from III, R = C_2H_5.

The isocyanate is further characterized by conversion into 1-(diethylamino-2,2,2-trichloroethyl)-3-diethylurea, mp 51–52°, using 3 equiv of diethylamine.

Anal. Calcd for $C_{11}H_{22}Cl_3N_3O$: N, 13.17. Found: N, 13.12.

Diethyl 1-Isocyanato-2,2,2-trichloroethylphosphonate (XII).—To 104.5 g (0.5 mol) of 1,2,2,2-tetrachloroethyl isocyanate in 1000 ml of carbon tetrachloride 83 g (0.5 mol) of triethyl phosphite is added and the reaction mixture is refluxed for 105 min. Evaporation of the solvent affords 155 g of diethyl 1-isocyanato-2,2,2-trichloroethylphosphonate. A small sample was purified by vacuum distillation: bp 92–98° (0.2 mm); $\lambda_{max}^{CHCl_3}$ (infrared) 2475 (NCO) and 1266 cm^{-1} (P=O). The compound was further characterized by reaction with 1 equiv of aniline to afford diethyl 1-phenylureido-2,2,2-trichloroethylphosphonate, mp 202–204°.

Anal. Calcd for $C_{13}H_{18}Cl_3N_2O_4P$: B, 6.94. Found: N, 7.14.

Dimethyl 1-Aminocarbethoxy-2,2,2-trichloroethylphosphonate (VIII, R = C_2H_5, R′ = CH_3). A. From Dimethyl 1-Isocyanato-2,2,2-trichloroethylphosphonate.—Addition of a sample of the isocyanate to excess ethanol, short refluxing in the presence of a catalytic amount of DABCO, and evaporation of the ethanol afford a quantitative yield of VIII (R = C_2H_5, R′ = CH_3): mp 88°; $\lambda_{max}^{CHCl_3}$ (infrared), 3425 (NH), 1730 (C=O), and 1266 cm^{-1} (P=O).

Anal. Calcd for $C_9H_{17}Cl_3NO_5P$: C, 25.59; H, 3.98; N, 4.26. Found: C, 25.42; H, 3.90; N, 4.43.

B. From Ethyl 1,2,2,2-Tetrachloroethylcarbamate (II, R = C_2H_5).—To 12.75 g (0.05 mol) of ethyl 1,2,2,2-tetrachloroethylcarbamate dissolved in 130 ml of carbon tetrachloride 6.2 g (0.05 mol) of trimethyl phosphite is added and the reaction mixture is refluxed for 2 hr. After evaporation of the solvent a quantitative crude yield (16.7 g) of VIII (R = C_2H_5, R′ = CH_3), is obtained, mp 83–88°. Recrystallization from benzene–ligroin raises the melting point to 88–89°.

C. From C-Trichloromethyl-N-carbethoxyazomethine (I, R = C_2H_5).—To 1.09 g (0.005 mol) of I, R = C_2H_5, in 15 ml of carbon tetrachloride 0.47 g (0.005 mol) of dimethylhydrogen phosphite and 4 drops of triethylamine are added and the reaction mixture is refluxed for 5 hr during which time the P–H absorption in the infrared spectrum at 2326 cm^{-1} disappears. Evaporation of the solvent and trituration with ligroin affords 1.3 g (83.5%) of VIII (R = C_2H_5, R′ = CH_3), mp 87–88°.

Registry No.—I, R = CH_3, 16723-29-8; I, R = C_2H_5, 16723-30-1; III, R = CH_3, 3659-10-7; ethyl 1-chloro-2,2,2-tribromoethylcarbamate, 16742-79-3; V, 16723-32-3; VII, R = C_2H_5, R′ = C_6H_5, 16723-33-4; VII, R = CH_3, R′ = CH_3, 1954-74-1; VII, R = CH_3, R′ = C_6H_{11}, 16723-35-6; VIII, R = R′ = C_2H_5, 16723-36-7; X, R = CH_3, R′ = 4-$CH_3C_6H_4$, 16723-37-8; XI, 15145-29-6; 1-(diethylamino-2,2,2-trichloroethyl)-3-diethylurea, 16723-39-0; XII, 16723-40-3; diethyl 1-phenylureido-2,2,2-trichlorodiethylphosphonate, 16723-41-4.

Acknowledgment.—We are indebted to Joseph Almaza for his assistance in the experimental aspects of this work.

The Chemistry of Aporphines. III. The Mechanism of Carbon–Carbon Cleavage with Potassium Borohydride. Reduction Products of Nitrobenzylisoquinolinium Salts[1]

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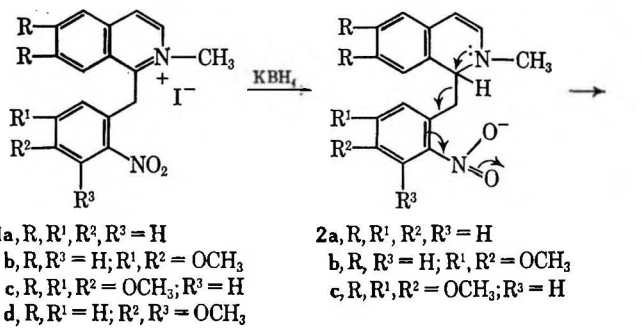
Received February 7, 1968

The recent synthesis of 1-nitrobenzylisoquinolinium salts has enabled a study of their reduction products with potassium borohydride. The unusual cleavage of a carbon–carbon bond in a number of these 1-benzylisoquinolinium salts 1 when treated with potassium borohydride was rationalized by a proposed mechanism. An intermediate (**2b**) in this mechanism was isolated and its structure was confirmed on the basis of its nmr, uv, and mass spectra, as well as by unequivocal synthesis. The structures of **2a**, which have been in dispute, and of similarly synthesized compounds are formulated as originally proposed by Gadamer, *et al.*

Our continued interest in the chemistry of aporphine and aporphine alkaloids led to the discovery of a novel method of preparing aporphine which can be similarly applied to the preparation of the related alkaloids.[2] Several recent reports have described other novel approaches to the synthesis of aporphines which are based either on a photocyclization of an aporphine precursor[3–5] or by a biogenetic-type oxidative coupling of a quaternary benzyltetrahydroisoquinoline[6] or of benzyltetrahydroisoquinoline followed by a dienol–benzene rearrangement.[7] We have not found these methods to be of general utility for the synthesis of naturally occurring or modified aporphine alkaloids.

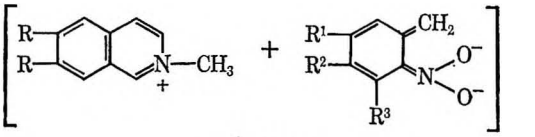
The classical methods used successfully for preparing aporphine types of structures have involved the Bischler–Napieralski cyclization–reduction–Pschorr cyclization sequence[8] or the Gadamer procedure[9] which involves the combination of a quaternary isoquinolinium salt with *o*-nitrotoluenes to form dihydroisoquinolines, reduction, and Pschorr cyclization. Our method,[2] which involved the alkylation of a Reissert compound with *o*-nitrobenzyl chloride, made available 1-(*o*-nitrobenzyl)isoquinoline, which could be readily converted into its quaternary salt **1a**. During the reduction of a number of these 1-benzylisoquinolinium salts (**1a**, **b**, or **c**) with potassium borohydride in refluxing ethanol, we observed the unusual cleavage of a carbon–carbon bond and suggested a mechanism for this reaction.[1] From the reduction of 1-(4,5-dimethoxy-2-nitrobenzyl)isoquinoline methiodide (**1b**) the intermediate 1,2-dihydroisoquinoline **2b** was isolated and characterized. Further treatment of this 1,2-dihydroisoquinoline (**2b**) with borohydride in methanol yielded the expected cleavage products (**3a** and **4b**).

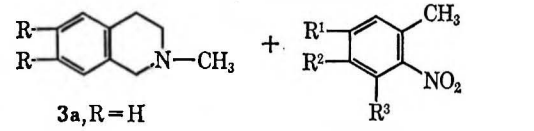
The reduction of pyridinium, quinolinium, and isoquinolinium ions to the dihydro- and the tetrahydro-N-substituted bases has been extensively investigated and recently reviewed.[10] The mechanism we proposed[1] for the reduction and cleavage of three 1-benzylisoquinolinium salts (**1a–c**) involves the initial nucleophilic attack of a hydride ion on the electrophilic 1 position of the isoquinoline nucleus to yield initially the 1,2-dihydro derivative 2 which we have now isolated in one instance (*viz.*, **2b**). The presence of



1a, R, R¹, R², R³ = H
b, R, R³ = H; R¹, R² = OCH_3
c, R, R¹, R² = OCH_3; R³ = H
d, R, R¹ = H; R², R³ = OCH_3

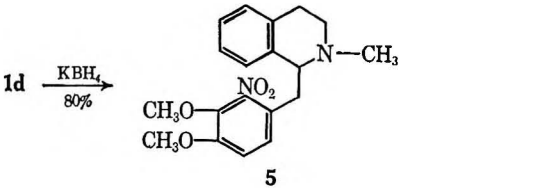
2a, R, R¹, R², R³ = H
b, R, R³ = H; R¹, R² = OCH_3
c, R, R¹, R² = OCH_3; R³ = H





3a, R = H
b, R = OCH_3

4a, R¹, R², R³ = H
b, R¹, R² = OCH_3; R³ = H



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the nitrobenzyl group provides the necessary resonance stabilization of the benzyl anion to weaken the carbon–carbon bond, causing the cleavage reaction to occur. The aromaticity produced by the formation of the isoquinolinium salt further assists this cleavage. Both effects must be present in order

(1) A preliminary communication of part of this work has appeared. See part I: J. L. Neumeyer, M. McCarthy, and K. K. Weinhardt, *Tetrahedron Lett.*, 1095 (1967).

(2) Part II: J. L. Neumeyer, B. R. Neustadt, and J. W. Weintraub, *ibid.*, 3107 (1967).

(3) M. P. Cava, S. C. Havlicek, A. Lindest, and R. J. Spangler, *ibid.*, 2937 (1966).

(4) N. C. Yang, G. R. Lenz, and A. Shari, *ibid.*, 2941 (1966).

(5) S. M. Kupchan and R. M. Kanojia, *ibid.*, 5353 (1966).

(6) B. Frank and G. Schlingloff, *Ann. Chem.*, **659**, 123 (1962); B. Frank and G. Blaschke, *ibid.*, **695**, 144 (1966).

(7) M. Shamma and W. A. Slusarchyk, *Chem. Commun.*, 528 (1965).

(8) J. M. Gulland and R. D. Haworth, *J. Chem. Soc.*, 581 (1928).

(9) J. Gadamer, M. Oberlin, and A. Schroeder, *Arch. Pharm.*, **263**, 81 (1925).

(10) R. E. Lyle and P. S. Anderson, *Advan. Heterocycl. Chem.*, **6**, 45 (1966); **6**, 68 (1966).

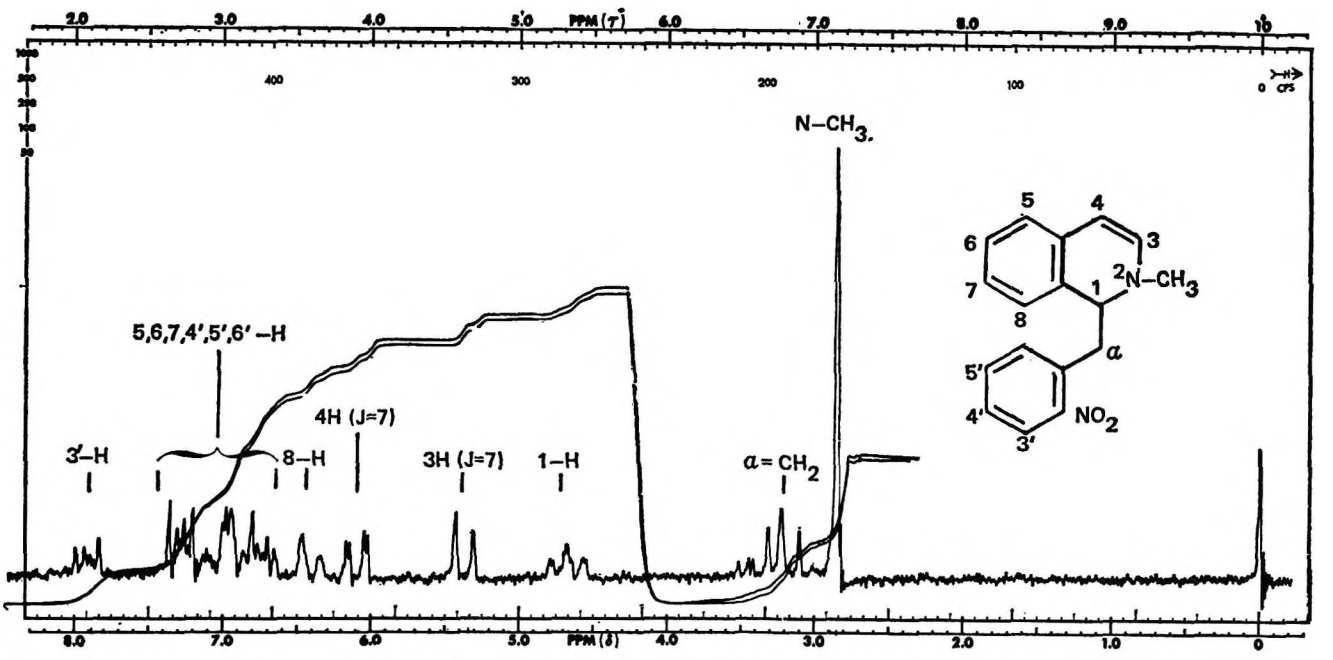
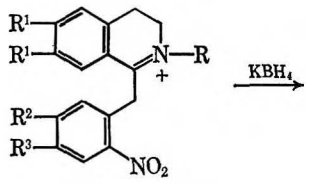
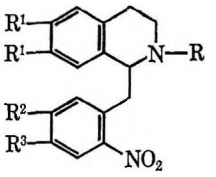


Figure 1.—Nuclear magnetic resonance spectrum of 2a

for the cleavage to take place. However, in the case of 1-(3,4-dimethoxy-2-nitrobenzyl)isoquinoline methiodide (**1d**), where the nitro group is forced out of the plane of the benzene ring because of the additional steric interaction of the *o*-methoxy group, the "normal" reduction product, 1-(3,4-dimethoxy-2-nitrobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**5**), was isolated in 80% yield. Thus, the resonance stabilization of the benzyl anion was not provided, precluding the formation of the nitrotoluene. The reported "normal" reduction of the 3,4-dihydroisoquinoline derivatives as in **6a**[11] and **6b**[12] to **7a** and **b** with sodium borohydride can be rationalized on the basis of the above mechanism if one assumes initial attack of the borohydride ion at the 1 position to yield the tetrahydro derivatives **7** which are stable to further reduction in the isoquinoline ring. In the instance where the double bond resides in the 3,4 position, as in the dihydro derivative **2b** referred to above, cleavage occurs on treatment with boro-



6a, R = CH_3, R^1 = OCH_3, R^2 = H, R^3 = OBz
b, R, R^2, R^3 = H; R^1 = —OCH_2—

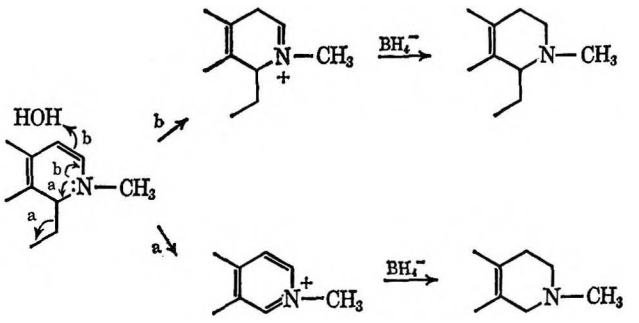


7a, R = CH_3, R^1 = OCH_3, R^2 = H, R^3 = OBz
b, R, R^2, R^3 = H; R^1 = —OCH_2O—

hydride. This indicates that elimination occurs (Scheme I, pathway a) prior to protonation of the

(11) W. H. Baarschers and R. R. Arndt, *Tetrahedron*, **21**, 2158 (1965).
(12) M. P. Cava and D. R. Dalton, *J. Org. Chem.*, **31**, 1281 (1966).

SCHEME I



enamine system of the 3,4 double bond in the isoquinoline ring (Scheme I, pathway b) and a subsequent reduction to the tetrahydro derivative, as per the mechanism proposed by Anderson and Lyle[13] for the reduction of pyridinium salts.

In a strongly basic medium a hydrolytic cleavage involving a nucleophilic attack by hydroxide ion at the 1 position of the isoquinolinium salt was proposed[14] as an explanation of the observations of Pschorr,[15] who found that boiling nitropapaverine methiodide **1c** with 33% potassium hydroxide yielded methylnitroveratrole (**4b**) and a methoxycarbostyril.

Aromatic nitro and nitroso compounds are not normally reduced by sodium borohydride in aqueous or alcoholic solution; however, Neilson, *et al.*,[16] reported that aromatic nitro compounds could be smoothly reduced to the corresponding amines by sodium borohydride with palladized charcoal in aqueous methanol. In attempting to apply this method to the reduction of **1b** we obtained a highly colored crystalline compound, the structure of which was established to be the 1,2-dihydroisoquinoline **2b** on the basis of elemental analysis, nmr, uv, and mass spectroscopy, and

(13) P. S. Anderson and R. E. Lyle, *Tetrahedron Lett.*, 153 (1964).
(14) W. J. Gensler, "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., N. Y., 1952, pp 479–480.
(15) R. Pschorr, *Ber.*, **37**, 1926 (1904).
(16) T. Neilson, H. C. S. Wood, and A. G. Wylie, *J. Chem. Soc.*, 371 (1962).

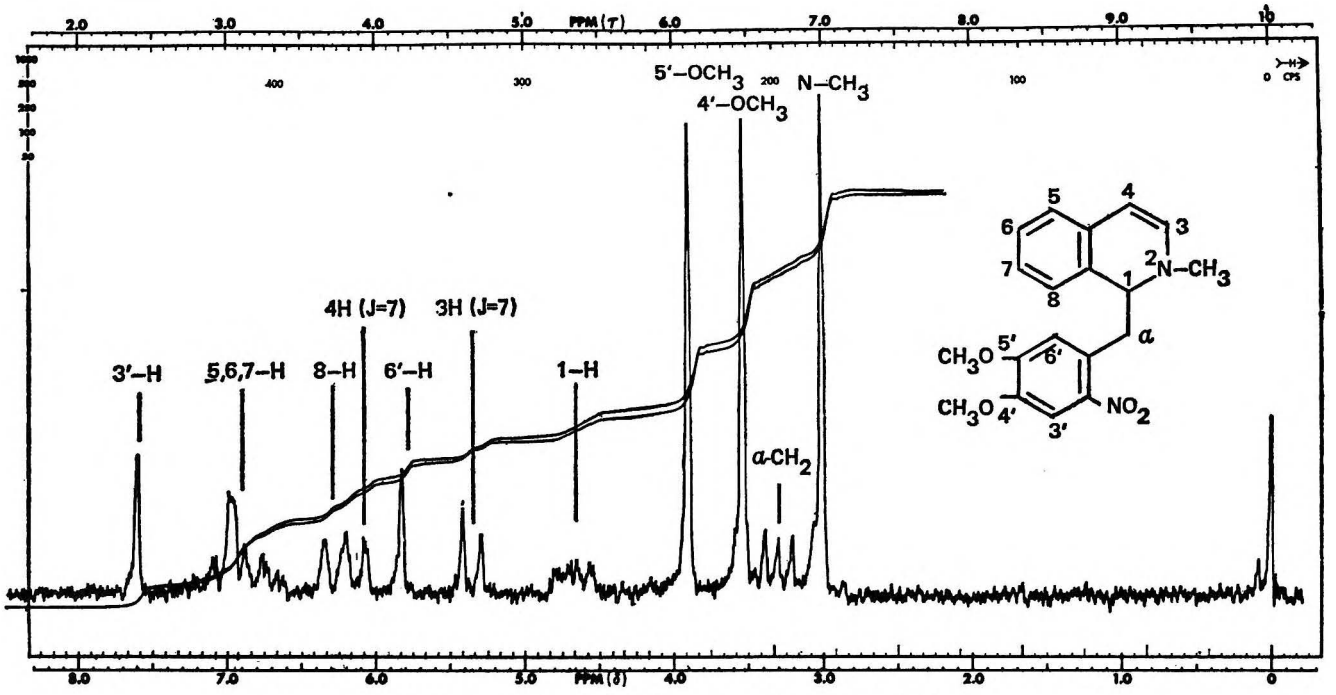
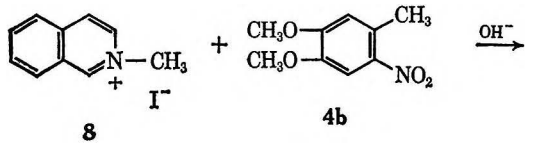
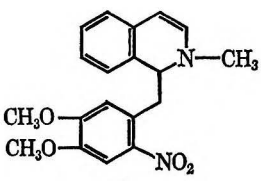


Figure 2.—Nuclear magnetic resonance spectrum of **2b**.

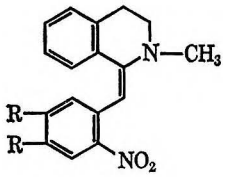
by an unequivocal synthesis. 4,5-Dimethoxy-2-nitrotoluene[1,15] (**4b**) was treated with isoquinoline methiodide (**8**) in alcoholic base by the procedure of Gadamer, *et al.*,[9] as applied to the synthesis of aporphine, to yield a product (**2b**) identical with that obtained by the borohydride reduction procedure. This compound became of considerable interest to us, since the location of the double bond of the adduct of 2-methylisoquinolinium iodide and *o*-nitrotoluene has recently been challenged. Weisbach, *et al.*,[17] on the basis of nmr and uv spectra, proposed that in the structure of this adduct, as well as a number of similar compounds, the double bond was located in the exocyclic position as in **9a** as opposed to the isomeric 3,4 positon in **2a** formulated earlier.[9,18]



8 **4b**



2b



9a, R = H
b, R = OCH_3

The formation of **9** from the potassium borohydride reduction was difficult to rationalize. This prompted us to study the structure of **2a** and **2b** in greater detail and to determine whether the 1,2-dihydroisoquinoline (as in **2a** and **b**) or a structure such as the 1-benzylidenetetrahydroisoquinoline (as in **9a** and **b**) properly described the product.[19]

The nmr spectra of **2a** and **2b** are shown in Figures 1 and 2. Although complete interpretation of the spectrum from **2a** was at first confusing, comparison of its spectrum with that obtained from **2b** led to a straightforward correlation of both structure and shift positions. The spectra may be clearly interpreted only in terms of the 1,2-dihydroisoquinoline structure. In both **2a** and **2b** there are two vinyl protons, exhibiting a normal 7-Hz *cis* coupling, as required by structure **2**, but not by **9**. The complexity of the resonance band at 3.2 and 4.67 ppm for **2a**, and 3.3 and 4.7 ppm for **2b** is due to the presence of the chiral center at carbon 1. The relative area of these two absorption signals is 2 to 1 in each case.

We conclude that the sample of **2a** prepared in our laboratories and that prepared by Weisbach, *et al.*,[17] were the same because of their identical melting points and their similar ultraviolet spectra (Figure 3). The formulation of the Gadamer product as **9** was based on its intense color and the electronic absorption spectrum which exhibited long tailing into the visible region having ϵ 323 at 470 mμ. It was believed unlikely that a compound with the alternative structure **2a** would have absorption of such intensity in the visible region.[17]

It seems reasonable to us that the long-wavelength absorption of **2a** and **2b** is due to a charge transfer band essentially established between the nitro aromatic nucleus and the dihydroisoquinoline ring. As expected,

(17) J. A. Weisbach, C. Burns, E. Macko, and B. Douglas, *J. Med. Chem.*, **6**, 91 (1963).

(18) M. Oberlin, *Arch. Pharm.*, **265**, 274 (1927); J. Muller, *Helv. Chim. Acta*, **31**, 1111 (1948).

(19) Schmid and Karrer [*ibid.*, **32**, 960 (1949)] obtained a dihydro compound from the reaction of papaverine methiodide with lithium aluminum hydride which was considered to be 1,2-dihydro-N-methylpapaverine. The location of the double bond in this instance has not been unambiguously established.

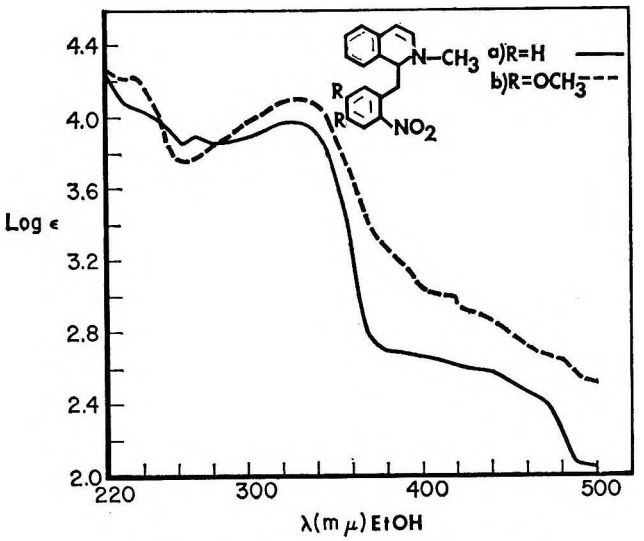
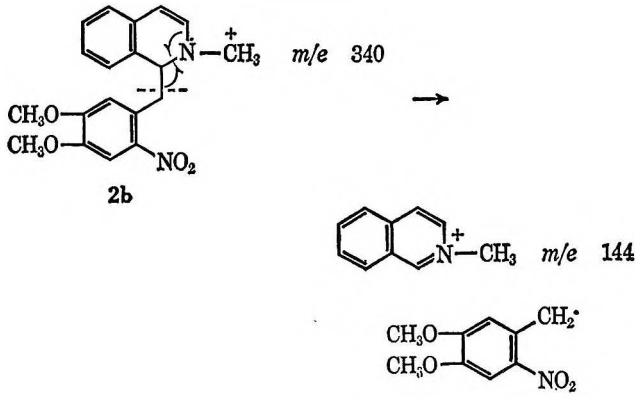


Figure 3.—Absorption spectra of **2a** and **2b**.

the absorption maximum at 470 mμ was shifted to a shorter wavelength as one examined the spectrum in less polar solvents, such as hexane.

Further proof of the structure of **2b** is afforded by its mass spectrum. The base peak in its spectrum occurs at *m/e* 144. All other peaks in the spectrum, including the parent at *m/e* 340, have less than 8% of the intensity of the *m/e* 144 peak. This may be readily explained in terms of simple cleavage of the bond on the carbon α to nitrogen, giving rise to the stable quinolinium ion and a stable radical species as shown in Scheme II.

SCHEME II



Experimental Section[20]

1-(2-Nitrobenzyl)isoquinoline Methodide (1a).—This compound was prepared from 1-(2-nitrobenzyl)isoquinoline[2] in 87% yield. The yellow needles were obtained from ethanol–acetone: dec pt 223°; uv, λ_{max}^{MeOH} 232 mμ (ε 44,000), 279 (s) (5000), 332 (4400), 342 (4400).

Anal. Calcd for $C_{17}H_{15}IN_2O_2$: C, 50.26; H, 3.72; N, 6.90. Found: C, 50.25; H, 3.72; N, 6.79.

1-(4,5-Dimethoxy-2-nitrobenzyl)isoquinoline Methiodide (1b).—A mixture of 1 g of 1-(4,5-dimethoxy-2-nitrobenzyl)isoquinoline[2] and 20 ml of methyl iodide was stirred and heated under reflux for 48 hr. It was cooled and the crystals that separated were washed with dry ether and dried under vacuum to yield 1.28 g (89%) of the quaternary salt as a yellow powder, mp 211–212°.

Anal. Calcd for $C_{19}H_{19}IN_2O_4$: C, 49.20; H, 4.08; N, 6.04; I, 29.25. Found: C, 49.42; H, 4.14; N, 6.44; I, 28.98.

6′-Nitropapaverine Methiodide (1c).—A mixture of 1 g of 6′-nitropapaverine[15] and 20 ml of methyl iodide was heated under reflux for 25 hr. The bright yellow precipitate that formed on cooling was washed with ether and dried under vacuum to yield 1.37 g (100%) of the quaternary salt **1c**, mp 230° dec (lit.[15] mp 235° dec).

1-(3,4-Dimethoxy-2-nitrobenzyl)isoquinoline Methiodide (1d).—1-(3,4-Dimethoxy-2-nitrobenzyl)isoquinoline[2] was converted quantitatively into the quaternary salt **1d** by heating under reflux with a 20- to 30-fold excess of iodomethane (without solvent) for 15–20 hr. The crude product, mp 190–193° dec, was recrystallized successively from water and from ethanol, but the melting point was unchanged.

Anal. Calcd for $C_{19}H_{19}IN_2O_4$: C, 48.94; H, 4.11; I, 27.22; N, 6.01. Found: C, 48.89; H, 4.10; I, 27.25; N, 6.14.

Potassium Borohydride Reductions. A. 6′-Nitropapaverine Methiodide (1c).—In a typical run 3 g of potassium borohydride was added slowly to a mixture of 2 g of 6′-nitropapaverine methiodide (**1c**), 30 ml of ethanol, and 14 ml of water. The mixture was stirred and heated at reflux for 7 hr and then was allowed to stand at room temperature for 30 hr. On work-up 0.51 g (68%) of 4,5-dimethoxy-2-nitrotoluene (**4b**) was isolated as yellow crystals, mp 117.5–119° (lit.[15] mp 118°). An nmr spectrum and elemental analysis further confirmed the structure. Also isolated by acid extraction of the reaction mixture and neutralization of the extract was 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**3b**), mp 64–74°. A picrate, mp 160–161° (lit.[21] mp 158–159°), was prepared in ether solution and recrystallized from ethanol. An authentic sample of the tetrahydroisoquinoline **3b**[22] was converted into its picrate, mp 160–162°. A mixture of the authentic sample and prepared picrates had mp 157.5–159.5°.

B. 1-(4,5-Dimethoxy-2-nitrobenzyl)isoquinoline Methiodide (1b).—Similarly reduced with 1.5 g of potassium borohydride was 1 g of the methiodide **1b** in 18 ml of ethanol and 8 ml of water. From the reaction mixture 0.29 g (72%) of 4,5-dimethoxy-2-nitrotoluene (**4b**), mp 117.5–118.5° (lit.[15] mp 118°), was isolated. Also isolated by acid extraction of the reaction mixture and neutralization was 2-methyl-1,2,3,4-tetrahydroisoquinoline (**3a**), a brown oil that was characterized by conversion into a picrate, which did not depress the melting point of the picrate made from an authentic sample of 2-methyl-1,2,3,4-tetrahydroisoquinoline, mp 148–150° (lit.[23] mp 148–150°).

The above reduction was attempted using buffered conditions. Thus, 1.29 g of potassium borohydride was added slowly to a mixture of 0.83 g of the methiodide **1b**, 1 g of sodium acetate, 1.93 ml of glacial acetic acid, 21 ml of ethanol, and 12 ml of water. The reaction mixture was stirred and heated at 84° for 2 hr and allowed to cool overnight. Potassium borohydride (1.29 g), 1 g of sodium acetate, and 1.93 ml of acetic acid were added and the reaction was stirred and heated at reflux for an additional 7 hr. On work-up, only the cleavage product **4b** was isolated.

C.—Under identical conditions as in A above, **1-(2-nitrobenzyl)isoquinoline methiodide (1a)** was reduced with potassium borohydride in refluxing aqueous ethanol to yield the tetrahydroisoquinoline **3a**, picrate mp 156° dec (lit.[23] mp 146°).

D. 1-(3,4-Dimethoxy-2-nitrobenzyl)isoquinoline Methiodide (1d).—An aqueous solution of 550 mg of potassium borohydride was added to a solution of 1.7 g of the methiodide **1d** in a mixture of 150 ml of ethanol and 100 ml of water, and the mixture was stirred for 45 min at 30°. The temperature of the mixture was raised slowly and finally the mixture was allowed to reflux for 1 hr.

(20) All melting points were recorded on a Thomas–Hoover melting point apparatus and were uncorrected; the microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The infrared spectra were recorded on a Perkin-Elmer grating spectrophotometer, Model 521; the nmr spectra were determined on a Varian A-60 spectrophotometer with tetramethylsilane as the internal standard; ultraviolet spectra were recorded with a Beckman Model DK-1A; and mass spectra were obtained with a CEC-21-110B spectrometer.

(21) R. Forsyth, C. I. Kelley, and F. L. Pyman, *J. Chem. Soc.*, **127**, 1659 (1925).

(22) Kindly supplied by Dr. A. Brossi, Hoffmann-La Roche Laboratories, Nutley, N. J.

(23) J. v. Braun and K. Wirz, *Ber.*, 60B, 102 (1927).

A thin layer chromatogram on Adsorbosil-2 from ethyl acetate showed one spot at the base line (potassium iodide or the methiodide or a mixture of them) and one spot each at R_f 0.9 and 0.85. Solid potassium borohydride was added in small portions to the boiling reaction mixture. Additional chromatograms showed a decrease in the upper spot (R_f 0.9). Potassium borohydride addition was continued until this spot (presumably the 1,2-dihydro compound) disappeared completely. The solution was refluxed for an additional 1 hr and allowed to stand at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in water. The solution was brought to pH 9 by addition of 20% sodium hydroxide and extracted with ether. The combined ether extracts were dried over magnesium sulfate in the presence of a little charcoal. The ether was removed under reduced pressure to yield 1.0 g (80%) of 1-(3,4-dimethoxy-2-nitrobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (5) as a nearly colorless solid, mp 90–93°. A portion was recrystallized from *n*-hexane and then from petroleum ether–ethanol (25:0.3) to give yellow-green crystals, mp 97–98.5°. The infrared and nmr spectra were consistent with the assigned structure. The ultraviolet spectrum showed bands at λ_{max}^{MeOH} 208 mμ (ε 26,000), 265 (2300), and 272 (2300).

Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.74; H, 6.40; N, 8.15.

1-(4,5-Dimethoxy-2-nitrobenzyl)-2-methyl-1,2-dihydroisoquinoline (2b). Method A. Borohydride Reduction of 1b.—To 0.05 g of 10% palladium on charcoal in 24 ml of water, through which nitrogen was bubbled, were added 0.15 g of potassium borohydride and 10 ml of water. A solution of 0.5 g of 1-(4,5-dimethoxy-2-nitrobenzyl)isoquinoline methiodide (**1b**) in 13 ml of ethanol and 13 ml of water was slowly added; the mixture was stirred 20 min more. An orange solid formed on the sides of the flask. The reaction mixture was extracted with ether and the ether was washed with 5% acetic acid and then was extracted with 1 *N* hydrochloric acid. The acid extract was made basic with potassium hydroxide and extracted into ether. The ether was evaporated yielding 0.37 g (75%) of an orange solid, which was recrystallized in methanol to give **2b**, mp 138–141°.

Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 66.19; H, 5.84; N, 8.34.

The nmr spectrum and the uv spectrum of **2b** are shown in Figures 2 and 3, respectively.

Method B. Treatment of Isoquinoline Methiodide and 4,5-Dimethoxy-2-nitrotoluene in Sodium Methoxide.—The method of Weisbach, *et al.*,[17] was used for the preparation of **2b**. Thus, 0.83 g of 4,5-dimethoxy-2-nitrotoluene (**4b**)[1,14] and 0.55 g of isoquinoline methiodide were added to a warm, stirred solution of sodium (0.15 g) in 15 ml of absolute methanol. The reaction mixture was stirred overnight, cooled to 0°, and filtered to yield 2 g of a yellow-orange solid. Recrystallization from methanol yielded **2b**, mp 140–141°. A mixture melting point with the sample of **2b** prepared by the borohydride reduction of **1b** was not depressed. All spectra (infrared, uv, nmr) were identical with those from the previously prepared sample.

1-(2-Nitrobenzyl)-2-methyl-1,2-dihydroisoquinoline (2a).—This compound was prepared from 2-nitrotoluene and isoquinoline methiodide by the procedure of Weisbach, *et al.*,[17] to give **2a**, mp 88–91°; (lit. mp 90°,[9] 95–96°[17]). The nmr spectrum of this compound is shown in Figure 1, the uv spectrum is shown in Figure 3.

Reduction of 2b with Potassium Borohydride.—To a suspension of 0.075 g of **2b** in 10 ml of ethanol and 5 ml of water was added 0.12 g of potassium borohydride. The mixture was heated at reflux and stirred overnight. The ethanol was evaporated and water was added. The reaction mixture was extracted with ether. The ether was extracted with 0.1 *N* hydrochloric acid, the acid extract was made basic with potassium hydroxide pellets, and the basic solution was extracted with ether, which was dried over potassium carbonate. Evaporation of the ether yielded 2-methyl-1,2,3,4-tetrahydroisoquinoline (**3a**) which was characterized by conversion into the picrate, mp 150–152°. Also isolated from the acid-washed ether solution was a yellow solid, mp 115–118°, previously identified as **4b**.

Registry No.—**1a**, 16472-48-3; **1b**, 16622-51-8; **1c**, 16620-92-1; **1d**, 16472-49-4; **2a**, 16620-94-3; **2b**, 16620-95-4; **3b**, 16620-96-5; **5**, 16472-50-7; potassium borohydride, 1303-72-6.

Acknowledgment.—We wish to thank Professor Robert E. Lyle, Jr., for many helpful discussions and Mr. Bernard R. Neustadt for the preparation of a number of compounds. We also wish to acknowledge the financial support of Arthur D. Little, Inc.

The Orientational Effects in Ring-Opening Reactions of Some Unsymmetrically Substituted Episulfides

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Received January 29, 1968

The reactions of propylene sulfide, isobutylene sulfide, and chloropropylene sulfide with hydrogen chloride, acetyl chloride, and anhydrous chlorine have been found, contrary to earlier reports, to yield mixtures of isomeric products resulting from ring opening at both C–S bonds. Propylene sulfide was treated with a number of other electrophilic reagents such as hydrogen bromide, acetyl bromide, bromine, acetic anhydride, and benzoyl chloride. In each case, mixtures of both possible isomeric products were found. The nucleophilic reagents, lithium aluminum hydride and sodium ethanethiolate, however, were found to give ring opening exclusively at the primary C–S bond of propylene sulfide. Some of the mechanistic implications of these results are discussed.

With one exception, all the ring opening reactions of unsymmetrically substituted episulfides that have been described in the literature reportedly yield products opened exclusively at either the least substituted C–S bond or the most substituted C–S bond to give only one of the two possible isomers.[1] The reaction of isobutylene episulfide with mercaptans and alcohols in the presence of either boron trifluoride or sodium ethoxide has been reported to give mixtures of both primary and tertiary thiol products.[2] Since some of the reactions of propylene oxide lead to mixtures of isomeric products, for example, the reactions with hydrochloric and hydrobromic acids,[3] it seems surprising that the same reagents should not give similar results with propylene sulfide.[4] The assignment of structure to the products reported in these earlier studies[4-6] rested entirely on chemical grounds, and it seemed worthwhile, therefore, to reexamine some of these reactions using the more sensitive techniques of gas–liquid partition chromatography (glpc) and nmr spectroscopy for the detection of isomers that might have been overlooked by the earlier workers.

By comparing the reactions of propylene sulfide, isobutylene sulfide and chloropropylene sulfide with certain electrophilic reagents, it was hoped to determine what influence the substituents on the episulfide had in determining the direction of ring opening.

After this work was started, a number of reports appeared on the addition of alkane-, arene-, and acetylthiosulfenyl chlorides to unsymmetrically substituted olefins which have been found to yield mixtures of isomeric adducts.[7-9] The sulfenyl chloride additions to olefins and the additions of electrophilic reagents to episulfides have both been postulated to involve episulfonium ion intermediates, and if this is the case, certain similarities should be found in the isomer ratios of the adducts from both types of reaction.

Results

Schemes I, II, and III show the reaction products of various reagents with propylene sulfide, isobutylene sulfide, and chloropropylene sulfide, respectively. The relative amounts of the a and b isomers obtained from each of these reactions are shown in parentheses. In all cases, the a isomer is the result of ring opening at the primary C–S bond and has the sulfur on the secondary or tertiary carbon and the b isomer is the result from cleavage of the secondary or tertiary C–S bond and has the sulfur on the primary carbon. Except where otherwise noted, the isomer ratios were determined by glpc and confirmed by nmr spectra. The nmr spectra of these products are described in the Experimental Section.

The disulfides that are obtained from the reactions of episulfides with anhydrous halogen (**1a**, **b**; **2a**, **b**; **14a**, **b**; **18a**, **b**) are shown as having a symmetrical structure for convenience in writing, but are more likely to be mixtures of both symmetrical and unsymmetrical disulfides.

Propylene Sulfide.—The nmr spectra of the products from the various reactions of propylene sulfide shown in Scheme I all had two doublets in the region 1.3–1.6 ppm but the methyl group of either the a or b isomer from any of these reactions should be one doublet. The doublets occurring at higher field were in these cases assigned to the more shielded methyl protons of the a isomers.[9] The thiol esters **6b**, **7b**, and **8b** (X = H) were prepared by the light-catalyzed addition of thiol acetic or thiolbenzoic acid to the appropriate 2-halopropene[10] and confirmed our nmr assignments for these cases.

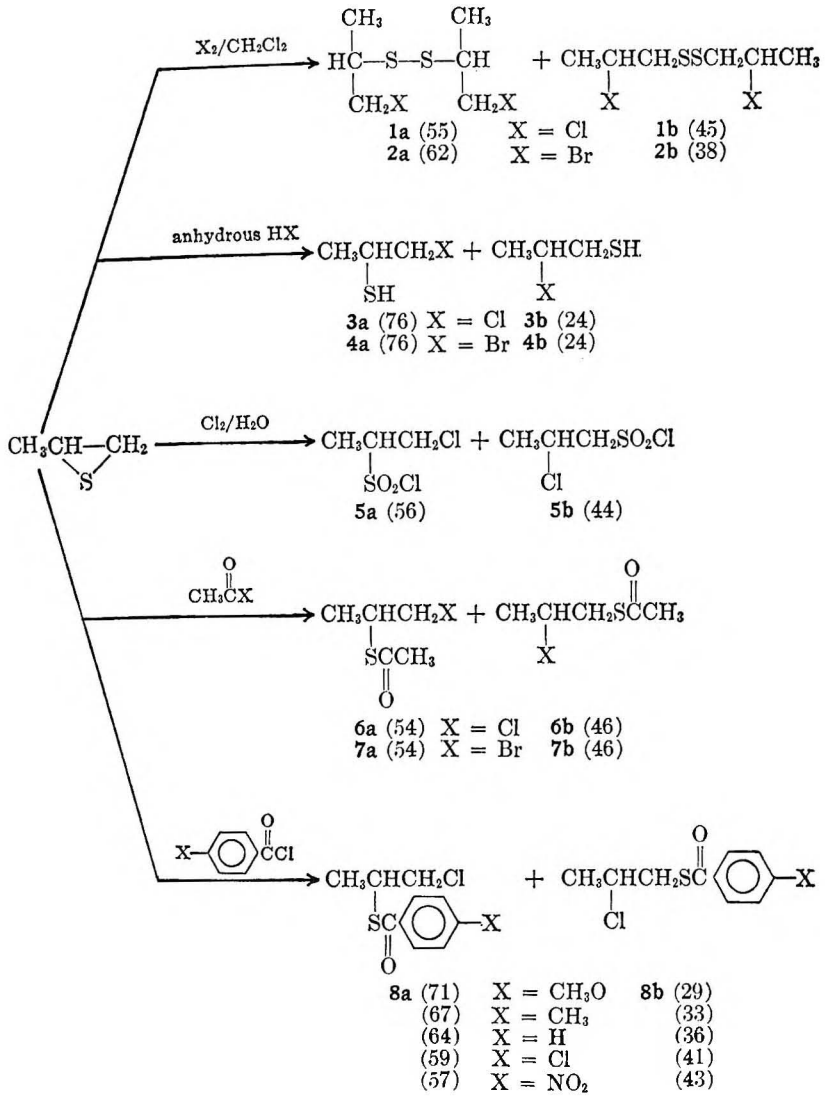
$$RC(=O)SH + CH_3CX{=}CH_2 \xrightarrow{h\nu} CH_3CH(X)CH_2SC(=O)R$$

6b, X = Cl; R = CH_3
7b, X = Br; R = CH_3
8b, X = Cl; R = C_6H_5

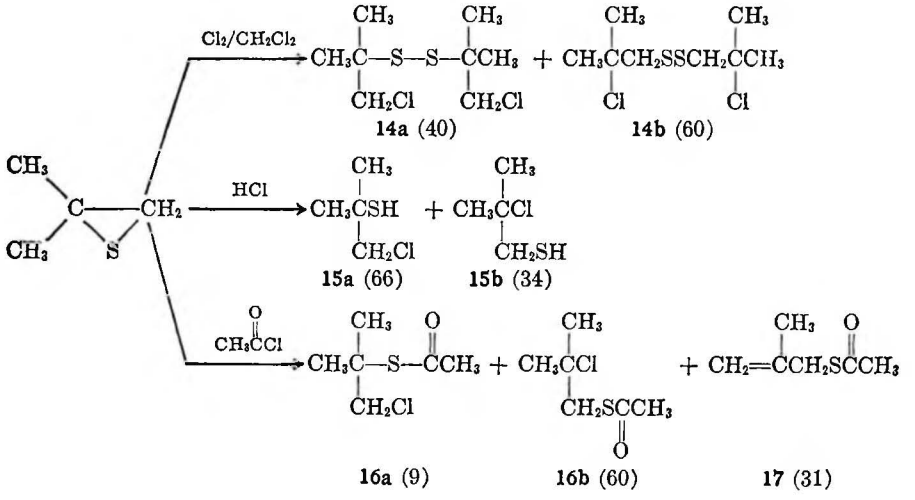
The pyridine-catalyzed reaction of propylene sulfide with acetic anhydride that was reported by Davies and Savige[4] was also reexamined. The relative amount of each isomer is shown in parentheses in Scheme IV. The earlier workers assigned the structure 1-acetoxypropane-2-thiol acetate (**9a**) to the reaction product on the basis of its hydrolysis to 2-mercaptopropanol (**10a**). Gas chromatographic analysis and the nmr spectrum of the propylene sulfide–acetic anhydride reaction product and of the mercaptopropanol derived from it show the presence of two isomers. The nmr spectra of these products have two doublets in the region 1.05–1.2 ppm due to the propylene methyl groups. The larger downfield doublets were assigned to the more deshielded

(1) For a recent review, see M. Sander, *Chem. Rev.*, **66**, 297 (1966).
(2) H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Amer. Chem. Soc.*, **69**, 2675 (1947).
(3) C. A. Stewart and C. A. VanderWerf, *ibid.*, **76**, 1259 (1954).
(4) W. Davies and W. E. Savige, *J. Chem. Soc.*, 317 (1950).
(5) W. Davies and W. E. Savige, *ibid.*, 774 (1951).
(6) J. M. Stewart and H. P. Cordts, *J. Amer. Chem. Soc.*, **74**, 5880 (1952).
(7) W. H. Mueller and P. E. Butler, *ibid.*, **88**, 2866 (1966).
(8) W. H. Mueller and P. E. Butler, *Chem. Commun.*, 646 (1966).
(9) W. H. Mueller and P. E. Butler, *J. Org. Chem.*, **32**, 2925 (1967).
(10) F. G. Bordwell and W. A. Hewett, *ibid.*, **23**, 636 (1958).

SCHEME I



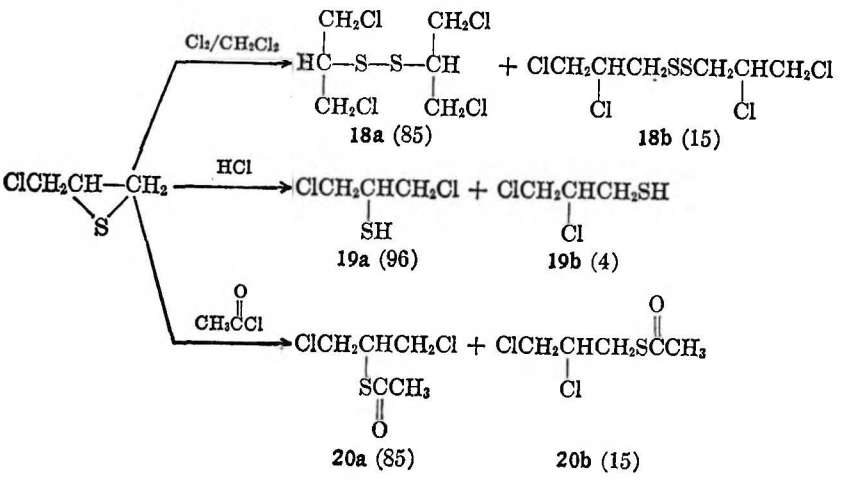
SCHEME II



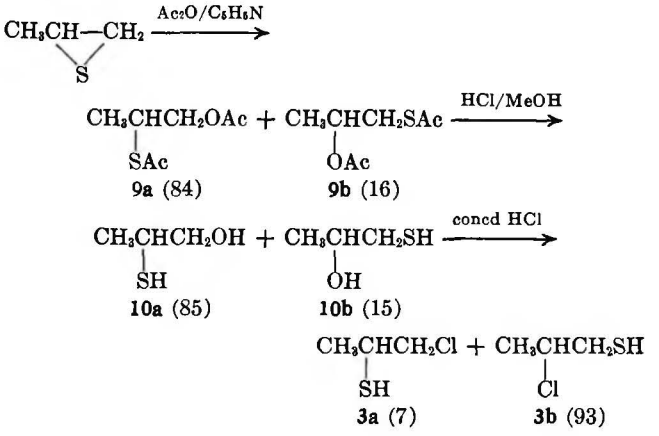
methyl protons of the a isomers in these two cases. Thus, propylene sulfide and acetic anhydride react to give a mixture of **9a** and **b** with the former predominating. Hydrolysis of this mixture yields mainly **10a**, but during the treatment of the latter with concentrated hydrochloric acid, a rearrangement takes place and the chloropropanethiol resulting is mainly the b isomer.

This facile rearrangement of 1-chloropropane-2-thiol was also observed during the reaction of propylene sulfide with aqueous hydrochloric acid. If the product is isolated after only short contact with the acid the thiol **3a** is the major isomer present, but the isomer ratio quickly changes to favor **3b**. The equilibrium ratio seems to be about 10:90 in favor of the b isomer, since

SCHEME III



SCHEME IV

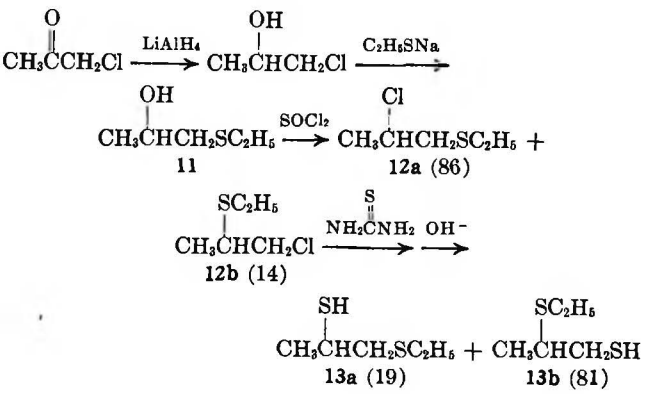


this ratio was also obtained when **3b** from hydrolysis of ester **6b** was stirred with concentrated hydrochloric acid for 18 hr. Water was also found to cause the rearrangement to take place. Thus, a mixture of **3a** and **b** in the ratio 71:29 stirred with water for several hours, contained **3a** and **b** in the ratio 10:90 along with about 60% propylene sulfide. A slower isomerization of the chloropropane thiols **3a** and **b** was observed to occur while standing for periods of several days at room temperature although little change occurred during distillation under reduced pressure, but the bromopropanethiol **4a** does isomerize during distillation at reduced pressure.

Although all the electrophilic reagents we examined gave appreciable ring opening of propylene sulfide at both the primary and secondary C–S bonds, two nucleophilic reagents that were examined opened propylene sulfide at the primary C–S bond with a high degree of selectivity. Thus, the monomeric product from the lithium aluminum hydride reduction of propylene sulfide was found to be 2-propanethiol as reported earlier[11] with only about 0.5% of 1-propanethiol detectable by glpc. In addition, the reaction of propylene sulfide with sodium ethanethiolate yielded 4-thiohexane-2-thiol (**13a**). None of the other isomer, 2-ethylthiopropane-1-thiol (**13b**), was detected by glpc. The identification of **13a** was based on nmr which shows a doublet at 1.90 ppm due to the secondary thiol proton. An attempt to synthesize the thiol **13a** *via* the chloride **12a** yielded instead a mixture of the isomeric thiols **13a** and **b** in the

(11) F. G. Bordwell, H. M. Anderson, and B. M. Pitt, *J. Amer. Chem. Soc.*, **76**, 1082 (1954).

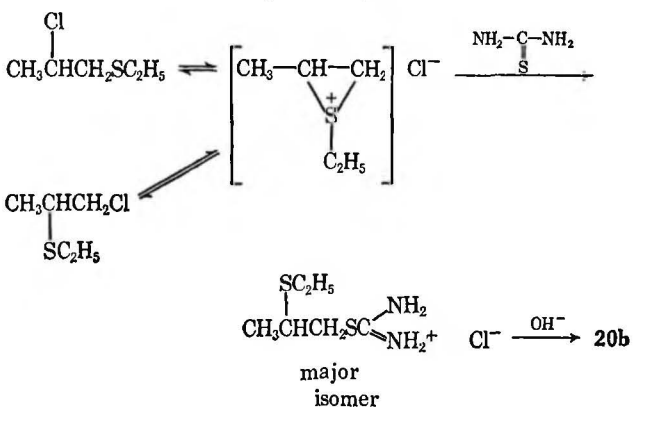
SCHEME V



ratio 19:81 (Scheme V). The ratio of **13a** and **b** in the product was determined by glpc, while the nmr spectrum confirmed the presence of two isomeric thiols, with a doublet at 1.90 ppm for the secondary thiol proton of **13a** and a larger triplet at 1.62 ppm for the primary thiol proton of **13b**. The product from the reaction of the alcohol **11** with thionyl chloride was a mixture of the two isomeric chlorides **12a** and **b** in the ratio 86:14 as determined by nmr spectroscopy. A rearrangement during the reaction of the chlorides **12a** and **b** with thiourea must have occurred.

The latter rearrangement can be explained as occurring through an episulfonium ion intermediate (Scheme VI).

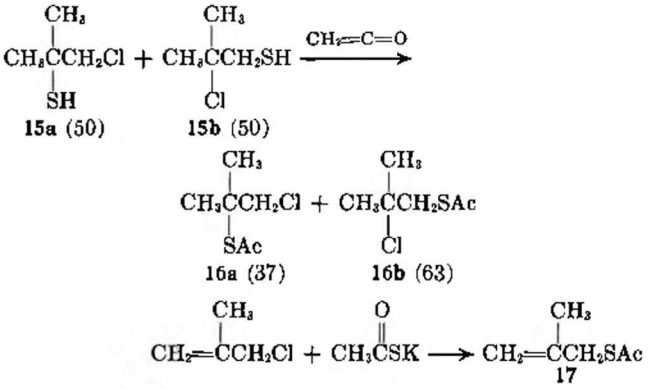
SCHEME VI



Isobutylene Sulfide.—The nmr spectrum of the reaction product of isobutylene sulfide and anhydrous

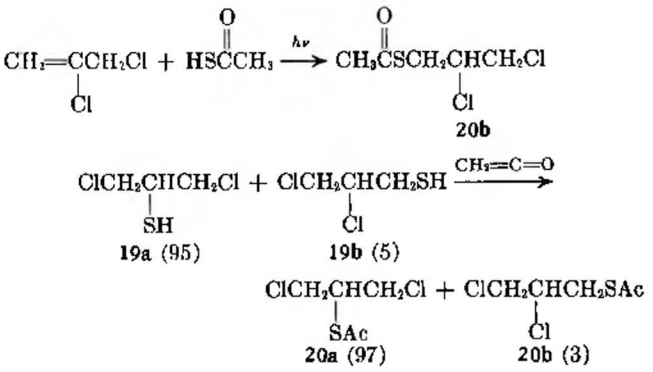
hydrogen chloride reveals the presence of the two isomers **15a** and **b**, which are readily separated by glpc. Similarly, the nmr spectrum of the product of the reaction of isobutylene sulfide with anhydrous chlorine shows the presence of the two species **14a** and **b** in the ratio 40:60. The nmr spectra of the products of these two reactions had a pair of singlets in the methyl region. The singlet occurring at lower field was assigned to the b isomer while the other was assigned to the a isomer. Like the chloropropanethiols **3a** and **b**, the chlorobutanethiols **15a** and **b** are fairly rapidly isomerized to an equilibrium mixture with a ratio of about 2:98 in favor of the b isomer. A mixture of **15a** and **b** was also found to isomerize, though more slowly, in the absence of water.

In contrast to the reactions of chlorine and hydrogen chloride with isobutylene sulfide, the addition of acetyl chloride (Scheme II) to this episulfide proceeds predominantly by ring opening at the tertiary C–S bond. The chlorobutylthiol ester **16b** (47%) and the unsaturated thiol ester **17** (24%) were the main products of the reaction. A small amount (7%) of the ester **16a** was also detected by glpc although the nmr spectrum of the crude reaction mixture did not reveal its presence. For purposes of comparison, a mixture of the esters **16a** and **b** (37:63) was prepared by adding ketene to the 1:1 mixture of chlorothiols **15a** and **b** from the reaction of isobutylene sulfide with anhydrous hydrogen chloride, while the unsaturated ester **17** was prepared from 1-chloro-2-methylpropene-2 and potassium thiolacetate.



Chloropropylene Sulfide.—The reaction of chloropropylene sulfide with hydrogen chloride yielded the two isomeric dichlorothiols **19a** and **b**. Because of extensive decomposition on the column, the ratio of these thiols could not be determined by glpc. The nmr spectra of these mixtures showed a doublet at 2.16 ppm due to the secondary thiol proton of **19a**, and two doublets at 1.72 ppm due to the primary thiol proton of **19b**. Evaluation of the ratios of **19a** and **b** was accomplished by integration of these peaks. It was found that the isomerization of **19a** to **b** in concentrated hydrochloric acid proceeds much more slowly than is the case for the isomerizations of the chlorothiols **3a** and **15a**, and reflects the lower reactivity of the chloropropylene sulfide with hydrogen chloride.[12]

The nmr spectrum of the acetyl chloride–chloropropylene sulfide adduct was not very revealing as to the structure of the adduct, but glpc showed the presence of two components. By the light-catalyzed addition of thiolacetic acid to 1,2-dichloropropene-2, the ester **20b** was obtained free from its isomer **20a**. Its identity with one of the components of the acetyl chloride–chloropropylene sulfide adduct was established by glpc. The addition of ketene to a mixture of the dichlorothiols **19a** and **b** (95:5) then yielded a mixture of the esters **20a** and **b** in the ratio 97:3. The unambiguous assignment of structures to the acetyl chloride–chloropropylene sulfide adducts followed from a comparison of the gas chromatograms. The addition of anhydrous chlo-



ride to chloropropylene sulfide produced predominantly the disulfide **18a**. The presence of about 15% of the disulfide **18b** was deduced from the nmr spectrum of the crude product.

Discussion

Oddon and Wylde, who recently reported on the kinetics of the reaction of anhydrous hydrogen chloride and hydrogen bromide with a number of substituted episulfides, found that the reactions with hydrogen chloride proceed with second-order kinetics.[12] On the basis of the observed kinetics as well as the work of Davies and Savige,[4,5] who reported that these reactions yield only primary thiols, Oddon and Wylde concluded that the reaction proceeds *via* attack by the halide ion on a carbonium ion intermediate, *i.e.*, an SN1Ac mechanism. Our work which shows that in anhydrous media hydrogen chloride yields mainly secondary thiol with both propylene sulfide and chloropropylene sulfide and yields more tertiary than primary thiol with isobutylene sulfide, is inconsistent with an SN1Ac mechanism. Attack by halide ion on an episulfonium ion intermediate would be consistent with our results since both steric as well as polar factors would have an effect on the site of attack by the nucleophile. The importance of steric factors in the direction of opening of some episulfonium ions has been demonstrated by Mueller and Butler.[7] However, the relatively larger amount of primary thiol obtained from isobutylene sulfide than is obtained from propylene sulfide on reaction with hydrogen chloride indicates that polar effects of the episulfide substituents are also important in this reaction.

The reaction products of the three episulfides studied with acetyl chloride indicate that polar effects become more important when the electron-withdrawing ability of the group attached to sulfur in the episulfonium ion is strong compared with hydrogen. In particular, the presence of the unsaturated ester **12** among the reaction products of the reaction of acetyl chloride with isobutylene sulfide strongly suggests that a tertiary carbonium ion is an intermediate in this reaction. A mixture of

(12) A. Oddon and J. Wylde, *Bull. Soc. Chim. Fr.*, 1607 (1967).

the two isomeric thiol esters **11a** and **b** prepared by the addition of a mixture of **10a** and **b** to ketene did not contain any of the ester **12**, hence **12** must arise by elimination of a proton from an intermediate of the ring-opening reaction (most likely a carbonium ion).

The reaction products of propylene sulfide with various 4-substituted benzoyl chlorides also indicate that as the electron-withdrawing ability of the electrophilic group is increased the proportion of b isomer also increases, although in this series, the effect is not very great.

Most of the work on the reactions of propylene sulfide with nucleophilic reagents leads to the conclusion that attack by the nucleophile occurs almost exclusively at the least hindered carbon of the episulfide. Thus, our results on the reaction of lithium aluminum hydride with propylene sulfide confirms the earlier work on this reaction.[11] A report[13] that propylene sulfide and dimethylamine yield the primary thiol rather than the secondary thiol has been shown to be incorrect,[14] while other work[15,16] has shown that attack of secondary amines on episulfides takes place at the least hindered carbon. In addition, we have found that the reaction of sodium ethanethiolate with propylene sulfide leads exclusively to primary thiol. All these results indicate that attack on propylene sulfide by nucleophilic reagents occurs at the least hindered carbon, and in the absence of strong polar effects these ring openings can be expected to be governed by steric factors.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a Varian A-60. Chemical shifts are reported in parts per million from tetramethylsilane as internal standard. All glpc analyses were carried out on a Perkin-Elmer Model 800 gas chromatograph. All columns were 6 ft × 0.125 in. o.d. stainless steel. Column A contained 15 wt % diisodecylphthalate on 80/100 mesh Chromosorb W. Column C contained 15 wt % DC 200 silicone oil on 80/100 mesh Chromosorb W. Column K contained 15 wt % Carbowax 1500 on 80/100 mesh Chromosorb W. The microanalyses were carried out by A. B. Gygli, Toronto.

Reactions of Episulfides with Anhydrous Hydrogen Halides. General.—The anhydrous hydrogen halide was bubbled through a 20–25% w/v solution of the episulfide in anhydrous ether or methylene chloride guarded from the atmosphere by a calcium chloride drying tube, until the reaction was judged to be complete by the absence of an episulfide peak in the gas chromatogram. With the exception of the product of the reaction of propylene sulfide with hydrogen bromide, the ratio of a to b isomers was determined by glpc on the crude product. The ratios determined from the nmr spectra of the crude products were in good agreement with the glpc determinations with the exception noted above. The crude reaction product was then purified by distillation under reduced pressure. The nmr spectra were determined on the purified products, which were again analyzed by glpc.

Propylene Sulfide and Hydrogen Chloride.—The crude reaction mixture was analyzed on column A at 60° and showed, in addition to the ether peak, peaks at 15.4 and 16.9 min in the ratio 76:24 (**3a**:**b**). Distillation of the crude product yielded the mixture of 1-chloropropane-2-thiol (**3a**) and 2-chloropropane-1-thiol (**3b**) (bp 47–51° (49 mm); n^{20}D 1.4850) in a yield of 74%. Gas chromatography of this material showed the same two peaks to be present in the ratio of 71:29; nmr (CS_2) peaks were at δ 1.35 (d, J = 6 Hz, CH_3CS), 1.51 (d, J = 6 Hz, CH_3CCl), 1.73 (four lines, S **H**), 2.71 (m, CH_2S), 3.05 (m, CHS), 3.48 (m, CH_2Cl), 3.94 (m, CHCl).

Propylene Sulfide and Hydrogen Bromide.—The addition was carried out at −10° in CH_2Cl_2. Analysis of the crude product on column A at 75° showed the product to consist of two components with retention times of 15.7 and 17.0 min in the ratio 55:45, respectively. The solvent was removed under reduced pressure and the nmr spectrum (CS_2) was determined: δ 1.42 (d, J = 6.5 Hz, CH_3CSH), 1.73 (d, J = 6.5 Hz, CH_3CBr), 2.5–3.7 (m, CH_2 and CHSH), 4.04 (m, CHBr). From the ratio of the doublets at 1.42 and 1.73 it was determined that 1-bromopropene-2-thiol (**4a**) and 2-bromopropane-1-thiol (**4b**) were present in the ratio 76:24, respectively. Distillation of the crude product under reduced pressure afforded a mixture of 4a and **4b** in 75% yield: bp 40–45° (12 mm); n^{20}D 1.5261. The nmr spectrum of this material showed the ratio of **4a** to **b** had changed to 33:67.

Isobutylene Sulfide and Hydrogen Chloride.—Analysis of the crude reaction product was carried out on column A at 75°. In addition to the ether peak, two other peaks were observed with retention times of 10.4 and 12.3 min in the ratio of 66:34, respectively (**15a**:**b**). Distillation of the crude material provided in 70% yield a mixture of 2-chloro-2-methylpropane-1-thiol (**15a**) and 1-chloro-2-methylpropane-2-thiol (**15b**), 56:44 by glpc: bp 37–39° (20 mm); n^{20}D 1.4762; nmr (CS_2), δ 1.42 (s, CH_3CS), 1.62 (s, CH_3CCl), 2.00 (s, MeCSH), 2.83 (d, J = 9 Hz, CH_2SH), 3.58 (s, CH_2Cl).

The isomer ratio of the above sample was found to change on standing at room temperature. Thus after 3 days it was found by glpc analysis that **15a** and **b** were present in the ratio of 28:72, and after 6 days in the ratio 11:89.

Chloropropylene Sulfide and Hydrogen Chloride.—Analysis of the crude reaction product by glpc could not be carried out due to extensive decomposition of the reaction products on the column. From the nmr spectrum of the crude product the ratio of **19a**:**19b** was determined as 97:3. Distillation of the product under reduced pressure yielded 25% of dichloropropane thiols: bp 62–64° (5.5 mm); n^{20}D 1.5213; nmr (CS_2), δ 1.72 (2d, J = 9 Hz, CH_2SH), 2.16 (d, J = 10 Hz, CHSH), 3.1–4.1 (complex envelope, CH_2 and CH). By integration of the thiol protons the ratio of 19a to b was found to be 95:5. In addition to the mixture of 19a and b, chloropropylene sulfide was recovered in 43% yield: bp 40–62° (5.5 mm); n^{20}D 1.5245. The ir spectrum of the latter showed some contamination by **19a** and **b**.

Reactions of Episulfides with Concentrated Hydrochloric Acid. General.—The episulfides were vigorously stirred with about ten volumes of 11.5 N hydrochloric acid for extended periods of time, the organic layer was then separated and the acid was extracted twice with methylene chloride. The combined organic phase and extracts, after drying over calcium chloride, were concentrated and distilled under reduced pressure. The isomer ratios were determined on the resulting products by glpc or nmr analysis.

For the shorter reaction times (1 to 10 min) a small amount of the episulfide was shaken with a larger volume of 11.5 N hydrochloric acid, the organic layer was quickly separated, washed with water, and then dried over calcium chloride. The chlorothiol isomer ratios were determined by glpc.

Propylene Sulfide.—The propylene sulfide was stirred with the acid for 18 hr. There was obtained a 52% yield of a mixture of of **3a** and **b** in the ratio 10:90 as determined by glpc (column A at 60°): bp 52–54° (52 mm); n^{20}D 1.4855.

When propylene sulfide was shaken with hydrochloric acid for about 1 min and worked up as described above, the ratio **3a**:**b** was found to be 56:44 by glpc. When the contact time with the acid was 10 min, the ratio **3a**:**b** was found to be 29:71.

Isobutylene Sulfide.—The isobutylene sulfide was stirred with the acid for 1 hr. There was obtained a 71% yield of a mixture of **15a** and **b** in the ratio 2:98 as determined by glpc (column A at 75°): bp 47–49° (30 mm); n^{20}D 1.4772; nmr (CS_2), δ 1.41 (s, CH_3CS), 1.62 (s, CH_3CCl), 1.63 (t, J = 9 Hz, CH_2SH), 2.82 (d, J = 4 Hz, CH_2SH). When isobutylene sulfide was shaken with hydrochloric acid for about 1 min the ratio **15a**:**b** was found to be 10:90 by glpc.

Chloropropylene Sulfide.—After 16 hr stirring with concentrated hydrochloric acid, the chloropropylene sulfide yielded 90% of dichloropropane thiols **19a** and **b** in the ratio 85 to 15: bp 61° (5 mm); n^{20}D 1.5257. Further stirring of this chlorothiol mixture with hydrochloric acid for another 84 hr yielded 60% of a mixture of **19a** and **b** in the ratio 30:70, whereas after stirring for a total of 14 days, the mixture was recovered in 51% yield

(13) B. Hansen, *Acta Chem. Scand.*, **13**, 151 (1959).

(14) S. D. Turk, R. P. Louthan, R. L. Cobb, and C. R. Bresson, *J. Org. Chem.*, **29**, 974 (1964).

(15) H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Amer. Chem. Soc.*, **69**, 2672 (1947).

(16) N. S. Isaacs, *Can. J. Chem.*, **44**, 395 (1966).

and had an isomer ratio of 23 to 77: bp 64° (5.5 mm); $n^{20}D$ 1.5240

All the isomer ratios were determined from the nmr spectra in CS_2 by integration of the peaks due to the thiol protons, which appeared as a doublet at δ 2.16 (J = 10 Hz) (19a) and a pair of overlapping doublets at δ 1.72 (J = 9 Hz) (19b).

Addition of Acetyl Halides to Episulfides. General.—The episulfide was added slowly with stirring to 1 equiv of the acetyl halide which was being cooled in an ice–water bath, except for the case of chloropropylene sulfide and acetyl chloride which were sealed together in an ampoule in a 1:1 molar ratio and heated to 45° for 18 hr. The reaction mixtures were stirred at 0° for 1 hr and then allowed to warm to room temperature. Gas chromatographic analysis was carried out on the crude reaction mixtures to determine the isomer ratios of the products.

Propylene Sulfide and Acetyl Chloride.—Analysis of the crude reaction product on column K at 80° showed components with retention times of 23.3 and 25.6 min in the ratio of 54:46, respectively. By admixture of this reaction product with 2-chloropropane-1-thiol acetate (6b) prepared from the addition of thiolacetic acid to 2-chloropropane (see below), the component with the longer retention time was identified as 6b. Distillation of the crude product yielded 79% of the mixture of esters 1-chloropropane-2-thiol acetate (6a) and 6b: bp 73° (12 mm); $n^{20}D$ 1.4900 (lit.[4] bp 70–71° (9 mm); $n^{15}D$ 1.491); nmr (CS_2), δ 1.32 (d, J = 6 Hz, CH_3 CS), 1.46 (d, J = 6 Hz, CH_3CCl), 2.21 (s, $CH_3C{=}O$), 2.23 (s, $CH_3C{=}O$), 3.2–4.2 (complex envelope, CH_2 and CH).

Propylene Sulfide and Acetyl Bromide.—Analysis of the crude mixture on column K at 100° showed only two large peaks with retention times of 14.8 and 16.2 min in addition to traces of low boiling impurity. The first component 1-bromopropane-2-thiol acetate (7a) made up 54% of the mixture, while the second, which had a retention time identical with that of 2-bromopropane-1-thiol acetate (7b), made up the remaining 46%. Distillation of the crude reaction mixture yielded 73% of the mixture of 7a and b in the same ratio as before: bp 53–54° (0.6 mm); $n^{22}D$ 1.5179 (lit.[4] bp 45° (0.2 mm); $n^{13}D$ 1.521); nmr (CS_2), δ 1.29 (d, J = 6 Hz, CH_3 CS), 1.56 (d, J = 6 Hz, CH_3 CBr), 2.11 (s, $CH_3C{=}O$), 2.15 (s, $CH_3C{=}O$), 2.85–3.95 (complex envelope CH_2 and CH).

Isobutylene Sulfide and Acetyl Chloride.—The gas chromatogram of the crude product on column A or column K at 125° showed a fairly complex mixture. The two main fractions were identified as 2-chloro-2-methylpropane-1-thiol (16b), and 2-methylprop-2-ene-1-thiol acetate (17) (24%). A small peak was assigned to 1-chloro-2-methylpropane-2-thiol (16a) (7%) by comparison of retention times on both columns A and K with a mixture of 16a and b prepared by the addition of a mixture of thiols 15a and b to ketene. The nmr (C_6H_6) of the crude product in benzene had peaks at δ 1.46 (s, CH_3 CCl), 1.67 (three-line pattern, CH_3 C=C), 2.09 (s, $CH_2C{=}O$), 3.26 (s, Me_2CClCH_2S), 3.47 (d, J = 1 Hz, $SCH_2C{=}C$), 4.72 (m, $H_2C{=}C$), 4.88 (m, $H_2C{=}C$).

Chloropropylene Sulfide and Acetyl Chloride.—The crude reaction product was analyzed on column A at 150° and was found to contain, in addition to unreacted starting material, 1,3-dichloropropane-2-thiol acetate (20a) and 2,3-dichloropropane-1-thiol acetate (20b) in the ratio 83:17. The latter two were identified by comparison with chromatograms of independently synthesized 20b and a mixture of 20a and b. Distillation of the crude reaction mixture under reduced pressure yielded 28% of predominantly unreacted chloropropylene sulfide (bp 40° (20 mm); $n^{20}D$ 1.5268) and 43% of a mixture of 20a and b: bp 80–85° (4 mm); $n^{20}D$ 1.5133 (lit.[5] bp 122° (25 mm), $n^{20}D$ 1.5155); nmr (CS_2), δ 2.35 (s, $CH_3C{=}O$), 3.83 (m, CH_2 and CH).

Preparation of 2-Chloropropane-1-thiol Acetate (6b).—The procedure of Bordwell and Hewett[10] for the light-catalyzed addition of thiolacetic acid to 2-chloropropene was followed to give 70% of 2-chloropropene-1-thiol acetate (6b): bp 74–76° (13 mm); $n^{20}D$ 1.4890 (lit.[10] bp 71° at 10 mm); nmr (CS_2), δ 1.42 (d, J = 6 Hz, CH_3CCl), 2.18 (s, $CH_3C{=}O$), 3.00 (three-line pattern, CH_2), 3.80 (m, CH).

Preparation of 2-Bromopropane-1-thiol Acetate (7b).—A solution of 12.0 g (0.1 mol) of 2-bromopropene and 7.6 g (0.1 mol) of thiolacetic acid was irradiated by a 60-W incandescent lamp for 12 hr. Distillation of the reaction mixture under reduced pressure yielded 4.9 g (25%) of 2-bromopropane-1-thiol acetate (7b): bp 46–47° (0.35 mm); $n^{20}D$ 1.5180; nmr (CS_2), δ 1.56 (d, J = 6 Hz, CH_3CBr), 2.17 (s, $CH_3C{=}O$), 3.08 (m, CH_2), 3.83 (m, CH). Gas chromatography of this sample on column K at 100° showed a single peak with retention time of 16.5 min.

Preparation of 2,3-Dichloropropane-1-thiol Acetate (20b).—A solution of 8.5 g (0.077 mol) of 2,3-dichloropropene and 5.8 g (0.077 mol) of thiolacetic acid were irradiated with a 100-W incandescent lamp for 12 hr and then distilled to yield 1.9 g (13%) of 2,3-dichloropropane-1-thiol acetate (20b): bp 64° (0.1 mm); $n^{20}D$ 1.5198. Gas chromatography of a mixture of this ester with the product of the addition of acetyl chloride to chloropropylene sulfide established the identity of the minor component of that reaction with 20b.

Addition of 1,3-Dichloropropane-2-thiol (19a) and 2,3-Dichloropropane-1-thiol (19b) Mixture to Ketene.—Ketene, 1.4 g (33 mmol), was condensed into a glass tube cooled to −70° and containing 5.0 g (34.5 mmol) of a mixture of 19a and b in the ratio 95:5 obtained from the reaction of chloropropylene sulfide with hydrogen chloride. The tube was sealed and after remaining at −70° for 18 hr, it was allowed to stand at room temperature for another 24 hr before being opened. Distillation of the contents under reduced pressure yielded 5.1 g (83%) of 1,3-dichloropropane-2-thiol acetate (20a): bp 53–55° (0.1 mm); $n^{20}D$ 1.5160. Gas chromatography of this material on column A at 150° showed the presence of 3% of the ester 20b. The main component 20a (97%) had the same retention time as the main component of the addition product of chloropropylene sulfide and acetyl chloride.

Additon of 2-Chloro-2-methylpropane-1-thiol (15a) and 1-Chloro-2-methylpropane-2-thiol (15b) Mixture to Ketene.—Ketene (2.2 g, 52 mmol) was condensed into a glass tube cooled to −70° and containing 6.6 g (53 mmol) of a mixture of 15a and b in the ratio 53:47, respectively, and sealed. Gas chromatographic analysis of the solution after 4 days at −70° showed much of the thiols 15a and b remained unreacted. Ketene was therefore bubbled through the solution at room temperature for 3 hr and the product was distilled at reduced pressure to yield 1.4 g (16%) of a mixture of the esters 16a and b boiling at 30–32° (0.15 mm), $n^{20}D$ 1.4898. Gas chromatographic analysis of this material on column A or column K at 125° showed the two esters 16a and b to be present in the ratio 33:67. The two components had the same retention times on both columns as the two components of the acetyl chloride–isobutylene sulfide reaction product which were assigned the structures 16a and b.

Anal. Calcd for $C_6H_{11}ClOS$: C, 43.23; H, 6.65; Cl, 21.27; S, 19.23. Found: C, 43.47; H, 6.68; Cl, 20.89; S, 18.97.

The nmr spectrum of this material in benzene had singlets at 1.45, 2.07, and 3.24 ppm in the ratio 6:3:2 assigned to 16b and a smaller set of singlets at 1.38, 1.96, and 3.81 ppm in the ratio 6:3:2 assigned to 16a.

Preparation of 2-Methylpropene-3-thiol Acetate (17).—A solution of potassium thiol acetate was prepared by adding 16.8 g (0.22 mol) of freshly distilled thiolacetic acid to 14 g (0.25 mol) of potassium hydroxide in 100 ml of methanol under a nitrogen atmosphere. During the dropwise addition of 20 g (0.22 mol) of 3-chloro-2-methylpropene to the stirred alcohol solution, a white precipitate formed and the temperature of the reaction mixture rose to 40°. When the addition was completed, the mixture was heated to reflux for 1 hr, and was then cooled and mixed with excess water. The oil which separated was removed and the aqueous layer was extracted with three 25-ml portions of ether. The combined oil and extracts were dried ($CaCl_2$) and concentrated. Distillation of the residue under reduced pressure yielded 18.0 g (46%) of 2-methylpropene-3-thiol acetate (17): bp 48–50° (18 mm); $n^{20}D$ 1.4822; nmr (C_6H_6), δ 1.67 (three-line pattern, $CH_3C{=}C$), 2.06 (s, $CH_3C{=}O$), 3.51 (d, J = 1 Hz, CH_2S), 4.79 (m, $C{=}CH_2$), 4.95 (m, $C{=}CH_2$).

Anal. Calcd for $C_6H_{10}OS$: C, 55.37; H, 7.74; S, 24.63. Found: C, 55.82; H, 7.62; S, 24.37.

The gas chromatographic behavior of this material agreed with that of the unsaturated ester present in the acetyl chloride–isobutylene sulfide reaction product.

Addition of 4-Substituted Benzoyl Chlorides to Propylene Sulfide.—Equimolar solutions of freshly distilled propylene sulfide with each of benzoyl chloride, 4-chloro-, 4-methyl-, 4-methoxy-, and 4-nitrobenzoyl chloride, were sealed in glass ampoules and maintained at 50° for 10 days in a constant temperature bath. Each of the solutions was then pumped down for a short time to remove any volatiles and the a:b ratio of the esters were determined from the nmr spectra of the crude reaction product by measuring the areas of the overlapping doublets of the methyl protons. The results are given in Scheme I. In

the case of the mixture of 1-chloropropane-2-thiol benzoate (8a, X = H) and 2-chloropropane-1-thiol benzoate (8b, X = H) the downfield doublet was shown to be due to the b isomer by comparison with the nmr spectrum of an authentic sample of 8b (X = H).

Preparation of 2-Chloropropane-1-thiol Benzoate.—Thiolbenzoic acid (bp 81–83° (8 mm), $n^{20}D$ 1.6022) was prepared according to Noble and Tarbell.[17] A solution of 13.8 g (0.1 mol) of thiolbenzoic acid and 7.8 g (0.1 mol) of 2-chloropropene was irradiated for 5 hr by a 150-W incandescent lamp. Distillation of the product yielded 15.9 g (74%) of 2-chloropropane-1-thiol benzoate (8b, X = H): bp 103–108° (1 mm); $n^{20}D$ 1.5754; nmr (C_6H_6), δ 1.35 (d, J = 6.5 Hz, CH_3), 3.29 (three-line pattern, CH_2), 3.99 (m, CH).

Anal. Calcd for $C_{10}H_{11}ClOS$: C, 55.94; H, 5.16; Cl, 16.51; S, 14.94. Found: C, 56.09; H, 4.96; Cl, 16.49; S, 15.29.

Reactions of Episulfides with Anhydrous Halogens. General.—The procedure of Stewart and Cordts[5] for the addition of chlorine or bromine to the episulfide was followed. Anhydrous methylene chloride was used as the solvent in each case. After removal of the solvent the reaction product was distilled under reduced pressure and the nmr spectrum of the distillate was used to determine the isomer ratios of the product formed.

Propylene Sulfide and Chlorine.—The mixture of bis(1-methyl-2-chloroethyl) disulfide (1a) and bis(2-chloropropyl)disulfide (1b) was obtained in 69% yield: bp 90–95° (0.25 mm); $n^{20}D$ 1.5405 (lit.[6] bp 98–101° (1 mm); $n^{20}D$ 1.5400); nmr (CS_2), δ 1.35 (d, J = 6 Hz, CH_3 CS), 1.56 (d, J = 6 Hz, CH_3 CCl), 2.8–4.2 (complex envelope, CH_2 and CH). The two methyl doublets had relative intensities of 55:45, respectively.

Propylene Sulfide and Bromine.—The mixture of bis(1-methyl-2-bromoethyl) disulfide (2a) and bis(2-bromopropyl) disulfide (2b) was obtained in 87% yield: bp 97–100° (0.4 mm); $n^{20}D$ 1.5839 (lit.[6] bp 114–117° (1 mm); $n^{20}D$ 1.5838); nmr (CS_2), δ 1.42 (d, J = 6.5 Hz, CH_3 C S), 1.80 (d, J = 7 Hz, CH_3 Br), 3.0–4.5 (complex envelope, CH_2 and CH). The two methyl doublets had relative intensities of 62:38, respectively.

Isobutylene Sulfide and Chlorine.—The mixture of bis(1,1-dimethyl-2-chloroethyl) disulfide (14a) and bis(2-chloro-2-methylpropyl) disulfide (14b) was obtained in 87% yield: bp 97–100° (0.75 mm); $n^{20}D$ 1.5262; nmr (CS_2), δ 1.36 (s, CH_3CS), 1.63 (s, CH_3CCl), 3.21 (d, J = 2.5 Hz, CH_2S), 3.55 (d, J = 3 Hz, CH_2Cl).

Anal. Calcd for $C_8H_{16}Cl_2S_2$: C, 38.87; H, 6.52; Cl, 28.69; S, 25.94. Found: C, 39.29; H, 6.57; Cl, 28.62; S, 26.06. From the nmr spectrum of this material it was determined that 14a and b were present in the ratio 40:60, respectively.

Chloropropylene Sulfide and Chlorine.—After removal of the solvent from the reaction mixture a solid melting from 56 to 62° was obtained in 99% yield. The nmr spectrum of this material had a distorted doublet at δ 3.58 (J = 5.5 Hz), a multiplet centered at 3.06, and a very small multiplet at 4.07. From the areas of the two larger sets of peaks, it was concluded that the doublet represented the protons of the chloromethyl groups of 18a and b, while the multiplet at 3.06 represented the methinyl proton of 18a and the remaining methylene protons of 18b, the two isomers being present in the approximate ratio 85:15, respectively. The small multiplet at 4.07 was assigned to the methinyl proton of 18b. Recrystallization of this material from CS_2, then hexane, raised its melting point to 65.5–67.5°: nmr (CS_2), δ 3.02 (m, 1, CHS), 3.55 (d, 4, J = 5.5 Hz, CH_2Cl).

Anal. Calcd for $C_6H_{10}Cl_2S_2$: C, 25.01; H, 3.50; Cl, 49.21; S, 22.25. Found: C, 25.07; H, 3.44; Cl, 49.44; S, 22.45.

The mother liquor from the recrystallization of 18a was chromatographed on a silica gel column. Elution with 20% benzene in hexane yielded an oil which proved to be a mixture of 18a and b enriched in the latter. From the nmr in CS_2 [δ 2.98 (m), 3.55 (d, J = 5.5 Hz), 4.04 (m)], it was calculated that 18a and b were present in the ratio 42:58, respectively.

Propylene Sulfide and Chlorine Water.—The procedure of Stewart and Cordts[5] for the addition of propylene sulfide to chlorine water was followed and gave a mixture of 1-chloro-2-propanesulfonyl chloride (5a) and 2-chloro-1-propanesulfonyl chloride (5b) in 54% yield: bp 57–60° (1 mm); $n^{20}D$ 1.4872 (lit.[5] bp 55–56° (1 mm); $n^{20}D$ 1.4859); nmr (C_6H_6), δ 1.36 (d, J = 6.5 Hz, CH_3CSO_2Cl), 1.38 (d, J = 6.5 Hz, CH_3CCl), 3.59 (m, CH_2, $CHSO_2Cl$), 4.22 (m, CHCl).

From the results of the oxidative chlorination of a 10:90 mixture of chlorothiols 3a and b, the component with longer retention time was assigned structure 5a while the other component was assigned structure 5b.

Addition of 2-Chloropropane-1-thiol (3b) to Chlorine Water.—A mixture of 3b containing about 10% of the isomer 3a which was obtained from the reaction of propylene sulfide and hydrochloric acid was added to chlorine water as described by Stewart and Cordts.[5] There was obtained a 66% yield of pale yellow oil: bp 55–60° (1 mm); $n^{20}D$ 1.4940; nmr (C_6H_6), δ 1.38 (d, J = 6.5 Hz, CH_3CCl), 3.59 (m, CH_2SO_2Cl), 4.23 (m, CHCl). Gas chromatography of this material on column C at 125° showed two components with retention times of 8.5 and 9.1 min in the ratio of 87:13, respectively. The component with shorter retention time was assigned the structure 5b, while the other was assigned the structure 5a.

Reaction of Acetic Anhydride with Propylene Sulfide.—The pyridine-catalyzed reaction of acetic anhydride with propylene sulfide was carried out as reported by Davies and Savige.[4] The product which was obtained in 66% yield proved to be a mixture of 1-acetoxy-2-propanethiol acetate (9a) and 2-acetoxy-1-propanethiol acetate (9b): bp 54–56° (1 mm); $n^{20}D$ 1.4651 (lit.[4] bp 103–105° (11 mm); $n^{15}D$ 1.4702); nmr (CS_2), δ 1.08 (d, J = 6 Hz, CH_3COAc), 1.15 (d, J = 6 Hz, CH_3C SAc), 1.77 (s, CHC(=O)O), 2.04 (s, CH_3C(=O)S), 2.71 (m, CH_2SAc), 3.30 (m, CHSAc), 3.72 (m, CH_2OAc), 4.38 (m, CHOAc). Since the doublet at 1.15 was much larger than the doublet at 1.08, it was concluded that 9a was the major isomer. Analysis by glpc on column C at 100° showed the presence of two components in the ratio 84:16.

Hydrolysis of the ester mixture in refluxing 1% hydrochloric acid in methanol for 1 hr gave in 75% yield, a mixture of 2-mercapto-1-propanol (10a) and 1-mercapto-2-propanol (10b): bp 58–59.5° (10 mm); $n^{20}D$ 1.4853 (lit.[4] bp 60–62° (12 mm); $n^{17}D$ 1.4818); nmr (CS_2), δ 1.08 (d, J = 6 Hz, CH_3COH), 1.15 (d, J = 6 Hz, CH_3CSH), 1.38 (t, J = 3.5 Hz, CH_2SH), 1.43 (d, J = 6 Hz, CH—SH), 2.15–3.45 (complex envelope, CH_2 and CH), 3.57 (s, OH). Since the doublet at 1.15 was much larger than the one at 1.08 it was concluded that 10a was the major isomer. Gas chromatographic analysis of this material on column A at 125° showed the presence of two components in the ratio 85:15.

Addition of Sodium Ethanethiolate to Propylene Sulfide.—Sodium (0.1 g, 0.004 g-atom) was dissolved in a solution of 20 g (0.32 mol) of ethanethiol in 50 ml of dry tetrahydrofuran (THF), and then 7.5 g (0.1 mol) of propylene sulfide was added dropwise. The reaction mixture was then heated to reflux for 16 hr during which time a white precipitate formed. Some of the excess thiol and THF were removed by distillation. The addition of 10 ml of 3 N hydrochloric acid to the residue caused the disappearance of the precipitate, and after separation of the organic layer, the aqueous layer was extracted twice with 20-ml portions of ether. The ether extracts were combined with the organic layer, dried ($CaCl_2$), and distilled under reduced pressure, to yield 4.4 g (32%) of 4-thiahexane-2-thiol (13a): bp 60° (4.5 mm); $n^{20}D$ 1.5105. Gas chromatographic analysis of the liquid was carried out on column A at 125° and showed it to be a single compound with retention time of 10.5 min contaminated by trace amounts of low boiling impurities. The nmr spectrum indicated that the compound was a secondary thiol with the thiol proton appearing as a doublet at δ 1.90 (J = 5 Hz).

Anal. Calcd for $C_5H_{12}S_2$: C, 44.05; H, 8.87; S, 47.06. Found: C, 44.08; H, 8.65; S, 46.94.

Preparation of 2-Chloro-4-thiahexane.—1-Chloropropane-2-ol (bp 48–51° (25 mm), $n^{20}D$ 1.4381) was prepared by the lithium aluminum hydride reduction of 1-chloropropan-2-one.[3] 1-Chloropropan-2-ol (47 g, 0.5 mol) was added dropwise with stirring to a solution of 40 g (0.62 mol) of ethanethiol in 500 ml of ethanol containing 0.5 mol of sodium ethoxide. A white precipitate formed during the addition and the temperature of the mixture rose to 40°. Two hours after the addition was completed about 2 l. of water were added and the mixture was extracted with 600 ml of ether. The ether layer was dried over $CaCl_2$ and after removal of the ether, the residue was distilled under reduced pressure to yield 23 g (38%) of 4-thiahexan-2-ol (11): bp 70–74° (18 mm); $n^{20}D$ 1.4771.

Thionyl chloride (25 g, 0.21 mol) was added dropwise to a solution of 1 ml of pyridine in 22 g (0.18 mol) of the 4-thiahexan-2-ol, and the mixture was heated to reflux for 1 hr. The reaction mixture was then treated with 200 ml of dilute hydro-

(17) P. Noble, Jr., and D. S. Tarbell, *Org. Syn.*, **32**, 101 (1952).

chloric acid and extracted three times with methylene chloride. The extracts were dried over $CaCl_2$ and concentrated and the residue was distilled under reduced pressure to yield 17.2 g (68%) of liquid: bp 55–57° (14 mm); $n^{20}D$ 1.4809; nmr (CS_2), δ 1.25 (t, J = 7.5 Hz, CH_3CH_2), 1.31 (d, J = 7.5 Hz, CH_3CS), 1.57 (d, J = 6 Hz, CH_3CCl). The mixture was calculated to contain 86% 2-chloro-4-thiahexane (12a) and 14% 1-ehloro-2-ethylthiopropane (12b).

Reaction of the Mixture of 12a and 12b with Thiourea.—A solution of 9.0 g (0.065 mol) of **12a** and **b** (86:14) obtained above with 5.5 g (0.072 mol) of thiourea in 100 ml of ethanol was heated to reflux for 16 hr and concentrated under reduced pressure. The solid residue was dissolved in water and was treated with 3.2 g (0.08 mol) of sodium hydroxide in 25 ml of water. An oil which separated was removed and the aqueous layer was extracted with ether. After combining the oil and the ether extract, drying ($CaCl_2$), and concentrating, the residue was distilled under reduced pressure to yield 5.1 g (58%) of liquid: bp 60–62° (2.5 mm); $n^{20}D$ 1.5127. Gas chromatography of this sample on column A at 125° showed, in addition to several minor impurities, a large peak at 11.2 min with a shoulder at 10.7 min. The shoulder was shown to correspond to the secondary thiol **13a**. The nmr spectrum (CS_2) confirmed the presence of the secondary thiol **13a** by the presence of a doublet at δ 1.90 (J = 5 Hz) due to the secondary thiol proton. A triplet at δ 1.62 (J = 8.5 Hz) was assigned to the primary thiol proton of **13b**. Integration of these two sets of peaks indicated that **13a** and **b** were present in the ratio 16:84. The ir spectra of **13a**, obtained from the base-catalyzed addition of ethanethiol to propylene sulfide, and of the mixture of **13a** and **b** obtained above, were very similar showing only some minor differences.

Lithium Aluminum Hydride Reduction of Propylene Sulfide.—Propylene sulfide (10 g, 0.135 mol) in an equal volume of dry ether was added with stirring to 5.0 g (0.13 mol) of lithium aluminum hydride in 40 ml of dry ether which was being cooled in an ice–water bath. When the addition was completed the mixture was heated to reflux for 1 hr. The mixture was then cooled and the excess hydride was destroyed by the careful addition of 220 ml of 3 N hydrochloric acid. After separation and drying over magnesium sulfate, the ether layer was analyzed by glpc (column A at 60°). The major monomeric product (99.5%) had a retention time identical with that of authentic 2-propanethiol while a trace component (0.5%) had a retention time identical with that of 1-propanethiol.

Registry No.—**1a**, 1561-70-2; **1b**, 16621-19-5; **2a**, 16621-20-8; **2b**, 16621-21-9; **3a**, 16621-22-0; **3b**, 814-64-2; **4a**, 16621-24-2; **4b**, 16621-25-3; **5a**, 16621-26-4; **5b**, 2386-59-6; **6a**, 16622-60-9; **6b**, 16621-28-6; **7a**, 16621-29-7; **7b**, 16621-30-0; **8a**, 16621-31-1; **8b**, 16621-32-2; **9a**, 16621-33-3; **9b**, 16621-34-4; **10a**, 3001-64-7; **10b**, 1068-47-9; **11**, 16621-37-7; **12a**, 692-30-8; **12b**, 16621-39-9; **13a**, 16621-40-2; **13b**, 16621-41-3; **14a**, 16621-42-4; **14b**, 16621-43-5; **15a**, 16621-44-6; **15b**, 16621-45-7; **16a**, 16621-46-8; **16b**, 16621-47-9; **17**, 16621-48-0; **18a**, 1561-69-9; **18b**, 16621-50-4; **19a**, 16621-51-5; **19b**, 7763-79-3; **20a**, 16621-53-7; **20b**, 16621-54-8.

Acknowledgment.—The author is grateful for the technical assistance of Messrs. K. C. Edwards, Z. Szentgyorgyi, and G. Takaki.

Acid-Catalyzed Brominations, Deuterations, Rearrangements, and Debrominations of Thiophenes under Mild Conditions

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Received February 28, 1968

Bromination and deuteration of some substituted thiophenes have been accomplished under remarkably mild conditions. Upon treatment with N-bromosuccinimide in acetic acid–chloroform solution at room or slightly elevated temperatures, 3-methyl, 3-phenyl, 3-phenylthio, and 3-bromothiophenes are rapidly brominated in the 2 position in nearly quantitative yields. Bromination of 2-methyl, 2-phenyl, 2-phenylthio, and 2-bromothiophenes under the same conditions yields the 5-bromo derivatives. In refluxing deuterioacetic acid 3-alkyl-, 3-phenyl-, and 3-phenylthio-substituted thiophenes undergo deuterium–hydrogen exchange at the 2 position while the corresponding 2-substituted derivatives are exchanged at the 5 position. In solutions of hydrogen bromide in acetic acid some 2-bromothiophenes undergo rearrangements. 2-Bromo-3-phenylthiophene, for example, forms 2-bromo-4-phenylthiophene, 3-phenylthiophene, and 2,5-dibromo-3-phenylthiophene. Preliminary investigations of the mechanism of this reaction have been made. Substitution of 3-phenylthiophene at the 2 position is the kinetically controlled reaction under all conditions investigated. When the bromine acceptor phenol is added to the hydrogen bromide–acetic acid mixture, bromothiophenes which are subject to rearrangement can be debrominated in good to high yields.

In the course of studies of the mechanisms of the photochemically induced rearrangements of thiophenes[1] we have needed a number of deuterium-labeled starting materials.[2,3] Our normal technique of introducing deuterium at a specific position in the thiophene ring involves conversion of a bromo into a deuterio substituent. The necessity of having isomer-free bromothiophene precursors led us to investigate conditions necessary to obtain selective, high-yield brominations. The possibilities of direct deuterium-hydrogen exchange were also explored. We find that with certain thiophene derivatives both bromination and direct hydrogen–deuterium exchanges occur under remarkably mild conditions to give selectively substituted products of kinetic control.[4] We have furthermore observed that some bromothiophenes readily undergo rearrangement in the presence of strong acid catalysts.

Bromination.—When treated with N-bromosuccinimide (NBS) in a 50:50 (v/v) mixture of chloroform and glacial acetic acid, 3-alkyl, 3-phenyl-,[5] and 3-phenylthiothiophenes are brominated nearly quantitatively at the 2 position (eq 1). Reaction is complete

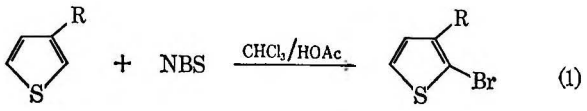
(1) See, for example, H. Wynberg, R. M. Kellogg, H. van Driel, and G. E. Beekhuis, *J. Amer. Chem. Soc.*, **89**, 3501 (1967).

(2) R. M. Kellogg and H. Wynberg, *ibid.*, **89**, 3495 (1967).

(3) R. M. Kellogg, J. J. C. Vermeer, and H. Wynberg, unpublished work.

(4) See, for an excellent review of bromination as well as other aspects of thiophene chemistry, S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 1 (1963).

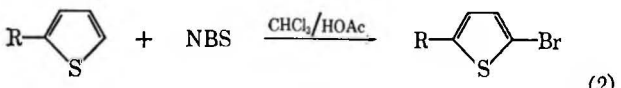
(5) Selective bromination of 3-phenylthiophene with NBS in carbon tetrachloride has recently been reported: S. Gronowitz, N. Gjös, R. M. Kellogg, and H. Wynberg, *J. Org. Chem.*, **32**, 463 (1967).



$$R = CH_3, C_6H_5,^5 C_6H_5S, Br \quad (1)$$

within a matter of minutes at ambient or slightly elevated temperatures. The reaction of 3-bromothiophene was slower and was about 80% complete after 30 min of refluxing.[6]

Under similar conditions some 2-substituted thiophenes were brominated in the 5 position (eq 2).[7]



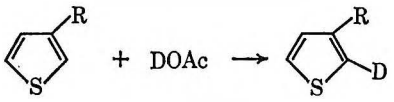
$$R = C_6H_5,^7 CH_3, C_6H_5S, Br, H \quad (2)$$

Thiophene was converted primarily into 2-bromothiophene but the overbromination product, 2,5-dibromothiophene, was formed as well.

Similar results are obtained using carbon tetrachloride–acetic acid mixtures.[8] Reactions in carbon tetrachloride or chloroform alone give the same products but proceed many times slower than in mixtures with acetic acid. The strongly deactivated acetylthiophenes could not be brominated with NBS under the reaction conditions used by us.

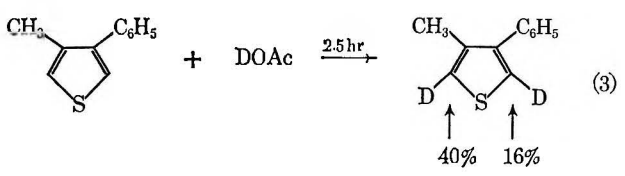
Deuterium–Hydrogen Exchange.—In refluxing deuterioacetic–deuterium oxide solutions various 3-substituted thiophenes undergo exchange exclusively at the 2 position. Results with some representative thiophenes are shown in Table I.

TABLE I
DEUTERIUM-HYDROGEN EXCHANGE WITH 3-SUBSTITUTED THIOPHENES



R	Time, hr	% exchange
CH_3	5	100
t-Bu	24	67
C_6D_5[3]	5	34
C_6H_5S	5	100

Exchange in 3-phenyl-4-methylthiophene occurred 2.5 times faster α to methyl as compared to substitution α to phenyl (eq 3).



(3)

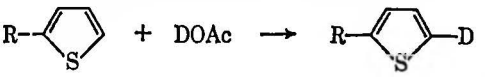
(6) Compare, however, with a recommended procedure for the preparation of 2,3-dibromothiophene which involves a 9.5 hr reaction between bromine and 3-bromothiophene: S. Lawesson, *Ark. Kemi*, **11**, 373 (1957).

(7) Preparation of 2-phenyl-5-bromothiophene by bromination of 2-phenylthiophene with NBS in carbon tetrachloride containing benzoyl peroxide has been reported: A. Kosak, R. J. F. Palchak, W. A. Steele, and C. M. Selwitz, *J. Amer. Chem. Soc.*, **76**, 4450 (1954).

(8) In one case (see Experimental Section) dibromodimethylhydantoin was used in place of NBS with excellent results. Both bromine atoms of the hydantoin were reactive. We thank Philips Duphar N.V. (The Netherlands) for a gift of dibromodimethylhydantoin.

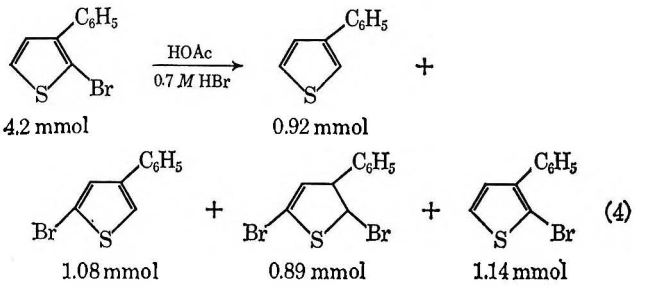
Exchange at the 5 position was observed with various 2-substituted thiophenes. The results of these experiments are summarized in Table II.

TABLE II
DEUTERIUM–HYDROGEN EXCHANGE WITH 2-SUBSTITUTED THIOPHENES



R	Time, hr	% exchange
CH_3	5	42
t-Bu	5	25
C_6H_5	5	40
C_6H_5S	5	33

Acid-Catalyzed Rearrangements.—Recently Gronowitz, Gjös, and two of the present authors[5] in a joint publication reported that 3-phenylthiophene gave exclusively 2-bromo-3-phenylthiophene when treated with NBS in carbon tetrachloride and a mixture consisting mainly of 2-bromo-4-phenylthiophene when treated with bromine in refluxing acetic acid. Although correct as reported, the reaction has since been found to be considerably more complex than was originally assumed. In refluxing acetic acid containing hydrogen

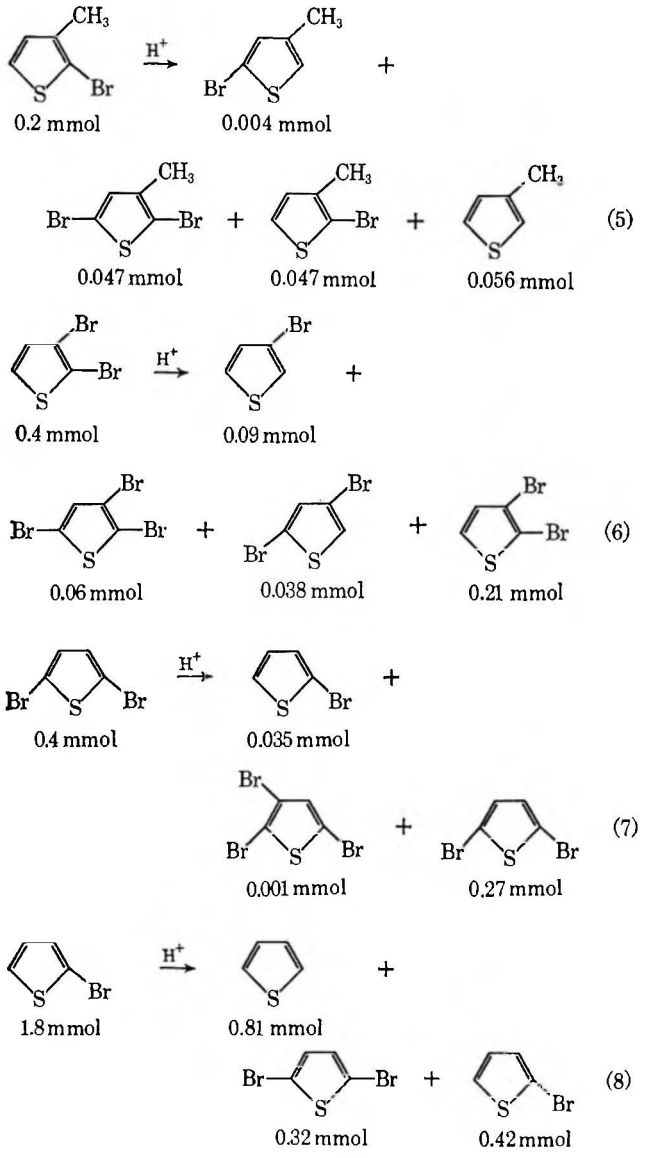


(4)

bromide, 2-bromo-3-phenylthiophene is transformed into a mixture of 2-bromo-4-phenylthiophene, 2,5-dibromo-3-phenylthiophene, and 3-phenylthiophene plus starting material. After 20 min reflux in acetic acid (0.7 *M* in hydrogen bromide) the product mixture shown in eq 4 was obtained.[9] Appreciable rearrangement could be detected after only 5 min reaction. In refluxing acetic acid alone no rearrangement of 2-bromo-3-phenylthiophene was detected after *ca.* 1 hr. Perchloric acid in acetic acid induced rearrangement, but considerably more decomposition took place than when hydrogen bromide was used.

The reactions of a number of other brominated thiophenes in solutions of acetic acid containing hydrogen bromide were examined. Results of these experiments are shown in eq 5–8. Only a slight amount of rearrangement of 2,4-dibromothiophene was noted while 3,4-dibromothiophene and 3-bromothiophene seemed to be completely stable under the conditions used (see Experimental Section).

(9) Some of these results were presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967. This rearrangement was simultaneously and independently discovered by Gjös and Gronowitz who have communicated their results in brief form: N. Gjös and S. Gronowitz, *Acta Chem. Scand.*, in press. We thank Professor Gronowitz for making their results available to us prior to publication. The previous rationalizations of the dependence of product on solvent did not take the possibility of a rearrangement into account.



Acid-Catalyzed Debrominations.—The products obtained from acid-catalyzed rearrangement of bromothiophenes suggested an intermolecular transfer of the bromo substituent. We reasoned that if this were the case a reaction in the presence of a good bromine (or bromonium ion) acceptor should induce debromination of bromothiophenes. Using an equimolar amount of phenol (based on bromothiophene) as acceptor, 2-bromo-3-phenylthiophene was debrominated in refluxing acetic acid containing hydrogen bromide to give an 84% yield (isolated) of 3-phenylthiophene (eq 9). Neither 2-bromo-4-phenylthiophene nor 2,5-dibromo-3-phenylthiophene were formed in detectable amounts. Debromination was noted even at room temperature. The results of debromination of some bromothiophenes are shown in Table III.

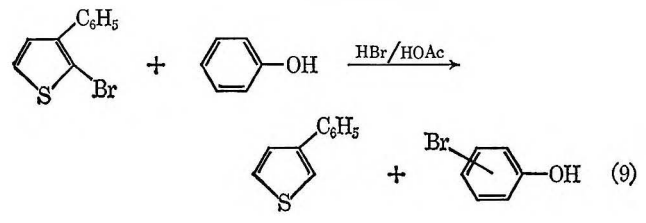


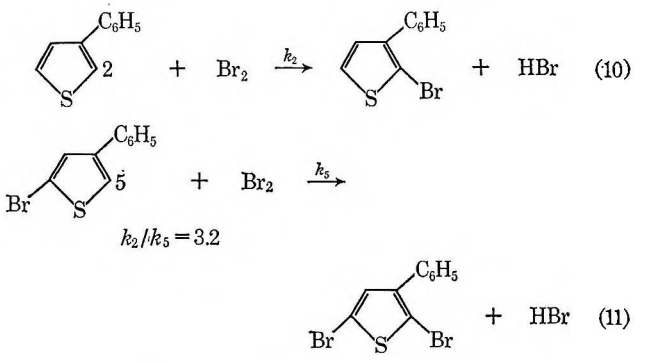
TABLE III
REACTIONS OF BROMOTHIOPHENES WITH PHENOL IN ACIDIC MEDIA[a]

Reactant	Product (yield)
2,3-Dibromothiophene	3-Bromothiophene (90%)
2,4-Dibromothiophene	3-Bromothiophene (20%) + starting material (30%)
2-Bromothiophene	Thiophene (72%)
2,5-Dibromothiophene	Thiophene (51%) + 2-bromothiophene (13%)
2,3,5-Tribromothiophene	2,3-Dibromothiophene (25%) + 3-bromothiophene (trace) + starting material (18%)
2-Bromo-3-methylthiophene	3-Methylthiophene (35%)

[a] Conditions were 0.2 *M* solutions of bromothiophene and phenol in acetic acid 1 *M* in hydrogen bromide. Reaction times were 5 hr.

Mechanism of Rearrangement of Bromothiophenes.—A preliminary study of the mechanism of rearrangements of bromothiophenes was deemed worthwhile. The rearrangements of the various bromo derivative of 3-phenylthiophene were chosen for detailed study. A solution of 3-phenylthiophene in chloroform–acetic acid held at 0° was treated with 0.1 equiv of bromine and the reaction was quenched with thiosulfate solution after 1 min. Reaction was complete within this time as shown by the disappearance of the bromine color. The ratio of 2-bromo-3-phenylthiophene to 2-bromo-4-phenylthiophene in the reaction mixture was *ca.* 660 to 1. A similar reaction carried out in refluxing acetic acid (*ca.* 120°) gave, after 1 min, 2-bromo-3-phenylthiophene and 2-bromo-4-phenylthiophenes in a ratio of *ca.* 190 to 1 (a small amount of 2,5-dibromo-3-phenylthiophene was also detected). These experiments show the 2 position of 3-phenylthiophene to be, dependent on temperature, 200–700 times more reactive than the 5 position toward bromination and 2-bromo-3-phenylthiophene to be, therefore, the primary *kinetically controlled* bromination product.

The relative reactivities of the 2 position in 3-phenylthiophene compared to the 5 position in 2-bromo-4-phenylthiophene were determined (eq 10 and 11).



Equimolar amounts of 3-phenylthiophene and 2-bromo-4-phenylthiophene were allowed to react at 0° for 1 min with 0.1 equiv of bromine (based on total thiophene); 2-bromo-3-phenylthiophene and 2,5-dibromo-3-phenylthiophene were formed in 3.2:1 molar ratio. This product ratio becomes the rate constant ratio under the assumption that the thiophene concentrations are large and unchanging compared to the bromine concentration.

The subsequent fate of 2-bromo-3-phenylthiophene under acid-catalyzed conditions was investigated

under the standard conditions of 70 ± 1° and 1 *M* hydrogen bromide in acetic acid. The change of composition with time of a reaction mixture originally 0.099 *M* in 2-bromo-3-phenylthiophene is shown in Figure 1. The disappearance of 2-bromo-3-phenylthiophene between 20 and 200 min follows a first-order rate plot well with a first-order rate constant for disappearance of 1.0×10^{-4} sec^{-1}. Deviation from first-order kinetics is serious after this time. A run 0.35 *M* in 2-bromo-3-phenylthiophene gave a first-order rate constant of 0.86×10^{-4} sec^{-1} over the first 200 min of reaction. 3-Phenylthiophene, the most important reaction product over the first stages of reaction (see Figure 1), failed to depress the initial rate of disappearance of starting material as shown by a run 0.093 *M* in 2-bromo-3-phenylthiophene and 0.018 *M* in 3-phenylthiophene; the first-order rate constant was 0.90×10^{-4} sec^{-1} for disappearance of 2-bromo-3-phenylthiophene over the first stages of reaction.

The reactions of 2,5-dibromo-3-phenylthiophene were investigated to determine whether this material is an intermediate in the rearrangements. Difficulties were experienced in the preparation of 2,5-dibromo-3-phenylthiophene; a sample, *ca.* 15% contaminated with 3-phenylthiophene and the monobromo isomer, was isolated by preparative gas chromatography. The first-order rate constant for disappearance of 2,5-dibromo-3-phenylthiophene in a 0.0084 *M* solution was 3×10^{-5} sec^{-1}. The products were 2-bromo-4-phenylthiophene and 2-bromo-3-phenylthiophene in a ratio of *ca.* 2 to 1. A trace of 3-phenylthiophene was also formed. Material balances accounted for 90–110% of the starting material.

Under the reaction conditions 2-bromo-4-phenylthiophene was not stable; the first-order rate constant for disappearance was 3×10^{-5} sec^{-1} for a 0.0324 *M* solution. The major reaction product was 3-phenylthiophene but in addition small amounts of 2-bromo-3-phenylthiophene as well as 2,5-dibromo-3-phenylthiophene could also be detected. Material balances accounted for roughly 90% of the starting material.

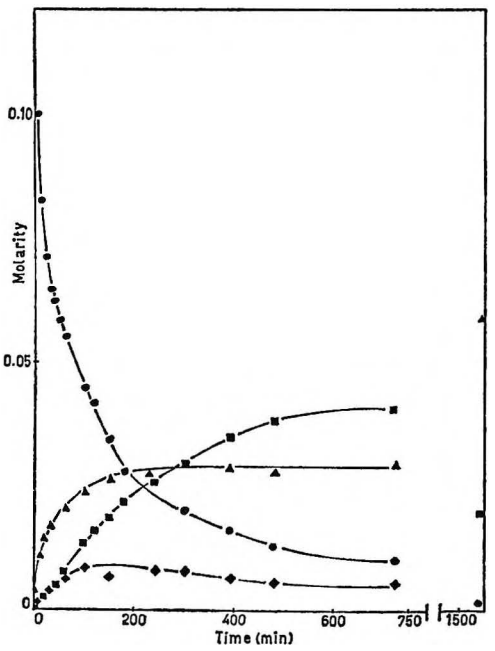


Figure 1.—Change of composition with time of 0.1 *M* 2-bromo-3-phenylthiophene in acetic acid 1 *M* in HBr: ●, 2-bromo-3-phenylthiophene; ▲, 3-phenylthiophene; ■, 2-bromo-4-phenylthiophene; ◆, 2,5-dibromo-3-phenylthiophene.

Discussion

Three aspects of this investigation need further comment: (a) the highly specific bromination and deuterations of various thiophenes under very mild conditions,[10] (b) the scope and mechanism of the facile acid-catalyzed rearrangements of some bromothiophenes under more rigorous conditions, and (c) the acid-catalyzed debrominations not requiring a strong reducing agent.

Brominations.—The exclusive formation of ring substitution products, the apparent catalysis by acetic acid,[11] the lack of substituent bromination with methylthiophenes, and the complete agreement of the position of substitution with that found in electrophilic deuterium–hydrogen exchange, all point to an electrophilic bromination by NBS under our conditions. Some confusion exists, however, regarding the reactions of NBS with thiophenes since allylic brominations *via* a free-radical mechanism may also be accomplished with this reagent. Bromination of 2-methyl- or 3-methylthiophenes with NBS in carbon tetrachloride solution, for example, gives side-chain bromination in addition to substantial quantities of ring-brominated products.[12] Allylic substitution is clearly a free-radical reaction but the ring-substitution products could, in principle, arise either from homolytic aromatic substitution or, alternatively, from the concurrent operation of an electrophilic bromination mechanism. Our results show ring substitution to be the exclusive reaction under conditions conducive to electrophilic reaction.[13,14] Electrophilic substitution has also been observed in the ring brominations of some other aromatics in reactions with NBS in the polar solvent, propylene carbonate.[15]

Gronowitz[4] has summarized the theoretical, mechanistic, and preparative aspects of most electrophilic substitutions of thiophene in 20 admirable pages. The preparative aspects of electrophilic bromination of thiophene have received more attention than the mechanism

(10) Bromination, deuteration, and lithiation applied to the dithienyls will be reported separately: R. M. Kellogg, A. P. Schaap, and H. Wynberg, unpublished data.

(11) Our experience has been that reactions of 3-phenylthiophene, for example, with NBS in carbon tetrachloride proceed with unreproducible reaction times varying from 10 to 80 hr.[6] The recommended procedure for the bromination of 2-bromothiophene with NBS in carbon tetrachloride involves a reaction time of 30 hr.[6]

(12) See, for typical references (a) K. Dittmer, R. P. Martin, W. Herz, and S. J. Cristol, *J. Amer. Chem. Soc.*, **71**, 1201 (1949); (b) T. W. Campbell and W. W. Kaeding, *ibid.*, **73**, 4018 (1951); (c) E. Campaigne and B. F. Tullar, *Org. Syn.*, **33**, 96 (1953).

(13) A slight modification of the known[14] mechanism of free-radical allylic or benzylic bromination by NBS provides an attractive rationalization of thiophene brominations. The free-radical reactions require free bromine in low concentrations as the active brominating agent; in our reactions the combination of polar medium and reactive substitution could promote electrophilic substitution by bromine (or bromonium ion) but the details of bromine formation could be analogous to the free-radical mechanism. We have no direct evidence for free bromine as an intermediate and only offer this as a tentative mechanistic suggestion.

(14) (a) C. Walling, A. L. Rieger, and D. D. Tanner, *J. Amer. Chem. Soc.*, **85**, 3129 (1963); (b) G. A. Russell and K. M. Desmond, *ibid.*, **85**, 3139 (1963); (c) R. F. Pearson and J. C. Martin, *ibid.*, **85**, 3142 (1963).

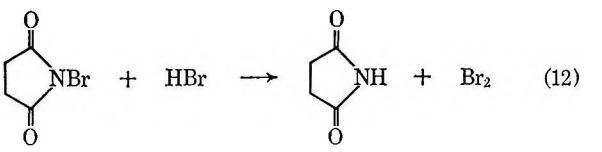
(15) S. D. Ross, M. Finkelstein, and R. C. Petersen, *ibid.*, **80**, 4327 (1958).

up to the present.[16] Our data with 3-substituted thiophenes indicate a selective activation of the 2 position to substitution. All the groups investigated (alkyl, phenyl, phenylthio, bromo) are capable of stabilizing the adjacent positive center that would be formed upon electrophilic substitution at the 2 position. This may, in part, explain the position of substitution.[17]

No selective activation is obvious with 2-substituted derivatives since, in any case, substitution should occur at the 5 position.[18] The mildness of the conditions necessary to obtain substitution with 2-substituted as well as 3-substituted thiophenes are noteworthy and have important implications particularly in synthetic applications.

Deuteration.—Thiophene and some other unsubstituted heterocycles are reported to be unaffected by refluxing deuterioacetic acid.[19] We have confirmed this observation for thiophene but have found that certain substituted derivatives are readily subject to exchange.[20,21] The position of substitution is analogous to that observed in kinetically controlled brominations. However, only thiophenes with activating substituents undergo exchange; bromothiophenes are unaffected by deuterioacetic acid while brominated by NBS in acidic media. The possibilities of synthesis of specifically labeled deuteriothiophenes *via* exchange are not to be overlooked.[22]

Acid-Catalyzed Rearrangements and Debrominations of Bromothiophenes.—Thiophenes brominated in the α positions are particularly sensitive to strong acid. The conditions under which rearrangements occur closely approximate those obtaining in brominations with bromine in acetic acid. Acetic acid alone is not sufficiently acidic but the hydrogen bromide generated during reaction can catalyze rearrangement of bromothiophenes. This problem is avoided in brominations using NBS since the hydrogen bromide generated during reaction is immediately consumed, most probably by reaction with NBS (eq 12).[13,23] The implicit dangers of all thiophene bromination methods which liberate hydrogen bromide should be apparent.



(12)

The acid-catalyzed rearrangements almost certainly proceed by *inter-* rather than *intra*molecular processes.[24-31] This is best shown by the debrominations in the presence of phenol in which bromo substituents are removed from acid-sensitive α positions without detectable formation of rearranged thiophenes whereas under identical conditions in the absence of phenol, rearrangement is observed. These reductive debrominations using phenol may also provide an alternative synthetic method when groups sensitive to other reducing agents are present in the molecule.[32]

For the case of 3-phenylthiophene, bromination in the 2 position is obviously the kinetically controlled reaction. The subsequent rearrangement of 2-bromo-3-phenylthiophene is best explained by initial protonation followed by loss of the bromo substituent *via* a disproportionation to give 3-phenylthiophene and 2,5-dibromo-3-phenylthiophene (eq 13). The *apparent* first-order kinetics for disappearance of starting material are not in conflict with this mechanism; the complex rate expression obtained for this process predicts *apparent* first-order kinetics if the rate of disproportionation is rapid compared to deprotonation.[33] In the first stages of the reaction debromination of 2,5-dibromo-3-phenylthiophene likely accounts for most of the rear-

(16) Thiophene is 10^7 and 10^9 times more reactive than benzene toward chlorination and bromination, respectively: G. I. Marino, *Tetrahedron*, **21**, 843 (1965). A substitution mechanism analogous to that involved in the bromination of benzene has been suggested: G. Marino, *Atti Accad. Nazl. Lincei, Rond., Classe Sci. Fis. Mat. Nat.*, **38**, 700 (1965). Studies of the relative reactivities of thiophene and furan toward electrophilic acylation have recently been published: P. Linda and G. Marino, *Tetrahedron*, **23**, 1739 (1967). Relative rates of deuterium exchange in thiophenes and other heterocycles have been measured: K. Schwetlick, K. Unverferth, and R. Mayer, *Z. Chem.*, **7**, 58 (1967).

(17) Note that 3-acetylthiophene is not substituted under the conditions used and that 3-bromothiophene appears to react more sluggishly than, for example, 3-methylthiophene (see Experimental Section).

(18) S. Gronowitz, *Ark. Kemi*, **13**, 295 (1958); S. Gronowitz and R. A. Hoffmann, *ibid.*, **16**, 539 (1960).

(19) B. Bak, *J. Org. Chem.*, **21**, 797 (1956).

(20) Several studies have been made of hydrogen–deuterium or hydrogen–tritium exchange in the presence of strong acid in thiophenes and these show the 2 position to be much more reactive than the 3 position: K. Halvarson and L. Melander, *Ark. Kemi*, **8**, 29 (1955); B. Östman and J. Olsson, *ibid.*, **15**, 275 (1960). Stable cations from thiophene protonated exclusively in the 2 position have been observed: H. Hogeveen, *Rec. Trav. Chim. Pays-Bas*, **85**, 1072 (1966). For hydrogen–deuterium exchange over Adams catalyst, see J. L. Garnett and W. A. Sollich, *Aust. J. Chem.*, **15**, 56 (1962). No exchange studies as a function of substituent appear to have been published.

(21) Bak[19] describes the reduction of bromothiophenes with Zn and deuterioacetic acid to prepare specifically deuterated thiophenes; Gronowitz[18] has also made extensive use of this technique to prepare specifically deuterated thiophenes. Neither author reports direct exchange with the thiophene ring and we have also never observed extraneous deuterium-hydrogen exchange in syntheses *via* these reductions[3] but did accidentally discover that "blind" exchange occurred at the position at which deuterium had been introduced by reduction of the bromo substituent. We have recently observed that deuterated thiophenes are subject to exchange over neutral aluminium oxide.[3]

(22) This method has been applied on a preparative scale for syntheses of 2-deuterio-3-*t*-butylthiophene and 2,4-di-*t*-butyl-5-deuteriothiophene: R. M. Kellogg, J. K. Dik, and H. Wynberg, unpublished results.

(23) The ionic reaction of hydrogen bromide with NBS is reportedly "instantaneous" even at −78° in neutral solvent.[14c]

(24) Precedence exists in the literature for acid-catalyzed substituent elimination and/or rearrangement of bromothiophenes. The $SnCl_4$ catalyzed acetylation of 5-bromo-2-ethylthiophene is known to give 2-ethyl-5-acetylthiophene.[25] Chloromethylation of 2,5-dibromothiophene gives, in addition to 2,5-dibromo-3-chloromethylthiophene, also 2-bromo-5-chloromethylthiophene.[26] The phosphorus oxychloride catalyzed formylation of bromothiophenes leads to exchange of bromine for chlorine at either the α[27] or β positions.[28] All of these reactions involving the loss of a bromo substituent under acid-catalyzed conditions could be related to the rearrangements of bromothiophenes reported here. A not unprecedented rationalization of the formation of 4-bromo-2-thiophene carboxaldehyde from thiophene carboxaldehyde and bromine in the presence of excess aluminium chloride[28] in place of 2-bromo-5-thiophene carboxaldehyde formed in direct bromination[30] would involve rapid acid-catalyzed debromination of this latter product and slow accumulation of the more stable 4-bromo-2-thiophene carboxaldehyde. Disproportionation reactions also occur with bromobenzenes but under much more drastic conditions.[31]

(25) Ya. L. Gol'dfarb and P. A. Konstantinov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 113 (1957).

(26) S. Gronowitz, *Ark. Kemi*, **8**, 441 (1955).

(27) A. W. Neaton and R. J. Michaels, *J. Amer. Chem. Soc.*, **72**, 1422 (1960).

(28) S. Gronowitz, P. Moses, A.-B. Hörnfeldt, and R. Håkansson, *Ark. Kemi*, **17**, 165 (1961), quoted in ref 4.

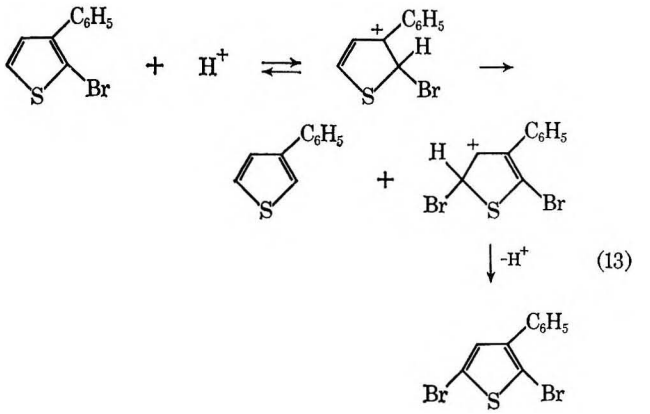
(29) Ya. L. Gol'dfarb, Yu. B. Vol'kenshtein, and B. V. Lopatin, *Zh. Obshch. Khim.*, **34**, 969 (1964); *Chem. Abstr.*, **61**, 629*d* (1964).

(30) S. Gronowitz, *Ark. Kemi*, **8**, 87 (1955).

(31) See, for example, G. J. P. Augustijn, E. C. Kooyman, and R. Louw, *Rec. Trav. Chim. Pays-Bas*, **82**, 965 (1963); E. C. Kooyman and R. Louw, *ibid.*, **81**, 365 (1962).

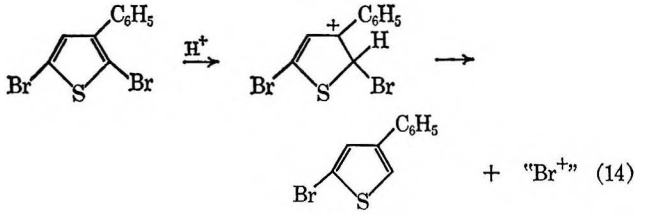
(32) Speculations can be made about the effect of other agents such as zinc which are used in reductive debromination. It could be that the first step is acid-catalyzed loss of "bromonium ion" and the zinc (or other agent) serves only as a trap for the eliminated substituent.

(33) See, for a solution of essentially the same kinetic problem: A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, New York, N. Y., 1961, pp 335–350.



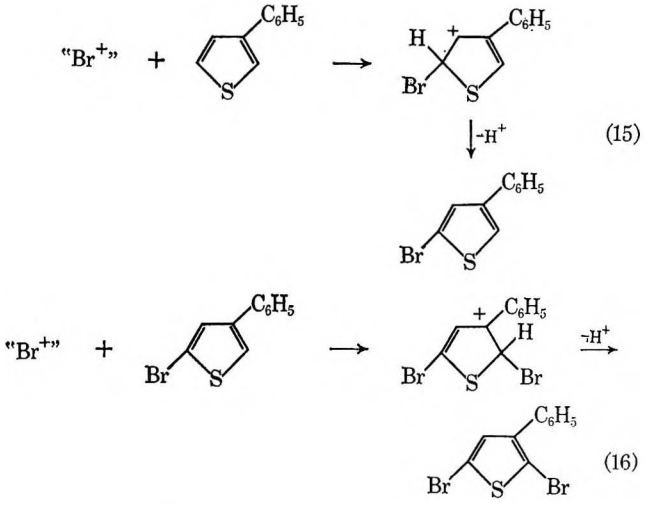
(13)

ranged 2-bromo-4-phenylthiophene (eq 14). Either 3-phenylthiophene or 2-bromo-3-phenylthiophene can be acceptors of the eliminated bromonium ion (represented as "Br^+" in eq 14–16; it is quite likely that



(14)

"Br^+" is not a simple bromonium ion, but the kinetic evidence does not allow positive identification of the bromonium ion carrying species). In later stages of the reaction 2-bromo-4-phenylthiophene probably also accumulates through bromination of 3-phenylthiophene in the 5 position in a slow but certainly real step (eq 15). Another kinetic complication is formation of 2,5-dibromo-3-phenylthiophene by rapid bromination of 2-bromo-4-phenylthiophene (eq 16). Since none



(15)

(16)

of the reaction products are completely stable, after *ca.* 200 min various complicated equilibria must be set up about which the present data justify no speculation.

Experimental Section

Melting points and boiling points are uncorrected. Ultraviolet spectra (uv) were obtained with a Zeiss PMQ II spectrophotometer. Infrared spectra (ir) were taken either on Perkin-Elmer Model 125 or Perkin-Elmer Model 257 infrared spectrophotometers. Nuclear magnetic resonance (nmr) spectra were measured with a Varian A-60 instrument with tetramethylsilane (TMS) as an internal standard. Spectra were taken at 500, 250, and 100 Hz sweep widths and integrations were done two times going from low to high field and two times from high to low field. The average value of the integrations was used. Gas chromatography (glpc) was done with an F & M Model 810 gas chromatograph equipped with hydrogen flame detectors. Preparative glpc separations were carried out on a Wilkens A-700 Autoprep.

Microanalyses were carried out by the analytical section of this department under the direction of Mr. W. Hazenberg.

Compounds cited without reference were either prepared by standard procedures or were available in stock.

3-(Phenylthio)thiophene was prepared from the reaction of 3-bromothiophene and benzene thiol with cuprous oxide in dimethyl formamide containing KOH following the general procedure given in the literature.[34] A 75% yield was obtained of 3-(phenylthio)thiophene: bp 88–94° (0.3 mm); $n^{20}D$ 1.6530; uv spectrum (C_2H_5OH), 247 mμ (ε 10500) and 268 (6400).

Oxidation with hydrogen peroxide–acetic acid gave the sulfone: mp 117.5–119°; uv spectrum (C_2H_5OH), 242 mμ (ε 12700), 266 (sh) (1400), and 274 (sh) (900).

Anal. Calcd for $C_{10}H_8O_2S_2$: C, 53.55; H, 3.59; S, 28.59. Found: C, 53.45; H, 3.61; S, 28.57.

2-Bromo-3-methylthiophene was obtained from the reaction of 3-methylthiophene (4.9 g, 50 mmol) and NBS (9.4 g, 52.7 mmol) in 60 ml of a 50:50 (v/v) solution of chloroform–acetic acid. Reaction occurred spontaneously at room temperature and was over within 2 min. The reaction mixture was diluted with an equal volume of water; the chloroform layer was separated, washed once with KOH solution and once with water, and dried over magnesium sulfate. Distillation gave 7.45 g (84%) of 2-bromo-3-methylthiophene: nmr (CCl_4), δ 7.82 (s, 3, CH_3), 3.30 (d, 1, J = 5.5 Hz, H-4), and 2.93 (d, 1, J = 5.5 Hz, H-5). No other peaks were detected in the nmr spectrum. Glpc under conditions capable of separating the different bromothiophenes (6 ft DEGS, 100°) showed the product to be >99% pure.

2,3-Dibromothiophene[6] was formed from the reaction of 3-bromothiophene (8.15 g, 50 mmol) with NBS (8.9 g, 50 mmol) in 60 ml of 50:50 (v/v) chloroform–acetic acid. The reaction mixture was gently refluxed for *ca.* 30 min. A deep red color formed indicative of free bromine. Work-up as described above gave, after distillation, 10.1 g of material consisting of 20% of starting bromide and 80% of 2,3-dibromothiophene (as determined by nmr spectroscopy). In addition a trace (2–3%) of 2,4-dibromothiophene could be detected by glpc (6 ft DEGS, 160°). This small amount of 2,4-dibromothiophene was also detected in 2,3-dibromothiophene prepared by addition of bromine to 3-bromothiophene.

2-Bromo-3-phenylthiophene[35] was formed in the reaction of 3-phenylthiophene (489 mg, 3.06 mmol) with NBS (543 mg, 3.06 mmol) in 16 ml of a 50:50 (v/v) mixture of chloroform–acetic acid. Reaction occurred upon mixing. The mixture was gently warmed for *ca.* 0.5 hr and worked up as described above to give 690 mg (94%) of 2-bromo-3-phenylthiophene shown to be pure by nmr spectroscopy.[2,3]

3-Phenylthiophene (320 mg, 2.0 mmol) in 12 ml of a 50:50 (v/v) mixture of chloroform–acetic acid when treated with dibromodimethylhydantoin (300 mg, 1.01 mmol) gave, after work-up, 455 mg (95%) of 2-bromo-3-phenylthiophene.

2-Bromo-3-(phenylthio)thiophene was prepared from the reaction of 3-(phenylthio)thiophene (174 mg, 0.91 mol) with NBS (167 mg, 0.94 mmol) in 6 ml of a 50:50 (v/v) solution of carbon tetrachloride–acetic acid. The mixture was warmed mildly for about 5 min. Work-up as described above gave 224 mg (91%) of 2-bromo-3-(phenylthio)thiophene: uv max (96% C_2H_5OH), 246 mμ (ε 13,000) and 274 (sh) (5600); nmr (C_3D_6O), δ 6.90 (d, 1, J = 5.6 Hz, H-4), 7.52 (d, 1, J = 5.6 Hz, H-5), and 7.27 (m, 5, C_6H_5).

Oxidation of the above product with H_2O_2–acetic acid gave 2-bromo-3-thienylphenyl sulfone: mp 71–73°; uv max (96% C_2H_5OH), 223 mμ (ε 13,100), 243 (14,400), and 267 (6600).

Anal. Calcd for $C_{10}H_7BrO_2S_2$: C, 39.61; H, 2.33; Br, 26.35; S, 21.15. Found: C, 39.47; H, 2.34; Br, 26.81; S, 21.01.

2-Bromo-5-phenylthiophene[7] was prepared from the reaction of 2-phenylthiophene (495 mg, 3.09 mmol) with NBS (546 mg, 3.07 mmol) in 6 ml of a 50:50 (v/v) mixture of chloroform–

(34) E. Jones and I. M. Moodie, *Tetrahedron*, **21**, 2413 (1965). We thank Dr. Jones for details of this procedure.

(35) The properties of this compound and the isomeric 2-bromo-4-phenylthiophene have been described.[6]

acetic acid. The solution was briefly warmed. Work-up gave 705 mg (95%) of 2-bromo-5-phenylthiophene: mp 82–84° (lit.[7] 84–85°).

2-Methyl-5-bromothiophene was prepared from the reaction of 2-methylthiophene (9.53 g, 0.097 mol) and NBS (18.9 g, 0.106 mol) in 120 ml of a 50:50 (v/v) mixture of chloroform–acetic acid. The solution was mildly heated. After work-up and flash distillation 17.82 g (103%) of 2-methyl-5-bromothiophene was obtained: $n^{19.8}$D 1.5575 (lit.[12a] n^{20}D 1.5687); nmr (C_6D_6O) δ 2.43 (d, 3, J = 1.2 Hz, CH_3), 6.62 (m, 1, J = 1.2, 3.5 Hz, H-3) and 6.92 (d, 1, J = 3.5 Hz, H-4). No extraneous peaks were observed in the nmr spectrum and glpc (6 ft DEGS, 100°) under conditions capable of separating the isomeric methyl bromothiophenes showed the product to be >99% pure.

2-Bromo-5-(phenylthio)thiophene was prepared from the reaction of 2-(phenylthio)thiophene[36] (161 mg, 0.84 mmol) with NBS (153 mg, 0.86 mmol) in 6 ml of 50:50 (v/v) mixture of CCl_4–acetic acid. Work-up gave 206 mg (90%) of 2-bromo-5-(phenylthio)thiophene: uv max (C_2H_5OH), 245 mμ (ϵ 16,300) and 276 (sh) (3640); nmr (C_6D_6O), δ 2.79 (s, 2, H-3,4), 2.69 (s, 5, C_6H_5).

A portion of this product was oxidized with H_2O_2–acetic acid to the sulfone: mp 116–118.5°; uv max (C_2H_5OH), 223 mμ (ϵ 9200), 252 (8600), and 276 (14,500).

Anal. Calcd for $C_{10}H_7BrO_2S_2$: C, 39.61; H, 2.33; Br, 26.35; S, 21.15. Found: C, 39.55; H, 2.45; Br, 26.27; S, 21.22.

2-Bromo-5-(*t*-butyl)thiophene[37] was prepared from the reaction of 2-(*t*-butyl)thiophene (210 mg, 1.50 mmol) with NBS (267 mg, 1.50 mmol) in 6 ml of a 50:50 (v/v) mixture of carbon tetrachloride–acetic acid. The material was worked up and the 2-bromo-5-(*t*-butyl)thiophene was concentrated in carbon tetrachloride: nmr, δ 1.35 (s, 9, $(CH_3)_3C$), 6.51 (d, 1, J = 3.6 Hz, H-4), and 6.77 (d, 1, J = 3.6 Hz, H-5) [lit.[36] nmr (CCl_4), δ 2.34 (s, 9, $(CH_3)_3C$), 6.50 (d, 1, J = 3.8 Hz, H-4), and 6.75 (d, 1, J = 3.8 Hz, H-3)]. The yield was estimated by nmr spectroscopy to be >95%.

2,5-Dibromothiophene[38] was prepared by allowing thiophene (13.0 g, 0.16 mol) to react with NBS (60.5 g, 0.34 mol) in 200 ml of a 50:50 (v/v) mixture of chloroform–acetic acid. The solution was held at *ca.* 30° and the NBS was added in small portions. After addition, the solution was heated to reflux for 10 min, allowed to cool, and worked up as described above. Distillation gave 32.2 g (86%) of 2,5-dibromothiophene shown to be absolutely pure by nmr spectroscopy and glpc (6 ft DEGS, 100°). An initial distillation fraction of *ca.* 2.5 g was not counted in the yield even though its refractive index was identical with that of the main fraction.

Bromination of thiophene occurred rapidly when a mixture of NBS (17.8 g, 100 mmol) and redistilled thiophene (8.4 g, 100 mmol) was gently refluxed for 0.5 hr with magnetic stirring in 120 ml of a 50:50 (v/v) solution of chloroform–acetic acid. After work-up as described above, the reaction mixture was rapidly distilled to give 10.9 g of product which contained 85% 2-bromothiophene and 15% 2,5-dibromothiophene as determined both from glpc (6 ft DEGS, 100°) and nmr analysis.

Attempted reactions of 2-acetyl and 3-acetylthiophenes under the conditions described above led only to the recovery of unchanged starting materials.

Deuterium exchange with 3-methylthiophene was carried out by refluxing a mixture of 3-methylthiophene (1.5 g, 15.2 mmol) for 5 hr in a mixture of 9 ml acetic anhydride and 11 ml of D_2O. After this time the reaction mixture was cooled, diluted with water, extracted with ether, and neutralized with Na_2CO_3 solution. After drying over magnesium sulfate the residue was distilled to give 1.4 g of exchanged 3-methylthiophene: nmr (C_3D_6O), δ 6.84 (d, 1, J = 5.0 Hz, H-4), 7.20 (d, 1, J = 5.0 Hz, H-5) and 2.21 (s, 3, CH_3). The peak at δ 7.20 was broadened due to coupling to deuterium at position 2. This identified the material as 2-deuterio-3-methylthiophene. No exchange occurred upon stirring 3-methylthiophene in deuterioacetic acid solution for 24 hr at room temperature.

Deuterium exchange with 3-pentadeuteriophenylthiophene[2,3] was carried out by refluxing 3-pentadeuteriophenylthiophene (90 mg, 0.545 mmol) with 2.25 ml of acetic anhydride and 2.75 ml of D_2O for 5 hr. The nmr spectrum of the worked up material in acetone showed a singlet located precisely at the point expected for 2-deuterio-3-pentadeuteriophenylthiophene.[23] From integration ratio 34% deuterium exchange at the 2 position was calculated.

Deuterium exchange with 3-*t*-butylthiophene (100 mg, 0.72 mmol) in 2.5 ml of acetic anhydride and 3.0 ml of D_2O for 5 hr led to 24% deuterium exchange as estimated from nmr. The same experiment carried out for 24 hr gave exchanged product: nmr (CCl_4), δ 6.95 (d, 1, J = 4.8 Hz, H-4), 7.12 (d, 1, J = 4.8 Hz, H-5), and 1.29 (s, 9, $(CH_3)_3C$–). Other peaks in the aromatic region were completely accounted for by the spectrum of unrearranged material. From integration ratios 67% exchange was calculated.

Deuterium exchange with 3-(phenylthio)thiophene was carried out by refluxing 3-(phenylthio)thiophene (195 mg, 1.01 mmol) for 5 hr in a mixture of 2.5 ml of acetic anhydride and 2.5 ml of D_2O. Work-up in the usual manner gave 174 mg of exchanged 3-(phenylthio)thiophene: nmr (C_3D_6O), δ 2.97 (d, 1, J = 5.1 Hz, H-4), 2.51 (d, 1, J = 5.1 Hz, H-5) and 2.79 (s, 5, C_6H_5). The doublet at δ 2.51 was slightly broadened owing to coupling with the deuterium in the 2 position. That exchange had only taken place in the 2 position was further confirmed by conversion of the product into 2-bromo-3-(phenylthio)thiophene whose nmr spectrum was completely identical with that of material prepared from undeuterated product.

Deuterium exchange with 3-phenyl-4-methylthiophene[39] was carried out by refluxing this compound (100 mg, 0.60 mmol) in a mixture of 2.5 ml of acetic anhydride and 3.0 ml of D_2O for 2.5 hr (longer refluxing led to complete deuteration). The reaction mixture was worked up in the usual manner: nmr (CCl_4), δ 6.90 (m, 40% reduced in intensity) 7.05 (m, 16% reduced in intensity), 7.25 (s, 5, C_6H_5), and 2.22 (d, 3, J = ~1 Hz, CH_3). The δ 6.90 peak was identified as being α to methyl group by the extra splitting arising from allylic coupling to the methyl protons.

Deuterium exchange with 2-methylthiophene was carried out by refluxing 2-methylthiophene (1.5 g, 15.2 mmol) in 9 ml of acetic anhydride and 11 ml of D_2O for 5 hr. The reaction mixture was worked up as normal: nmr (C_3D_6O), δ 2.91 (m, 0.58, H-5), *ca.* 3.2 (m, 2.0, 3,4-protons), 7.59 (d, 3.0, J = *ca.* 1 Hz, CH_3). The loss of integration in the low-field portion indicates 5 substitution (42%).

Deuterium exchange with 2-phenylthiophene was carried out with 2-phenylthiophene (164 mg, 1.02 mmol) in 2.5 ml of acetic anhydride and 2.5 ml of D_2O. After refluxing for 5.5 hr the reaction mixture was worked up in the usual manner to give 153 mg (0.96 mmol) of 2-phenylthiophene. The nmr (C_3D_6O) was substantially different from that of undeuterated 2-phenylthiophene. The deuterated product was converted into 2-bromo-5-phenylthiophene by treatment with an equivalent amount of NBS in chloroform–acetic acid. The nmr (C_3D_6O) of this product was identical with that of undeuterated 2-bromo-5-phenylthiophene indicating exchange only in the 5 position. Comparison of the nmr spectra of the partially deuterated and undeuterated 2-phenylthiophenes allowed calculation (using a section of the phenyl absorptions as standard)[2,3] of 40% deuterium content at the 5 position.

Deuterium exchange with 2-*t*-butylthiophene was carried out by refluxing 2-*t*-butylthiophene (203 mg, 1.45 mmol) for 5 hr in a mixture of 2.5 ml of acetic anhydride and 2.5 ml of D_2O. The reaction mixture was worked up in the usual manner. The solution was carefully concentrated to a 3-ml volume and an nmr spectrum was taken of the concentrated material. The complex aromatic region was appreciably changed and the integration for the aromatic protons was 25% reduced in intensity.

The solution above was diluted with 3 ml of acetic acid, NBS (255 mg, 1.43 mmol) was added, and the solution was warmed briefly. The product was extracted into carbon tetrachloride solution, and this solution was concentrated to a 3-ml volume. The nmr spectrum (CCl_4) was identical with that of authentic 2-bromo-5-*t*-butylthiophene; no trace of exchange in the 3,4 positions could be seen. Exchange is thus confined to the 5 position and is 75% complete after 5 hr.

Deuterium exchange with 2-(phenylthio)thiophene was carried out by refluxing 2-(phenylthio)thiophene (192 mg, 1.0 mmol) in 2.5 ml of acetic acid and 2.5 ml of D_2O. After work-up 161 mg of material was obtained: nmr (C_3D_6O), δ 2.40 (m, 33% de-

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(37) A.-B. Hornfeldt, *Acta Chem. Scand.*, **21**, 1952 (1967).

(38) We thank Mr. F. de Jong of these laboratories for carrying out this reaction.

(39) A. S. Broun, M. G. Voronkov, and F. G. Gol'dburt, *Nauchn. Byul. Leningr. Gos. Univ.*, **18**, 14 (1947); *Chem. Abstr.*, **43**, 5392d (1949); H. Wynberg, G. E. Beekhuis, H. van Driel, and R. M. Kellogg, *J. Amer. Chem. Soc.*, **89**, 3498 (1967).

creased in intensity compared to starting material) and *ca.* 7.2 (m, rest of protons).

The deuterated product was treated with an equimolar amount of NBS in carbon tetrachloride–acetic acid. The product obtained had a nmr spectrum completely identical with that of authentic 2-bromo-5-(phenylthio)thiophene. Exchange is thus confined to the 5 position and is 33% complete.

Deuterium exchange failed to take place with thiophene or bromothiophenes when under the conditions described above.

Acid-catalyzed rearrangement of 2-bromo-3-phenylthiophene was carried out with 2-bromo-3-phenylthiophene (1.0 g, 4.2 mmol) in 20 ml of acetic acid *ca.* 0.7 *M* in HBr. The acid solution was brought to reflux and the 2-bromo-3-phenylthiophene was added. At the end of 5 and 20 min 0.5-ml samples were withdrawn which were injected into a mixture of 1 ml of carbon tetrachloride and 5 ml of water in a test tube; these were washed once with KOH solution and twice with water, and the carbon tetrachloride layer was dried over magnesium sulfate. The samples were analyzed by glpc (6-ft Apiezon, 200°) using a trace of biphenyl as an internal standard. At the end of 5 min the reaction mixture consisted of 2.3 mmol of starting material, 0.76 mmol of 3-phenyl thiophene, 0.34 mmol of 2-bromo-4-phenylthiophene, and 0.75 mmol of 2,5-dibromo-3-phenylthiophene. After 20 min, 1.14 mmol of starting material remained and 0.92 mmol of 3-phenylthiophene, 1.08 mmol of 2-bromo-4-phenylthiophene, and 0.89 mmol of 2,5-dibromo-3-phenylthiophene were present. No other products were detected.

Rearrangement failed to occur with 2-bromo-3-phenylthiophene in refluxing acetic acid over a period of *ca.* 1 hr. Rearrangement occurred in mixtures of perchloric acid in acetic acid but was accompanied by considerable decomposition. Refluxing of 2-bromo-3-phenylthiophene in carbon tetrachloride solution in the presence of aqueous 48% HBr led to no apparent reaction.

Acid-catalyzed rearrangement of 2-bromo-3-methylthiophene was carried out by refluxing 2-bromo-3-methylthiophene (35 mg, 0.2 mmol) for 1.5 hr in 1 ml of acetic acid (*ca.* 0.5 *M* in HBr). Work-up as described above and analysis by glpc (6 ft Apiezon, 90°) showed 0.047 mmol of starting material, 0.004 mmol of 2-bromo-4-methylthiophene, 0.056 mmol of 3-methylthiophene, 0.047 mmol of 2,5-dibromo-3-methylthiophene to be present. Longer reaction times led to extensive decomposition.

General Procedure for Acid-Catalyzed Reactions of Bromothiophenes.—Solutions (0.2 *M*) of 2,3-dibromothiophene, 2,4-dibromothiophene, 2,5-dibromothiophene, and 2-bromothiophene in acetic acid (1 *M* in HBr) were made up. (Reactions failed to occur in 0.1 *M* HBr solutions.) A 2-ml sample of each of these solutions was gently refluxed with magnetic stirring for 5 hr. The solutions were cooled, diluted with 2 ml of 1 *N* KOH solution, and extracted with 1 ml of carbon tetrachloride. Analyses were carried out by glpc (6 ft DEGS, programmed at 6°/min from 100 to 185°). An appropriate internal standard was weighed into each reaction mixture; relative responses were determined by comparison with known mixtures. The product distributions given in the results were found.

Acid-catalyzed reactions of 3,4-dibromothiophene and 3-bromothiophene failed to give any detectable products other than recovered starting materials.

The acid-catalyzed debromination of 2-bromo-3-phenylthiophene was carried out by refluxing 2-bromo-3-phenylthiophene (50 mg, 0.21 mmol) for 3.5 hr in 1 ml of acetic acid (*ca.* 1 *N* in HBr containing phenol (20 mg, 0.21 mmol)). The solution was diluted with H_2O and extracted with carbon tetrachloride, the carbon tetrachloride layer was washed with KOH solution and then with water and dried over $MgSO_4$, and the solvent was removed to leave pure 3-phenylthiophene (28 mg, 84% yield). Examination of the reaction mixtures by glpc (6-ft Apiezon, 200°) showed that no 2-bromo-4-phenyl or 2,5-dibromo-3-phenylthiophene had been formed.

General Procedure for Debrominations with Phenol.—Solutions (0.2 *M*) of 2,3-dibromothiophene, 2,4-dibromothiophene, 2-bromothiophene, 2,5-dibromothiophene, 2,3,5-tribromothiophene and 2-bromo-3-methylthiophene were made up in acetic acid which was 1 *M* in HBr and 0.2 *M* in phenol. The reaction mixtures were refluxed 5 hr after which time 2 ml of 1 *N* KOH solution was added. The resulting mixture was extracted with 1 ml of carbon tetrachloride. Analysis was carried out by glpc (6-ft DEGS, programmed at 6°/min from 100 to 185°). An appropriate internal standard was added to the reaction mixture so as to allow yield calculations. The quantitative results of these experiments are given in the Results.

The debromination of 2-bromo-3-methylthiophene carried out as described above led to the formation of 3-methylthiophene (0.14 mmol, 35% yield). No other identifiable products could be detected. A considerable amount of black decomposition material was formed during the course of the reaction.

Kinetic studies of the acid-catalyzed reactions of 2-bromo-3-phenylthiophene were carried out normally at 70° in an automatic temperature-regulated water bath (*ca.* ± 1° control). The various bromophenylthiophenes were prepared as described[6] and purified by preparative glpc when necessary. A much improved synthesis of 2,5-dibromo-3-phenylthiophene has been described by Gronowitz.[9] 2-Bromo-3-phenylthiophene was dissolved in an acetic acid solution 1 *M* in HBr and 0.005 *M* in adamantanone (used as an internal standard and shown to be unreactive under the conditions used). Samples of this solution (0.5–0.8 ml) were put in glass tubes provided with a rubber seal. Four to seven of these tubes were held in the water bath by means of a large cork containing holes for each tube. At various time intervals samples (usually 50 μl) were withdrawn from a tube by means of a hydrodermic syringe which punctured the rubber stoppers. Samples were injected in sufficient Na_2CO_3 solution to neutralize the acid. Chloroform (50 μl) was added, the tube was centrifuged, and the chloroform layer was withdrawn by means of a syringe. The tubes were protected from light and stored in the freezer. The samples were subjected to gas chromatographic analysis (6 ft Carbowax on Chromosorb, 170°). A disk integrator was used to indicate relative peak areas and relative response factors calculated from gas chromatograms of known mixtures. The same technique was used to study the behavior of 2-bromo-4-phenylthiophene and 2,5-dibromo-3-phenylthiophene under acid-catalyzed conditions.

Competitive reactions of 3-phenylthiophene or the various bromo isomers were carried out by dissolving the components in a chloroform–acetic acid mixture held at the temperature stated in the discussion. An insufficient amount of bromine was added and the reaction was quenched as quickly as possible with sodium thiosulfate solution. Analyses of the reaction mixtures were by glpc.

Registry No.—Sulfone of 3-(phenylthio)thiophene, 16718-05-1; 2-bromo-3-methylthiophene, 14282-76-9; 2-bromo-3-(phenylthio)thiophene, 16718-07-3; 2-bromo-3-thienylphenyl sulfone, 16718-08-4; 2-bromo-5-(phenylthio)thiophene, 16718-09-5; sulfone of 2-bromo-5-(phenylthio)thiophene, 16718-10-8; thiophene, 110-02-1; 3-(phenylthio)thiophene, 16718-11-9; 3-methylthiophene, 616-44-4; 3-*t*-butylthiophene, 1689-79-8; 2-methylthiophene, 554-14-4; 2-phenylthiophene, 825-55-8; 2-*t*-butylthiophene, 1689-78-7; 2-(phenylthio)-thiophene, 16718-12-0; 2-bromo-3-phenylthiophene, 10341-87-4.

Acknowledgments.—We thank Mr. J. Buter for help in the synthesis of some of the starting materials. Several helpful suggestions were made by Dr. M. J. Janssen of this department.

Synthesis of Pyridazine Derivatives. XX. Orientational Effects in Some New Polynuclear Systems Containing a Pyridazine Ring[1]

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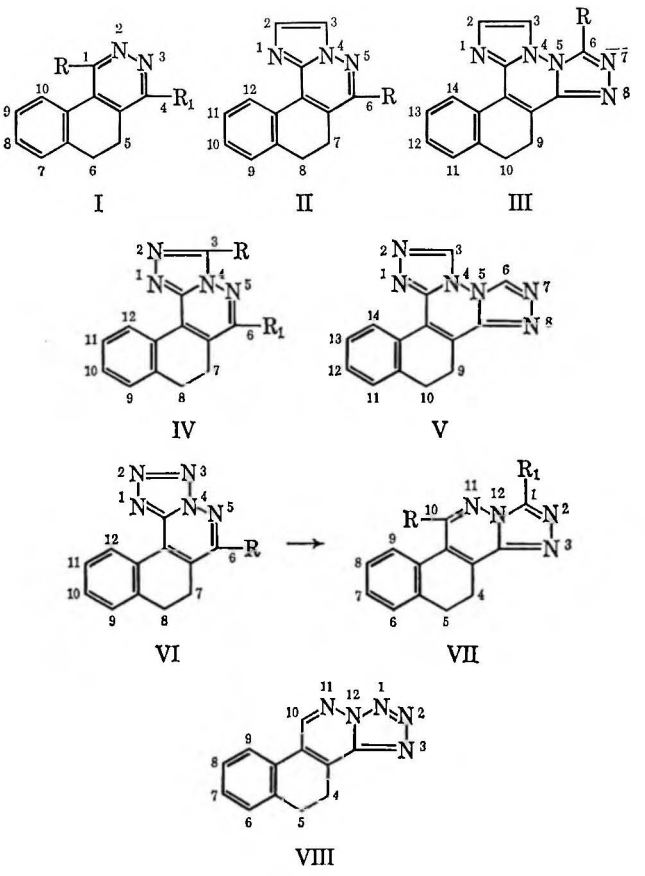
Received February 5, 1968

Starting from 5,6-dihydrobenzo[*f*]phthalazines (I) several new polyazaheterocyclic systems (II–VIII) were prepared and their structures were determined. Azidoazomethine–tetrazole equilibrium has been used for selective orientation of some fused rings. Thus, in VI (R = N_3) only one tetrazole ring is present, the other being transformed in an azido group. However, if a new condensed hetero ring has been formed by transforming VI in VII, the originally present tetrazole ring spontaneously assumes the azido form. We could now present evidence that also a fused triazolo ring can efficiently destabilize the adjacent tetrazole ring and compel it to assume the azido form.

As an extension of our recent report on condensed polyazaheterocycles containing a pyridazine ring, fused with another heterocyclic ring,[2-7] it seemed of interest to synthesize and study the aromaticity and orientational effects on polynuclear systems, based on 5,6-dihydrobenzo[*f*]phthalazine.

In order to obtain on the starting ring system different functional groups necessary for further cyclizations, the 1,4-dichloro compound (I, R = R_1 = Cl) was submitted to nucleophilic displacement with ammonia, hydrazine, thiolate, and alkoxide ion. From available data about nucleophilic substitutions on 4-alkyl-3,6-dichloropyridazines it is known that a selective or competitive exchange of halogen atoms is possible and usually the 6-substituted 3-chloro-4-alkylpyridazine isomer prevails.[8-11] Exceptions are reactions with alkoxides and thiolate ion.[8,9,12,13] Since 1,4-dichloro-5,6-dihydrobenzo[*f*]phthalazine can be regarded as a 4-alkyl-5-aryl-3,6-dichloropyridazine and since alkyl substituents are expected to exert a moderately deactivating effect, while the aryl group a slightly activating effect, the replacement of the 1-chlorine atom would be expected to proceed preferentially. This direction of nucleophilic displacement has been indeed observed and in all cases only one isomer (I, R = NH_2, $NHNH_2$, SH or OR′, R_1 = Cl) could be isolated. The presence of a small amount of the second hydrazino isomer (I, R = Cl, R_1 = $NHNH_2$) could be established from the formation of a mixture of triazolo derivatives as discussed later. The above structure assignments have been made on the basis of nmr correlations and chemical evidence.

From the corresponding amino or hydrazino derivatives (I, R = NH_2 or $NHNH_2$, R_1 = Cl) a new fused imidazole (II), triazole (IV) or tetrazole ring (VI) could be formed in the manner, described already in earlier communications on related systems.[2-5] However, if the crude product, obtained from hydrazinolysis of I (R = R_1 = Cl), was treated in the usual way with triethyl orthoformate, two isomerict riazolo derivatives could be isolated in about 6:1 ratio, the isomer IV (R =



H, R_1 = Cl) prevailing. The structure of the other isomeric triazolo compound (VII, R = Cl, R_1 = H) has been established by converting it into the corresponding hydrazino compound (VII, R = $NHNH_2$, R_1 = H) and subsequent nitrosation afforded the azide (VII, R = N_3, R_1 = H), which was identical with the product obtained from VI (R = $NHNH_2$) by reaction with diethoxymethyl acetate. The residual 6-chlorine atom in the above systems was submitted to nucleophilic displacement with different nucleophiles, thus producing compounds capable of ring closure to another five-membered azaheterocycle. In this way systems III and V were built up. However, in the case of fused tetrazole rings, azidoazomethine–tetrazole equilibrium could be expected, and therefore such systems were investigated in some detail.

(1) Paper LVII on Heterocycles.

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Azidoazomethine–tetrazole equilibrium has been investigated in several heterocyclic systems[5,14-17] and besides structural features, the equilibrium was found to be solvent and temperature dependent and influenced by the presence of other groups present in the heterocyclic ring.[15,18] In the case of present polyazaheterocycles when only one tetrazole ring was fused to the pyridazine ring, no azido form could be detected as judged from infrared spectra of compounds of type VI. However, the formation of a new fused triazolo ring from the corresponding hydrazino derivative (VI, R = $NHNH_2$) with the action of diethoxymethyl acetate or cyanogen bromide resulted in a destabilization and ring opening of the adjacent tetrazole ring, and the azido form (VII, R = N_3, R_1 = H or NH_2) is the predominant form present as judged from the intense azide band in the infrared spectrum. Nevertheless, this does not preclude the possibility that in solution the tetrazole form of this compound could also be present, as already shown in other cases.[18]

Similar observations were made also with compounds of the type VI where a ditetrazole, two isomeric azidotetrazole forms and a diazido form are theoretically possible. The same compound (VI, R = N_3) was obtained, however, by treatment of the 1,4-dichloro compound (I, R = R_1 = Cl) or chlorotetrazole VI (R = Cl) with sodium azide, or by conversion of the latter into the hydrazinotetrazole VI (R = $NHNH_2$) and subsequent nitrosation. Compound VI (R = N_3) exhibited a strong azide band in the infrared spectrum and its structure, as proposed, is assigned also on the basis of nmr correlations.

This facile tetrazole ring opening thus provided a simple way to synthesize compounds structurally related to aza steroids (VII), since the azido group is easily transformed with hydrogen sulfide to the corresponding amino derivative. An alternative possible way to obtain compounds VII (R = R_1 = H) or VIII was to remove the 1-hydrazino group in I (R = $NHNH_2$, R_1 = Cl), to replace the residual 4-chlorine atom with hydrazino group and cyclize this compound with diethoxymethyl acetate or by nitrosation, or treat the 4-chloro derivative (I, R = H, R_1 = Cl) directly with sodium azide to obtain VIII. Compounds of the type VII and VIII are representatives of polyaza steroids[19] of which those containing a pyridazine ring have been reported only recently.[20-24] They are very stable under conditions of electrophilic substitution and they are easily fully aromatized.

An examination of nmr spectra of some representatives of the above mentioned types of compound confirmed the structural assignments. Significant deshielding effect of hindered protons facing a cyclic nitrogen atom or another hindered proton in polycondensed angular aza- or thiaaromatics have been observed in several cases.[25-27] A comparison of nmr spectra of some compounds where sterical effects of substituents or fused rings with regard to the proton of the benzenoid part of the molecule can be anticipated with those of the sterically unhindered derivatives reveals a significant downfield shift of the hindered aromatic proton. The deshielding is evident from data collected in Table I. The methylene protons of the bridging $-CH_2CH_2-$ group appear as singlets (τ 6.88–7.10) except for I (R = SH, R_1 = Cl) and VII (R = R_1 = H or R = Cl, R_1 = H) where they appear as multiplets (centered at τ 7.08 and 6.73 or 6.88, respectively), typical for an AA'BB' pattern.

TABLE I

Compd	R	R_1	Proton	τ
I	H	Cl	H_{10}	2.25
I	Cl	Cl	H_{10}	1.70
I	NH_2	Cl	H_{10}	2.07
I	$NHNH_2$	Cl	H_{10}	1.53
I	OCH_3	Cl	H_{10}	1.72
II	Cl		H_{12}	0.72
IV	H	Cl	H_{12}	0.75
VII	H	H	H_9	2.22
VII	Cl	H	H_9	1.73

Experimental Section[28]

1,4-Dichloro-5,6-dihydrobenzo[*f*]phthalazine (I, R = R_1 = Cl) was prepared from 3,4-dihydro-1,2-naphthalic anhydride[29] according to the procedure of Dreiseitel and Kocwa.[30] Crystallization was conveniently performed from ligroin and benzene (1:1): mp 124–126° (lit.[30] mp 125–127°); nmr ($CDCl_3$), τ 1.70 (multiplet, H_{10}), 2.63 (multiplet, H_7, H_8, H_9), 7.10 (singlet 4 H, $-CH_2CH_2-$). The nmr spectrum was recorded at lower temperatures also and the signal for the last mentioned group becomes somewhat broadened at −92° (in CD_2COCD_3) and at −100° (in CS_2).

1-Amino-4-chloro-5,6-dihydrobenzo[*f*]phthalazine (I, R = NH_2, R_1 = Cl).—Compound I (5 g, R = R_1 = Cl) and liquid ammonia (150 ml) were placed in an autoclave and the mixture was heated at 126–130° for 5 hr. After cooling the autoclave was vented and the residue was treated with water (50 ml). The suspension was filtered and washed with water and alcohol. The crude product is pure enough for further synthetic work, but for analytical purposes it was crystallized from N,N-dimethylformamide (yield 90%): mp 245–246°; nmr (CF_3COOH), τ 2.07 (multiplet, H_{10}), 2.50 (multiplet, H_7, H_8, and H_9), 6.88 (singlet 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{12}H_{10}ClN_3$: C, 62.20; H, 4.35; N, 18.13. Found: C, 62.13; H, 4.40; N, 18.64.

4-Chloro-1-hydrazino-5,6-dihydrobenzo[*f*]phthalazine (I, R = $NHNH_2$, R_1 = Cl).—Compound I (1 g, R = R_1 = Cl), hydrazine hydrate (7 ml of 80%), and ethanol (3 ml) were heated under reflux for 1 hr, cooled, and filtered. The crude product (yield 71%) was crystallized from ethanol with the addition of char-

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coal three times: mp 175–178°; nmr (CF_3COOH), τ 1.53 (multiplet, H_{10}), 2.50 (multiplet, H_7, H_8, and H_9), 6.88 (singlet 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{12}H_{11}ClN_4$: C, 58.42; H, 4.49; N, 22.72. Found: C, 58.71; H, 4.58; N, 22.60.

The benzylidene derivative (I, R = NHN=CH_6H_5, R_1 = Cl) had mp 231–233° (from ethanol).

Anal. Calcd for $C_{19}H_{15}ClN_4$: N, 16.76. Found: N, 17.04.

The thiosemicarbazide derivative (I, R = $C_6H_5NHCSNHNH$, R_1 = Cl) was obtained in the reaction with phenyl isothiocyanate, mp 198–200° (from ethanol).

Anal. Calcd for $C_{19}H_{16}ClN_5S$: C, 59.75; H, 5.31; N, 18.34; S, 8.40. Found: C, 60.04; H, 5.32; N, 18.68; S, 8.18.

4-Chloro-1-methoxy-5,6-dihydrobenzo[*f*]phthalazine (I, R = OCH_3, R_1 = Cl).—To a suspension of 2.51 g of I (R = R_1 = Cl) in 20 ml of absolute methanol a solution of sodium methylate, prepared from 0.23 g of sodium and 5 ml of methanol, was added. Upon heating under reflux for 15 min the reaction mixture was filtered hot, the filtrate was evaporated to one-third of its original volume and poured into 30 ml of iced water. The crude product was crystallized from ethanol to yield 1.9 g (76%): mp 145–147°; nmr ($CDCl_3$), τ 1.72 (multiplet, H_{10}), 2.70 (multiplet, H_7, H_8, and H_9), 7.17 (singlet 4 H, $-CH_2CH_2-$), 5.82 (singlet 3 H, CH_3O).

Anal. Calcd for $C_{13}H_{11}ClN_2O$: C, 63.28; H, 4.49; N, 11.36. Found: C, 63.02; H, 4.65; N, 11.39.

4-Chloro-1-ethoxy-5,6-dihydrobenzo[*f*]phthalazine (I, R = OC_2H_5, R_1 = Cl) was prepared in an analogous manner, mp 110° (from ethanol).

Anal. Calcd for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 5.03; N, 10.75. Found: C, 64.26; H, 5.17; N, 10.73.

1-Methoxy-5,6-dihydrobenzo[*f*]phthalazine (I, R = OCH_3, R_1 = H).—To a solution of 0.68 g of I (R = OCH_3, R_1 = Cl) in 50 ml of methanol, 3 ml of concentrated ammonia and 0.5 g of 5% palladized charcoal were added and the mixture was stirred in an atmosphere of hydrogen at room temperature until absorption of hydrogen stopped. Upon filtration, the solution was evaporated to dryness *in vacuo* and the residue was crystallized from *n*-hexane (yield 86%), mp 114–115°.

Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.77; H, 5.85; N, 13.00.

Similarly, the 1-ethoxy compound (I, R = OC_2H_5, R_1 = H) was prepared in 67% yield, mp 93–94° (from *n*-hexane).

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.12; H, 6.15; N, 12.45.

5,6-Dihydrobenzo[*f*]phthalazine sulfate (I, R = R_1 = H; H_2SO_4) was prepared in essentially the same way. After evaporation of the filtrate to dryness the residual oil was treated with *n*-hexane (5 ml for 1.5 g of the oil) and concentrated sulfuric acid (0.8 ml) was then added. Upon cooling on ice the sulfate was separated and was crystallized from ethanol (yield 72%), mp 200–201°.

Anal. Calcd for $C_{12}H_{12}N_2O_4S$: C, 51.43; H, 4.32; N, 9.99; S, 11.42. Found: C, 51.33; H, 4.24; N, 9.82; S, 11.31.

4-Chloro-1-mercapto-5,6-dihydrobenzo[*f*]phthalazine (I, R = SH, R_1 = Cl).—To 0.25 g of I (R = R_1 = Cl) a freshly prepared cold ethanolic solution of KSH (0.3 g of KOH were dissolved in 15 ml of ethanol and hydrogen sulfide was introduced for 1 hr) was added. The mixture was gently heated on water bath for a short time to dissolve the starting compound. The filtered solution was treated with 15 ml of cold water and neutralized with acetic acid to pH 7. The crude product (yield 80%) was dissolved in hot aqueous solution of $NaHCO_3$ and filtered, and the filtrate was acidified upon cooling with acetic acid. The product was filtered, washed with water, and dried (yield 41%): mp 108–111°; nmr ($CDCl_3$), τ 1.75 (multiplet, H_{10}), 2.70 (multiplet, H_7, H_8, and H_9), 7.08 (multiplet, 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{12}H_9ClN_2S$: C, 57.94; H, 3.65; N, 11.27. Found: C, 58.23; H, 3.64; N, 11.08.

The corresponding S-methyl derivative (I, R = SCH_3, R_1 = Cl) was prepared in the usual way, using methyl iodide as alkylating agent, mp 83–85° (from methanol).

Anal. Calcd for $C_{13}H_{11}ClN_2S$: C, 59.41; H, 4.22. Found: C, 59.70; H, 4.51.

6-Chloro-7,8-dihydrobenz[*h*]imidazo[2,1-*a*]phthalazine (II, R = Cl).—To an ethanolic solution (50 ml) of bromoacetaldehyde, prepared from its dimethyl acetal (5 g) according to the procedure described in an earlier paper,[4] 5 g of I (R = NH_2, R_1 = Cl) was added and the mixture was heated under reflux for 4 hr. The cooled solution was poured into 50 ml of water and the resulting suspension was neutralized with solid $NaHCO_3$ until pH 7. After standing on ice overnight, the crude product was collected and crystallized from ethanol (yield 52%): mp 154–155°; nmr ($CDCl_3$), τ 2.28 (doublet, H_2), 2.17 (doublet, H_3), 2.66 (multiplet, H_9, H_{10}, and H_{11}), 0.72 (multiplet, H_{12}), 7.05 (singlet, 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{14}H_{10}ClN_3$: C, 65.75; H, 4.34; N, 16.44. Found: C, 65.98; H, 4.33; N, 16.63.

7,8-Dihydrobenz[*h*]imidazo[2,1-*a*]phthalazine (II, R = H).—A mixture of 0.25 g of II (R = Cl), 50 ml of methanol, 0.1 g of powdered KOH, and 0.5 g of 5% palladized charcoal was stirred in an atmosphere of hydrogen at room temperature until the uptake subsided. The filtered solution was evaporated to dryness at 35° (17 mm). The residue was suspended in 30 ml of water, filtered and crystallized from aqueous ethanol (1:1) (yield 48%), mp 106–108°.

Anal. Calcd for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 75.85; H, 5.21; N, 19.08.

6-Hydrazino-7,8-dihydrobenz[*h*]imidazo[2,1-*a*]phthalazine (II, R = $NHNH_2$).—A mixture of II (6.6 g, R = Cl), 50 ml of 80% hydrazine hydrate, and 10 ml of ethanol was heated under reflux for 5 hr. The product was purified by crystallization from ethanol (yield 40%), mp 200–202°.

Anal. Calcd for $C_{14}H_{13}N_5$: C, 66.93; H, 5.21; N, 27.87. Found: C, 66.98; H, 5.34; N, 27.72.

It forms a benzylidene derivative, mp 125–127°.

Anal. Calcd for $C_{21}H_{17}N_5$: N, 20.64. Found: N, 20.89.

The *p*-dimethylaminobenzylidene derivative had mp 117–119°

Anal. Calcd for $C_{23}H_{22}N_6$: N, 21.98. Found: N, 21.93.

6-(4′-Phenylthiosemicarbazido)-7,8-dihydrobenz[*h*]imidazo-[2,1-*a*]phthalazine (II, R = $C_6H_5NHCSNHNH$).—Compound II (0.25 g, R = $NHNH_2$) was dissolved in 15 ml of hot ethanol, 0.14 g of phenyl isothiocyanate were added, and the mixture was left aside to cool slowly to room temperature. The separated product was filtered and washed with 5 ml of hot ethanol (yield 52%), mp 196–198°.

Anal. Calcd for $C_{21}H_{18}N_6S$: C, 65.26; H, 4.70; N, 21.75. Found: C, 65.12; H, 4.70; N, 21.85.

6-Mercapto-9,10-dihydrobenz[*f*]imidazo[1,2-*c*]-*s*-triazolo[3,4-*a*]phthalazine (III, R = SH).—The above compound II (0.1 g, R = $C_6H_5NHCSNHNH$) was heated under reflux in 10 ml of 1,2-propylene glycol for 20 min. Upon cooling, 30 ml of cold water was added and, after standing on ice for some time, the product was filtered off and crystallized from ethanol (yield 80%), mp 327° dec.

Anal. Calcd for $C_{15}H_{11}N_5S$: C, 61.43; H, 3.78; N, 23.88; S, 10.91. Found: C, 61.33; H, 3.83; N, 23.76; S, 10.74.

9,10-Dihydrobenz[*f*]imidazo[1,2-*c*]-*s*-triazolo[3,4-*a*]phthalazine (III, R = H).—A mixture of 0.3 g of II (R = $NHNH_2$) and 0.5 ml of diethoxymethyl acetate was refluxed on an oil bath for 10 min, cooled, and treated with 0.5 ml of ethanol. After standing on ice for 15 min the separated product was filtered and washed with 1 ml of ethanol (yield 17%), mp 311–313°.

Anal. Calcd for $C_{15}H_{11}N_5$: C, 68.95; H, 4.24; N, 26.81. Found: C, 69.13; H, 4.56; N, 26.61.

6-Chloro-3-mercapto-7,8-dihydrobenzo[*h*]-*s*-triazolo[3,4-*a*]-phthalazine (IV, R = SH, R_1 = Cl).—Compound I (0.2 g) (R = $C_6H_5NHCSNHNH$, R_1 = Cl) and 20 ml of 1,2-propylene glycol were heated under reflux for 20 min and the reaction mixture was thereafter diluted with 50 ml of water. The crude product was collected and purified by dissolution in hot saturated aqueous $NaHCO_3$, addition of charcoal, and filtration, and the cooled filtrate was acidified with glacial acetic acid to neutral reaction to yield 42% of product, mp 129–131°. The compound is present in the thioamide form since in the ir spectrum (Nujol) no SH bands are discernible.

Anal. Calcd for $C_{13}H_9ClN_4S$: C, 53.87; H, 3.13; N, 19.33. Found: C, 53.55; H, 3.08; N, 19.02.

The S-methyl derivative was prepared in the usual way, mp 142–143° (aqueous ethanol).

Anal. Calcd for $C_{14}H_{11}ClN_4S$: N, 18.45; S, 10.55. Found: N, 18.13; S, 10.55.

6-Chloro-7,8-dihydrobenzo[*h*]-*s*-triazolo[3,4-*a*]phthalazine (IV, R = H, R_1 = Cl).—Diethoxymethyl acetate (0.5 ml) was added to 0.4 g of I (R = $NHNH_2$, R_1 = Cl) and the mixture was heated under reflux for 5 min. Upon cooling, the reaction mixture was diluted with 1.5 ml of ethanol and, after standing on ice for 15 min, the separated product was crystallized from ethanol to give the pure compound in 57% yield, mp 240–242°.

Anal. Calcd for $C_{13}H_9ClN_4$: C, 60.81; H, 3.53; N, 21.83. Found: C, 60.41; H, 3.90; N, 21.70.

7,8-Dihydrobenzo[*h*]-*s*-triazolo[3,4-*a*]phthalazine (IV, R = R$_1$ = H).—To a solution of 0.25 g of the above compound IV (R = H, R$_1$ = Cl) in 50 ml of absolute methanol 0.1 g of KOH and 0.5 g of 5% palladized charcoal were added and the mixture was stirred in an atmosphere of hydrogen at room temperature until the uptake of hydrogen ceased. The filtered solution was evaporated to dryness, the residue was suspended in water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and filtered, the solvent was evaporated, and the residue was crystallized from ethanol to give the pure compound in 56% yield, mp 215–216°.

Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.08; H, 4.38; N, 25.34.

6-Hydrazino-7,8-dihydrobenzo[*h*]-*s*-triazolo[3,4-*a*]phthalazine (IV, R = H, R$_1$ = NHNH$_2$).—A reaction mixture consisting of 0.4 g of IV (R = H, R$_1$ = Cl), 3 ml of 80% hydrazine hydrate, and 0.5 ml of ethanol was heated under reflux for 20 min. The product which separated was filtered, washed with ethanol, and recrystallized from ethanol with the addition of charcoal (yield 91%), mp 246–248°.

Anal. Calcd for $C_{13}H_{12}N_6$: C, 61.89; H, 4.79; N, 33.32. Found: C, 61.81; H, 4.92; N, 33.45.

9,10-Dihydrobenzo[*f*]bis-*s*-triazolo[3,4-*a*,4,3-*c*]phthalazine (V).—A mixture of 0.5 g of compound IV (R = H, R$_1$ = NHNH$_2$) and 2 ml of diethoxymethyl acetate was heated under reflux for 10 min. Upon cooling, 5 ml of ethanol were added, the precipitate was filtered and washed with ethanol. Crystallization was performed from N,N-dimethylformamide to yield 0.45 g (83%), mp 333–334°.

Anal. Calcd for $C_{14}H_{10}N_6$: C, 64.11; H, 3.84; N, 32.05. Found: C, 64.23; H, 4.11; N, 31.85.

6-Chloro-7,8-dihydrobenzo[*h*]tetrazolo[5,1-*a*]phthalazine (VI, R = Cl).—Compound I (0.6 g) (R = NHNH$_2$, R$_1$ = Cl) was dissolved in 6 ml of 2 *N* hydrochloric acid, the solution was cooled on ice, and a saturated aqueous solution of $NaNO_2$ was added dropwise until a positive reaction on starch–KI paper. During this reaction, temperature was kept below 5°. The resulting precipitate was filtered, washed with ice water, air dried, and crystallized from ethanol with the addition of charcoal (yield 58%), mp 163–165°. The compound exhibited no azide band in the ir spectrum.

Anal. Calcd for $C_{12}H_8ClN_5$: C, 55.93; H, 3.13; N, 27.17. Found: C, 55.73; H, 3.44; N, 27.35.

6-Amino-7,8-dihydrobenzo[*h*]tetrazolo[5,1-*a*]phthalazine (VI, R = NH$_2$). **A.**—The above chloro compound VI (1 g, R = Cl) and 150 ml of liquid ammonia were placed in an autoclave and the mixture was heated at 120° for 4 hr. Ammonia was then left to evaporate and the brown residue was purified by crystallization from ethanol to yield 68%, mp 236–238°.

Anal. Calcd for $C_{12}H_{10}N_6$: C, 60.49; H, 4.23; N, 35.28. Found: C, 60.69; H, 4.52; N, 35.36.

B.—Into a hot ethanolic solution (20 ml) of 0.5 g of VI (R = N$_3$) hydrogen sulfide was bubbled for about 15 min until no more precipitate was formed. After crystallization from ethanol the pure compound melted at 236–238° to yield 0.4 g. Mixture melting point with the compound prepared as under A was undepressed. Ir (Nujol) bands were at 3279 and 3175 cm^{-1} (NH); no azide band appeared.

6-Hydrazino-7,8-dihydrobenzo[*h*]tetrazolo[5,1-*a*]phthalazine (VI, R = NHNH$_2$).—A mixture of 2.57 g of VI (R = Cl), 10 ml of 80% hydrazine hydrate, and 1 ml of ethanol was heated under reflux for 30 min. The separated crude product was crystallized from N,N-dimethylformamide with the addition of charcoal to yield 2.0 g (79%), mp 265–267° dec.

Anal. Calcd for $C_{12}H_{11}N_7$: C, 56.91; H, 4.38; N, 38.72. Found: C, 56.92; H, 4.70; N, 38.92.

6-Azido-7,8-dihydrobenzo[*h*]tetrazolo[5,1-*a*]phthalazine (VI, R = N$_3$). **A.**—A mixture of 2.5 g of I (R = R$_1$ = Cl), 2.6 g of sodium azide, and 30 ml of ethanol was heated on a water bath for 5 hr under reflux. The cooled reaction mixture was diluted with 50 ml of water and the obtained product was crystallized from ethanol to yield 54%: mp 192–195°; ir (Nujol), strong band at 2128 cm^{-1} (N_3); nmr ($CDCl_3$), τ 2.57 (multiplet, H_9, H_{10}, H_{11}, and H_{12}), 7.02 (singlet, 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{12}H_8N_8$: C, 54.54; H, 3.05; N, 42.41. Found: C, 54.22; H, 3.24; N, 42.54.

B.—A solution of 0.3 g of VI (R = Cl) in 20 ml of ethanol was treated with an aqueous solution of sodium azide (0.2 g in 1 ml of water) and then heated under reflux for 3 hr. The resulting product was collected, washed with ethanol, and water to give 0.2 g of the compound, identical with that prepared as under A.

C.—A solution of 0.3 g of VI (R = NHNH$_2$) in 6 ml of 2 *N* hydrochloric acid was treated dropwise with a saturated solution of sodium nitrite in that manner that the temperature did not exceed 5°. The end point of the reaction was detected by means of KI–starch paper. The separated product was purified from ethanol and charcoaled. The compound was identical with compounds as prepared under A or B. Mixture melting points were undepressed and ir spectra were identical.

7,8-Dihydrobenzo[*h*]tetrazolo[5,1-*a*]phthalazine (VI, R = H).—The 6-chloro derivative (VI, R = Cl, 1.27 g) was suspended in 100 ml of methanol, 3 ml of concentrated ammonia and 0.5 g of 5% palladized charcoal were added and the mixture stirred in an atmosphere of hydrogen at room temperature until uptake was no more discernible. The filtered solution was evaporated *in vacuo* to dryness, and the residue was crystallized from ethanol to give 0.4 g (36%) of the pure compound, mp 193–195°.

Anal. Calcd for $C_{12}H_9N_5$: C, 64.56; H, 4.06; N, 31.38. Found: C, 64.40; H, 4.31; N, 31.54.

10-Chloro-4,5-dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII, R = Cl, R$_1$ = H).—The crude reaction product (1 g) obtained in hydrazinolysis of I (R = R$_1$ = Cl) as described for the preparation of I (R = NHNH$_2$, R$_1$ = Cl) was heated with triethyl orthoformiate (5 ml) under reflux for 3 hr. From the hot reaction mixture a product was filtered off, crystallized from ethanol, and identified as compound IV (R = H, R$_1$ = Cl) to yield 72%, mp 240–242°, a mixture melting point with an authentic specimen was undepressed.

From the filtrate another product separated upon cooling, this was crystallized from ethanol and identified as compound VII (R = Cl, R$_1$ = H) to yield 15%: mp 176–177°; nmr ($CDCl_3$), τ 0.79 (singlet, H_1), 1.73 (multiplet, H_9), 2.54 (multiplet, H_6, H_7, and H_8), 6.88 (multiplet, 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{13}H_9N_4Cl$: C, 60.81; H, 3.53; N, 21.83. Found: C, 60.71; H, 3.82; N, 21.86.

1-Amino-10-azido-4,5-dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII, R = N$_3$, R$_1$ = NH$_2$).—To a boiling solution of 1.25 g of VI (R = NHNH$_2$) in 25 ml of ethanol 0.53 g of cyanogen bromide were added and heating was continued for further 5 min. Upon cooling, the crude hydrobromide salt separated and was filtered off and suspended in 3 ml of water. The suspension was treated with a saturated aqueous solution of Na_2CO_3 (5 ml) and stirred at room temperature for 15 min. The free base was collected (0.65 g, 47%) and crystallized from N,N-dimethylformamide: mp 255–256° dec; ir (Nujol), strong azide band at 2128 cm^{-1}.

Anal. Calcd for $C_{13}H_{10}N_8$: C, 56.11; H, 3.62; N, 40.27. Found: C, 56.40; H, 3.85; N, 40.53.

1,10-Diamino-4,5-dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII, R = R$_1$ = NH$_2$).—The above compound VII (278 mg, R = N$_3$, R$_1$ = NH$_2$) was dissolved in 10 ml of boiling ethanol and hydrogen sulfide was bubbled in this solution for 15 min. The crude product, which separated, was collected and crystallized from N,N-dimethylformamide to yield 138 mg (55%), mp >325°.

Anal. Calcd for $C_{13}H_{12}N_6$: C, 61.89; H, 4.79; N, 33.32. Found: C, 61.63; H, 4.92; N, 33.08.

10-Hydrazino-4,5-dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII, R = NHNH$_2$, R$_1$ = H).—The corresponding chloro compound (VII, R = Cl, R$_1$ = H, 1 g) was heated with hydrazine hydrate (10 ml of 80%) under reflux for 1 hr. Upon cooling the separated product was filtered off and crystallized from N,N-dimethylformamide to yield 0.87 g, mp 285–290° dec.

Anal. Calcd for $C_{13}H_{12}N_6$: C, 61.89; H, 4.79; N, 33.32. Found: C, 61.63; H, 5.14; N, 33.69.

10-Azido-4,5-dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII, R = N$_3$, R$_1$ = H). **A.**—A mixture of VI (R = NHNH$_2$, 0.5 g) and diethoxymethyl acetate (2 ml) was heated under reflux for 5 min. Some product separated already during heating and the rest separated after addition of 2 ml of ethanol. The filtered product was washed several times with ethanol. For analytical purposes it was crystallized from 0.5 ml of diethoxymethyl acetate to yield 0.35 g (67%): mp 220–222°; ir (Nujol), strong azide band at 2128 cm^{-1}.

Anal. Calcd for $C_{13}H_9N_7$: C, 59.31; H, 3.45; N, 37.25. Found: C, 59.66; H, 3.48; N, 37.35.

B.—Compound VII (R = NHNH$_2$, R$_1$ = H, 0.5 g), dissolved in an ice cold solution of 5 ml of 10% hydrochloric acid, was

treated dropwise with an aqueous solution of sodium nitrite (0.15 g of $NaNO_2$ in 1 ml of water). The reaction mixture was cooled and stirred for 30 min, the product was separated and washed with 5 ml of ice-cold water. Upon crystallization from ethanol the compound (0.25 g) had mp 220–222°. Its ir spectrum was identical with that of the compound obtained under A.

4-Chloro-5,6-dihydrobenzo[*f*]phthalazine (I, R = H, R_1 = Cl).—To a boiling solution of 1.23 g of I (R = $NHNH_2$, R_1 = Cl) in a mixture of water and ethanol (4:1) a solution of hydrated cupric sulfate (2.5 g in 10 ml water) was added and the mixture was heated under reflux until it became clear. It was then made alkaline by adding a 10% aqueous solution of NaOH and filtered hot, and the residue was washed with 50 ml of hot water. The combined filtrates were evaporated to about 30 ml and then left on ice overnight. The collected crystals (250 mg, 24%) were crystallized for analytical purposes from ethanol: mp 118–119°; nmr ($CDCl_3$), τ 2.78 (multiplet, H_7, H_8, and H_9), 2.25 (multiplet, H_{10}), 7.03 (singlet, 4 H, $-CH_2CH_2-$), H_1 was covered with the multiplet of H_7, H_8, and H_9.

4-Hydrazino-5,6-dihydrobenzo[*f*]phthalazine (I, R = H, R_1 = $NHNH_2$).—The above compound (I, R = H, R_1 = Cl) (1.08 g), 8 ml of 80% hydrazine hydrate, and 1 ml of ethanol were heated under reflux for 3 hr. After addition of 10 ml of ethanol, the mixture was left aside overnight. Water (20 ml) was added and the mixture was extracted five times with an equal volume of benzene. The collected benzene extracts were dried and evaporated to an oily residue. Ethanol (15 ml) was added and hydrogen chloride introduced for few minutes. The solution was again evaporated and to the oily residue 10 ml of *n*-hexane was added. Upon standing on ice the dihydrochloride salt crystallized to yield 0.8 g (77%), mp 253–254°.

Anal. Calcd for $C_{12}H_{14}Cl_2N_4$: C, 50.51; H, 4.95; N, 19.64. Found: C, 50.28; H, 4.78; N, 19.52.

The free base, which can be obtained from the salt, appears to be sensitive to oxidation and upon attempted crystallization or after standing on air decomposes slowly.

4,5-Dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII, R = R_1 = H).—A mixture of the above free base (I, R = H, R_1 = $NHNH_2$, 0.53 g) and 2 ml of diethoxymethyl acetate was heated under reflux for 5 min and cooled, and the reaction mixture was treated with 2 ml of ethanol. The crude product was separated, washed with ethanol, and crystallized from 0.5 ml of diethoxymethyl acetate to give 0.41 g (74%) of the pure product: mp 220–222°; nmr ($CDCl_3$), τ 2.22 (multiplet, H_9), 2.58 (multiplet, H_1, H_6, H_7, H_8, and H_{10}), 6.73 (multiplet, 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{12}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.46; H, 4.77; N, 25.05.

10-Amino-4,5-dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII R = NH_2, R_1 = H).—A hot solution of 100 mg of VII (R = N_3, R_1 = H) in 10 ml of ethanol was treated with hydrogen sulfide for 15 min. Purification of the separated product was performed from N,N-dimethylformamide and afforded 63 mg of the pure product, mp >320°.

Anal. Calcd for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52. Found: C, 65.72; H, 4.51; N, 29.28.

4,5-Dihydrobenzo[*f*]tetrazolo[5,1-*a*]phthalazine (VIII). A.—Compound I (0.54 g, R = H, R_1 = Cl), 0.35 g of sodium azide, and 4 ml of 1,3-propylene glycol were heated under reflux for 2 hr. Upon cooling, 10 ml of water was added and the mixture was left on ice overnight. The separated product was crystallized from N,N-dimethylformamide to give 0.4 g (71%) of the product with mp 236–238°. The ir spectrum exhibited no bands characteristic for the presence of azide group. Nmr ($CDCl_3$) peaks were at τ 2.55 (multiplet, H_6, H_7, H_8, H_9), 2.75 (singlet, H_{10}), 6.90 (singlet, 4 H, $-CH_2CH_2-$).

B.—A solution of 0.3 g of I (R = H, R_1 = $NHNH_2$) in 3 ml of 50% acetic acid was cooled on ice and treated dropwise with a solution of 0.12 g of sodium nitrite in 1 ml of water. The separated product (0.21 g) was crystallized from N,N-dimethylformamide. Melting point and mixture melting point with the compound prepared as under A were undepressed.

Registry No.—I (R = R_1 = Cl), 16719-59-8; I (R = NH_2; R_1 = Cl), 16749-03-4; I (R = $NHNH_2$; R_1 = Cl), 16719-60-1; I (R = NHN = CHC_6H_5; R_1 = Cl), 16719-61-2; I (R = $C_6H_5NHCSNHNH$; R_1 = Cl), 16719-62-3; I (R = OCH_3; R_1 = Cl), 16719-63-4; I (R = OC_2H_5; R_1 = Cl), 16753-63-2; I (R = OCH_3; R_1 = H), 16719-64-5; I (R = OC_2H_5; R_1 = H), 16719-65-6; I (R = R_1 = $H\cdot H_2SO_4$), 16753-64-3; I (R = SH; R_1 = Cl), 16719-66-7; I (R = SCH_3; R_1 = Cl), 16719-67-8; I (R = H; R_1 = Cl), 16719-68-9; I (R = H; R_1 = $NHNH_2$), 16719-69-0; II (R = Cl), 16719-70-3; II (R = H), 16719-71-4; II (R = $NHNH_2$), 16719-72-5; II (R = *p*-$Me_2NC_6H_5CH$=NNH), 16719-73-6; II (R = C_6H_5-NHCSNHNH), 16719-74-7; III (R = SH), 16719-75-8; III (R = H), 16719-76-9; IV (R = H; R_1 = Cl), 16719-94-1; IV (R = R_1 = H), 16719-77-0; IV (R = H; R_1 = $NHNH_2$), 16719-78-1; V, 16719-79-2; VI (R = Cl), 16719-80-5; VI (R = NH_2), 16719-81-6; VI (R = $NHNH_2$), 16719-82-7; VI (R = N_3), 16719-83-8; VI (R = H), 16719-84-9; VII (R = Cl; R_1 = H), 16719-85-0; VII (R = N_3; R_1 = NH_2), 16719-86-1; VII (R = R_1 = NH_2), 16719-87-2; VII (R = $NHNH_2$; R_1 = H), 16719-88-3; VII (E = N_3; R_1 = H), 16719-89-4; VII (R = R_1 = H), 16719-90-7; VII (R = NH_2; R_1 = H), 16719-91-8; VIII, 16719-92-9; IV (R = SH; R_1 = Cl), 16719-93-0; IV (R = SMe; R_1 = Cl), 16753-65-4.

Acknowledgment.—We wish to thank Mr. K. L. Loening, Director of Nomenclature, Chemical Abstracts Service, for valuable suggestions in connection with the nomenclature of new systems, and to Dr. S. Murakami, JEOL, Paris, for some recording of nmr spectra.

The 1,2-Dithiolium Cation. VII. Methylation of Thiothiophthene No-Bond Resonance Compounds and Their Nitrogen Isosteres[1]

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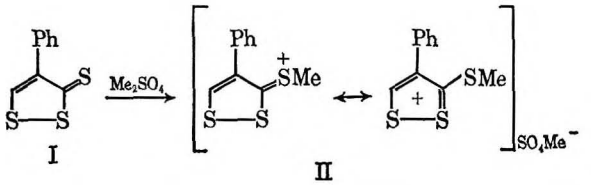
Received January 11, 1968

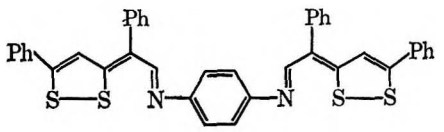
The vinylogous relationship between thiothiophthene no-bond resonance compounds and 1,2-dithiole-3-thiones ("trithiones") is shown by methylation. The dithiolethione I gives the methylthiodithiolium salt II, and thiothiophthenes III and IV give methylthiovinyldithiolium salts V and VI. The latter react with aniline to give anils that have been obtained by two other syntheses and are the first known thiothiophthene isosteres in which sulfur is replaced by a fifth group element. Like thiothiophthenes, anils can also be methylated; both reactions are discussed in terms of the no-bond resonance hypothesis. Electronic absorption characteristics are examined.

Thiothiophthene "no-bond resonance" compounds are vinylogs of the "trithiones" (1,2-dithiole-3-thiones);[2] this relationship is a source of useful insights. Thus, the methylation of trithiones such as I to give "trithionium salts" (3-methylthio-1,2-dithiolium salts) (II) is paralleled by the smooth addition of methyl iodide, under mild conditions, to thiothiophthenes III and IV. The resulting methiodides react readily with primary aromatic amines, eliminating methanethiol to give anils. Since the latter are also obtainable from the carbonyl compounds VIII and IX, they must have structures X and XI, and the thiothiophthene methiodides must have the corresponding structures V and VI. They are vinylogs of the trithionium salts and, like them, can doubtless be considered as hybrid 1,2-dithiolium derivatives[3] in which the positive charge may be withdrawn from the ring by the extracyclic sulfur atom (Va, VIa).



I II

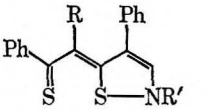
The condensation reaction of VIII and IX with aromatic amines, a new example of carbonyl reactivity in aldehydic compounds in this series, was used to prepare the series of weakly basic anils Xa and XIa; VIII condenses twice with *p*-phenylenediamine to give XIV. As might be expected, ketones in the series[4] are inert. The same anils are obtained from the methiodides V and VI in the form of hydriodides that are converted into the parent base by water or alkali. Alkyl and aralkyl amines react with V (but not with VIII) to give XIIa, b, and c.



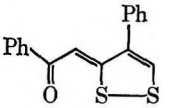
XIV

In a third synthesis, treatment of the thiothiophthene III with sulfur dichloride in benzene gave an insoluble product that reacted with aniline to give a modest yield of anil Xa. This synthesis also parallels the chemistry of 1,2-dithiole-3-thiones, which are converted by sulfur chloride into 3-chloro-1,2-dithiolium salts, highly reactive substrates with amines and other nucleophiles.[3] However, the structure of the thiothiophthene–sulfur chloride reaction product remains obscure at present (see Scheme I).

The question of S–N bonding, *i.e.*, contributions from structure XV, naturally arises from the fact that these imines are nitrogen isosteres of the thiothiophthene no-bond resonance compounds (III, IV), the first known isosteres in which sulfur is replaced by a fifth group element. Bond-length determination by X-ray crystallography is of course needed to determine whether the compounds are best considered as dithioles (X and XI), isothiazoles (XV), or a hybrid of both. The corresponding questions have already been answered for the oxygen[5] and selenium[6] isosteres.



XV



XVI

Like thiothiophthenes III and IV, the anil Xa readily adds methyl iodide; the product must be an S-methyl derivative, since it is different from the N-methyl derivative (VII) obtained unequivocally from V and N-methylaniline. A simple cyclic sulfonium structure seems unlikely, inasmuch as the carbonyl compound VIII is inert to methyl iodide. Evidently the nitrogen atom, though not the site of methylation, is essential to the reaction. (*Cf.* III, where the terminal sulfur atom which is not the site of methylation is essential to the reaction, and carbonyl compound XVI is inert under the same conditions.) Pending investigation by X-ray crystallography, the isothiazolium structure XIII seems probable. On the assumption that the anil has the essentially "normal" dithiole structure Xa, its S-methylation is accompanied by S–S bond cleavage and S–N bond formation, again recalling thiothiophthene III, in which Hordvik, Sletten, and Sletten have recently found that the sulfur atoms are not equally spaced.[7] Both S–S bonds are abnormally weak, but methylation to V *breaks the stronger bond* and

(1) Paper VI: E. Klingsberg, *J. Org. Chem.*, **31**, 3489 (1966).

(2) E. Klingsberg, in "Organosulfur Chemistry," M. J. Janssen, Ed., John Wiley and Sons, Inc., New York, N. Y., 1967, p 173.

(3) H. Prinzbach and E. Futterer, in "Advances in Heterocyclic Chemistry," Vol. 7, A. R. Katritzky and A. J. Boulton, Ed., Academic Press Inc., New York, N. Y., 1966, pp 39 ff.

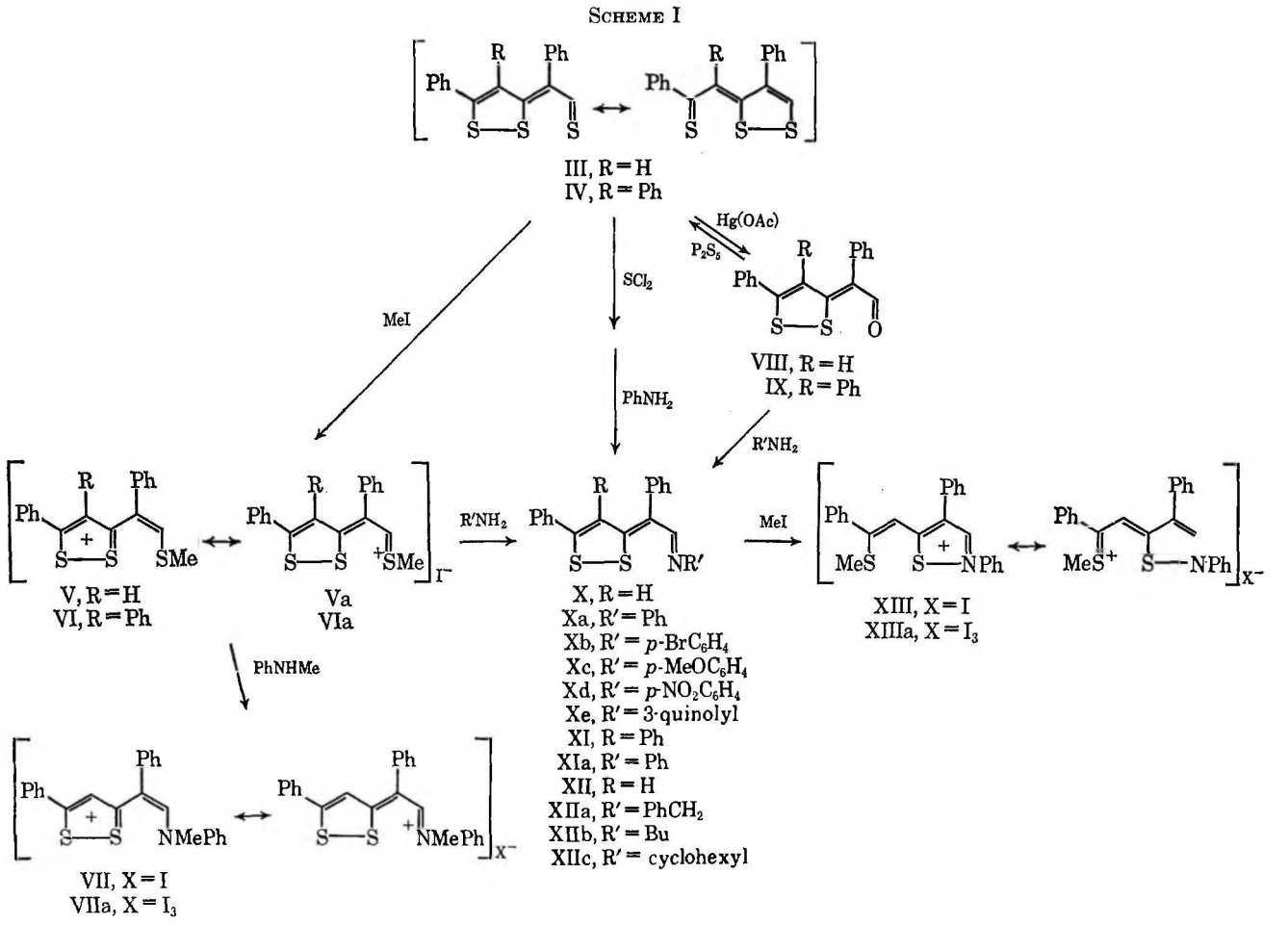
(4) E. Klingsberg, *J. Amer. Chem. Soc.*, **85**, 3244 (1963).

(5) M. Mammi, R. Bardi, G. Traverso, and S. Bezzi, *Nature*, **192**, 1282, (1961).

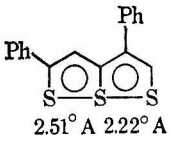
(6) J. H. van den Hende and E. Klingsberg, *J. Amer. Chem. Soc.*, **88**, 5045 (1966).

(7) A. Hordvik, E. Sletten, and J. Sletten, *Acta Chem. Scand.*, **20**, 2001 (1966).

SCHEME I



normalizes the weaker. (In the absence of evidence to the contrary, the S–S bond length in V is assumed normal.)



S–S bond lengths in thiothiophthene III[7]

In the delicately poised thiothiophthene system, the sulfur bonding, which has lost its symmetry under the influence of the unsymmetrical diphenyl substitution, does not govern the chemistry of III but instead accommodates itself to other influences, perhaps steric. The least hindered sulfur atom reacts with mercuric acetate[4] or methyl iodide, despite having a lower degree of thiocarbonyl character than the other terminal sulfur. The same flexibility seems to characterize the N isostere; here perhaps the course of methylation is governed by the greater nucleophilicity of sulfur as against nitrogen, with bonding adjustments corresponding to those observed in the thiothiophthene methylation.

In their electronic absorption spectra, III and V (Figure 1) show the characteristics to be expected of vinylogs of I and II (Figure 2). The more extended systems absorb at higher wavelength, and S-methylation causes a marked hypsochromic shift. S-Methylation of Xa causes a similar hypsochromic shift, whereas N-methylation has almost no effect on the first peak, recalling N-methylation of a π deficient system such as pyridine[8,9] (Figure 3).

Experimental Section

Melting points are corrected. Absorption spectra were determined in alcohol at a concentration of 10 mg/l.

3-(2-Methylthio-1-phenylvinyl)-5-phenyl-1,2-dithiolium Iodide (V).—Stirring and refluxing of a solution of 8.0 g (26 mmol) of *meri*-bicyclo-3,5-epidithio-1,4-diphenyl-2,4-pentadienethione-1 (III)[4] in 120 ml of nitromethane were continued overnight after addition of 80 ml of methyl iodide through the condenser. Filtration, followed by washing with nitromethane or benzene, gave 10.4 g (90%) of brick-red solid, mp 190–191° dec. Nitromethane gave purple crystals, mp 193–194° dec.

Anal. Calcd for $C_{18}H_{15}IS_3$: C, 47.6; H, 3.3; I, 28.0; S, 21.1. Found: C, 47.9; H, 3.4; I, 28.3; S, 21.0.

3-(2-Methylthio-1-phenylvinyl)-4,5-diphenyl-1,2-dithiolium Iodide (VI).—Stirring and refluxing of a solution of 0.60 g (1.5 mmol) of *meri*-bicyclo-3,5-epidithio-1,2,4-triphenyl-2,4-pentadienethione-1 (IV)[4] in 20 ml of nitromethane were continued for 1.5 hr after addition of 5.0 ml of methyl iodide through the condenser. Filtration gave 0.76 g (93%) of an orange-brown solid, mp 188–189°. Acetic acid gave orange crystals, mp 189–191°.

Anal. Calcd for $C_{24}H_{19}IS_3$: C, 54.4; H, 3.6; S, 18.1. Found: C, 54.5; H, 3.6; S, 17.8.

3,5-Epidithio-2,4,5-triphenyl-2,4-pentadienal (IX).—Stirring and refluxing of a solution of 1.50 g (3.9 mmol) of IV in 150 ml of acetic acid were continued for 5 min after addition of 1.50 g,

(8) A. Albert, "Heterocyclic Chemistry," Athlone Press, London, 1959, p 303.

(9) E. Shaw in "Pyridine and Its Derivatives," part 2, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p 32.

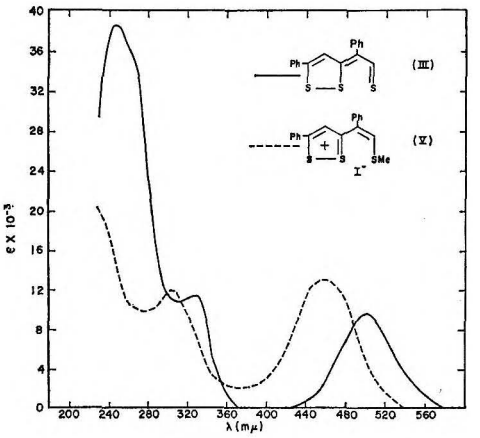


Figure 1.—Electronic absorption spectra of thiothiophthene (III) and its methyl derivative (V).

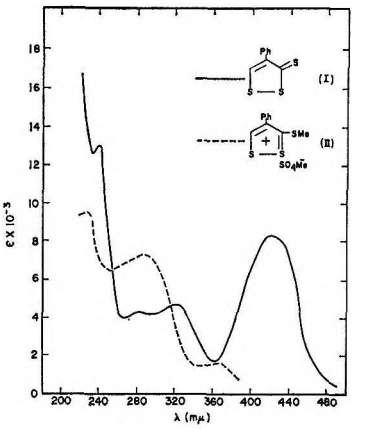


Figure 2.—Electronic absorption spectra of 4-phenyl-1,2-dithiole-3-thione (I) and its methyl derivative (II).

(4.7 mmol) of mercuric acetate.[10] Filtration of the black mixture, followed by cooling and dilution of the orange filtrate, gave 1.25 g (87%) of tan solid, mp 213–215°. Recrystallization from ethanol gave orange crystals, mp 214.5–215.5°. There was a marked melting point depression on admixture with the isomeric 3,5-epidithio-1,2,4-triphenyl-2,4-pentadieneone-1.[4]

Anal. Calcd for $C_{23}H_{16}OS_2$: C, 74.2; H, 4.3; S, 17.2. Found: C, 73.8; H, 4.5; S, 17.2.

Reaction with phosphorus pentasulfide in refluxing toluene rapidly regenerated IV.

3,5-Epidithio-2,5-diphenyl-2,4-pentadienylideneaniline (Xa).—Aniline (1000 ml, 1.02 g, 11.0 mmol) and 2.40 g (5.30 mmol) of V were stirred at reflux for 5 min in 25 ml of acetic acid, cooled, and filtered. The product was digested in warm water, filtered, and dried, giving a quantitative yield (1.96 g) of orange product, mp 199–200°. Crystallization from toluene, nitromethane, or methylcyclohexane did not affect the melting point.

Anal. Calcd for $C_{23}H_{17}NS_2$: C, 74.4; H, 4.6; N, 3.8; S, 17.3. Found: C, 74.4; H, 4.4; N, 3.6; S, 17.3.

Preparation from III.—A solution of 0.62 g (2.0 mmol) of III in 35 ml of warm benzene was treated dropwise with 0.25 ml (0.41 g, 3.9 mmol) of sulfur dichloride. The orange precipitate was filtered and washed with a little benzene or ether to yield 0.75 g. This was warmed on the steam bath for 5 min in 6–7 ml of aniline, cooled, filtered, and washed with a little methanol to yield 0.25 g (33%) of Xa, mp 194–196°. Recrystallization from methylcyclohexane raised the melting point to 198–199°, unaffected by admixture with specimens prepared from V or VIII. The identity was confirmed by elemental analysis.

The same compound was obtained by warming 10.0 g (0.0338 mol) of 3,5-epidithio-2,5-diphenyl-2,4-pentadienal (VIII)[4] and 3.50 ml (3.58 g, 0.0384 mol) of aniline in 50 ml of acetic acid. After 10 min the solution became a slurry, which was kept on the steam bath for 2 hr, cooled, and filtered, yielding 11.8 g (93%) of product, mp 198–200°.

The following analogs were prepared from VIII in comparable yields.

p-Bromoaniline gave Xb, red, mp 196–197° (methylcyclohexane).

Anal. Calcd for $C_{23}H_{16}BrNS_2$: C, 61.3; H, 3.6; N, 3.1; S, 14.3. Found: C, 61.3; H, 3.7; N, 3.3; S, 14.3.

p-Anisidine gave Xc, orange, mp 160–161° (methylcyclohexane or hexane).

Anal. Calcd for $C_{24}H_{19}ONS_2$: C, 72.0; H, 4.7; N, 3.5; S, 16.0. Found: C, 72.3; H, 4.6; N, 3.4; S, 15.9.

p-Nitroaniline gave Xd, purple, mp 216–217° dec (toluene). At a concentration of 10 mg/l. of alcohol, this showed uv absorptions at λ_{max} 510 (ϵ 27,800) and 315 (18,000).

Anal. Calcd for $C_{23}H_{16}O_2N_2S_2$: C, 66.4; H, 3.8; N, 6.7; S, 15.4. Found: C, 66.6; H, 3.6; N, 6.5; S, 15.3.

3-Aminoquinoline gave Xe, red, mp 227–228° dec (toluene).

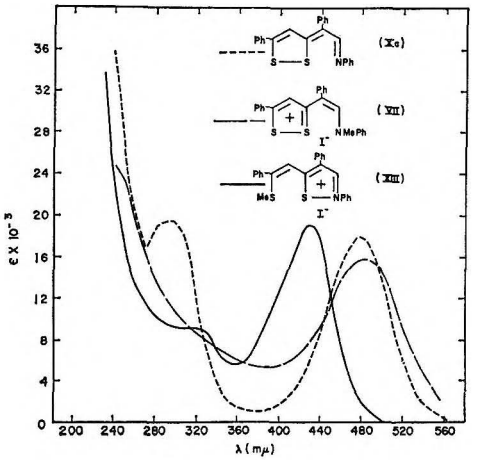


Figure 3.—Electronic absorption spectra of anil Xa, its N-methyl derivative VII, and its S-methyl derivative XIII.

Anal. Calcd for $C_{28}H_{18}N_2S_2$: C, 74.0; H, 4.3; S, 15.0. Found: C, 74.0; H, 4.3; S, 15.0.

p-Phenylenediamine gave XIV, purple, mp 298–299° dec (pyridine).

Anal. Calcd for $C_{40}H_{28}N_2S_4$: C, 72.3; H, 4.2; N, 4.2; S, 19.3. Found: C, 72.1; H, 4.1; N, 4.2; S, 18.9.

3,5-Epidithio-2,4,5-triphenyl-2,4-pentadienylideneaniline (XIa).—A mixture of 0.70 g (1.3 mmol) of VI and 0.30 ml (0.28 g, 3.0 mmol) of aniline in 10 ml of acetic acid was stirred at reflux for 10 min, cooled, and filtered, yielding 0.62 g (82%) of brick-red iodide, mp 210° dec, which was quantitatively converted into the orange base, mp 180–181°, by treatment with alcoholic alkali. Nitromethane or methylcyclohexane gave bright orange crystals of unchanged melting point.

Anal. Calcd for $C_{29}H_{21}NS_2$: C, 77.9; H, 4.7; N, 3.1; S, 14.3. Found: C, 78.0; H, 4.7; N, 3.1; S, 14.0.

The same product was obtained from the corresponding carbonyl compound (IX) and aniline in refluxing acetic acid.

3,5-Epidithio-2,5-diphenyl-2,4-pentadienylidenebenzylamine (XIIa).—A mixture of 0.30 ml (0.29 g, 2.7 mmol) of benzylamine and 1.05 g (2.3 mmol) of V in 5 ml of acetic acid was stirred at reflux for 5 min, cooled, and filtered to yield 1.13 g of the brown-orange iodide of the product, mp 185–187° dec. This was converted into the base by stirring in about 40 ml of ethanol with freshly precipitated silver oxide (from 1.0 g of silver nitrate), followed by evaporation to dryness, extraction of the solids with hot pyridine, filtration, and dilution, yielding 0.63 g (71%) of a yellow solid, mp 208–212°. Methylcyclohexane gave orange-yellow crystals, mp 213–213.5°.

Anal. Calcd for $C_{24}H_{19}NS_2$: C, 74.8; H, 4.9; S, 16.6. Found: C, 74.7; H, 4.9; S, 16.8.

Under similar conditions *n*-butylamine gave a 70% yield of hydriodide of XIIb, which was converted into the bright yellow base by treatment with pyridine and crystallized from alcohol or hexane, mp 122.5–123.5°.

(10) Refluxing with mercuric acetate in acetic acid is a useful technique for desulfurization of thiothiophthenes like IV that resist the usual room temperature conditions. By this technique meribicyclo-2-cyano-3,5-epidithio-1,5-diphenyl-2,4-pentadienethione-1 is converted into 2-cyano-3,5-epidithio-1,5-diphenyl-2,4-pentadienone-1 in good yield.[4] Here the cyano group directs the attack to the nearer of the two sterically equivalent thiocarbonyl groups.

Anal. Calcd for $C_{21}H_{21}NS_2$: C, 71.8; H, 6.0; N, 4.0; S, 18.2. Found: C, 71.8; H, 5.8; N, 3.9; S, 18.2.

Cyclohexylamine gave XIIc, orange, mp 160–161° (methylcyclohexane).

Anal. Calcd for $C_{23}H_{23}NS_2$: C, 73.2; H, 6.1; N, 3.7; S, 17.0. Found: C, 73.1; H, 5.9; N, 3.6; S, 16.9.

Methylation of Xa to XIII.—Methyl iodide (5 ml) was added through the condenser to a stirred refluxing mixture of 1.35 g (3.64 mmol) of Xa in 20 ml of nitromethane. After 1 hr, the solution was cooled, diluted with a little ether, and filtered, yielding 1.85 g (99%) of orange product. In an ordinary capillary melting point determination, it lost methyl iodide around 160° and then gave the melting point (199–200°) of Xa. A melting point of 166° could be observed by insertion into the bath at 160°, but this seems less reproducible. Crystallization occurred readily from ethanol or methanol. Aniline or methylaniline in refluxing acetic acid reversed the methylation reaction, regenerating Xa.

Anal. Calcd for $C_{24}H_{20}INS_2$: C, 56.1; H, 3.9; I, 24.8; N, 2.7; S, 12.5. Found: C, 56.3; H, 3.7; I, 24.7; N, 2.9; S, 12.4.

This combined rapidly with 1 mol of iodine in methanol solution to give the *triiodide* (XIIIa), mp 150–150.5°, which separated as golden crystals from *n*-propyl alcohol.

Anal. Calcd for $C_{24}H_{20}I_3NS_2$: C, 37.6; H, 2.6; I, 49.7; N, 1.8. Found: C, 37.8; H, 2.6; I, 49.6; N, 1.8.

3-(2-N-Methylanilino-1-phenylvinyl)-5-phenyl-1,2-dithiolium Iodide (VII).—A mixture of 2.27 g (5.0 mmol) of 3-(2-methylthio-1-phenylvinyl)-5-phenyl-1,2-dithiolium iodide (V) and 0.65 ml (0.64 g, 6.0 mmol) of N-methylaniline in 50 ml of methanol was stirred at reflux for 5 hr, cooled, diluted with ether, and chilled to −78°, yielding 1.24 g (49%) of greenish product, mp 185–187°. *n*-Propyl alcohol gave dark brown crystals, mp 196.5–197°, showing marked melting-point depression on admixture with XIII.

Anal. Calcd for $C_{24}H_{20}INS_2$: C, 56.1; H, 3.9; I, 24.8; N, 2.7; S, 12.5. Found: C, 56.1; H, 3.8; I, 24.4; N, 2.7; S, 12.4.

When the reaction was continued somewhat longer, the product was obtained in lower yield together with VIII, which separated on cooling before dilution with ether.

The corresponding triiodide VIIa gave bronze crystals, mp 149–150° dec, from *n*-propyl alcohol, showing a marked melting point depression on admixture with XIIIa.

Anal. Calcd for $C_{24}H_{20}I_3NS_2$: C, 37.6; H, 2.6; I, 49.7; N, 1.8; S, 8.3. Found: C, 37.6; H, 2.6; I, 50.1; N, 1.7; S, 8.5

At a concentration of 10 mg/l. in ethanol containing a little Cellosolve, VII showed an absorption band at λ_{max} 480 (ϵ 16,100) (Figure 3). Absorption in the same region is reported in a recent brief communication on salts of similar type.[11]

Registry No.—I, 3354-37-8; II, 16717-54-7; III, 16717-55-8; V, 16717-56-9; VI, 16717-57-0; VII, 16717-58-1; VIIa, 16717-59-2; IX, 16717-60-5; Xa, 16753-66-5; Xb, 16753-67-6; Xc, 16753-68-7; Xd, 16753-69-8; Xe, 16753-70-1; XIa, 16753-71-2; XIIa, 16753-72-3; XIIb, 16753-73-4; XIIc, 16753-74-5; XIII, 16717-61-6; XIIIa, 16717-62-7; XIV, 16717-63-8.

Acknowledgment.—The author is greatly indebted to Mrs. Maryellen Kish for technical assistance, to J. J. Kobliska and his staff for microanalyses, and to Miss Vera Jordan for absorption spectra.

(11) R. Meyer and H. Hartmann, *Z. Chem.*, **6**, 312 (1966).

Preparation of Silylalkanethiols

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Received January 23, 1968

Silylalkyl ethanethiolates with chloro, acetoxy, hydroxy, and alkoxy substituents attached to silicon were prepared by the reaction of ethanethiolic acid with corresponding alkenylsilanes. The effects of the substituents on silicon on the reactivity of vinylsilanes toward thiols or ethanethiolic acid were found to be additive. Ethanethiolic acid reacts with most vinylsilanes to give two adducts, $\equiv SiCH_2CH_2SAc$ (major) and $\equiv SiCHCH_3SAc$ (minor). Silylalkanethiols were prepared by methanolysis or ammonolysis of some of these esters. Several new types of silylalkanethiols prepared in this manner are $HN(SiMe_2CH_2CH_2SH)_2$ and $Me_2XSiCH_2CH_2SH$ where X is Cl-, MeO-, HO-, and AcO-. The log of the relative rate constants (the rate constant for hexene-1 ÷ 1) for addition of thiols and also of silicon hydrides was found to show a linear correlation with the sum of substituent constants C for the groups R, R′, and R″ in compounds of the formula $RR'R''SiCH{=}CH_2$.

Ethanethiolic acid adds to the double bond of olefins by a free-radical process with great efficiency. Olefins substituted in nearly all possible ways form corresponding alkyl ethanethiolates in good yields. A few examples of silicon-containing olefins of the types $R_3SiC_nH_{2n-1}$ and $O(SiR_2C_nH_{2n-1})_2$ have been used in which R was either an alkyl or phenyl group.[1-6]

We have found that alkenylsilanes with chloro, alkoxy, and acetoxy substituents on silicon can be converted into corresponding silylalkyl ethanethiolates in excellent yield. We observed no interference from any of these substituents. Aminosilylalkyl ethanethiolates could not be prepared in the same manner, however, because ethanethiolic acid reacts rapidly with amino groups on silicon to form thionoacetoxysilanes.[7]

Ethanethiolic acid reacts with vinylsilanes to form two isomeric adducts (eq 1). Only terminal adducts to

$$\equiv SiCH{=}CH_2 + AcSH \longrightarrow \underset{\text{major}}{\equiv SiCH_2CH_2SAc} + \underset{\text{minor}}{\equiv SiCH(CH_3)SAc} \quad (1)$$

vinylsilanes had been reported by workers previous to Wetterlin[8] who was the first to report that two adducts analogous to the above form during the reaction of vinylsilanes with some thiols.

Silylalkyl ethanethiolates were converted into silylalkanethiols by methanolysis or ammonolysis. Methanolyses were run in an excess of methanol containing

(1) P. V. Bonsignore, C. S. Marvel, and S. Bonerjee, *J. Org. Chem.*, **25**, 235 (1960).
(2) P. W. Gawrys and H. W. Post, *ibid.*, **27**, 634 (1962).
(3) W. Stamm, *ibid.*, **28**, 3264 (1963).
(4) C. S. Marvel and H. N. Cripps, *J. Polym. Sci.*, **9**, 53 (1953).
(5) V. F. Mironov and N. A. Pogonkina, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **85**, (1959).
(6) A. D. Petrov, V. F. Mironov, and V. G. Glukhontsev, *J. Gen. Chem. USSR*, **27**, 1535 (1957).
(7) G. A. Gornowicz and J. W. Ryan, *J. Org. Chem.*, **31**, 3439 (1966).
(8) K. Wetterlin, *Acta Chem. Scand.*, **18**, 899 (1964).

a catalytic amount of sodium methoxide. Bases were found to be more effective than acids as catalysts. A large excess of methanol was needed to prevent the formation of considerable amounts of by-products. These appeared to be condensation products of the esters.

A variety of silylalkanethiols and related compounds can be prepared by ammonolysis of silylalkyl ethanethiolates. Ammonolysis of 2-dimethylchlorosilylethyl ethanethiolate gave a somewhat indefinite product (I) believed to have formed by loss of NH_3 from *sym*-bis(2-mercaptoethyl)tetramethyldisilazane (eq 2). Nmr analysis of the product indicated the

$$2Me_2ClSiCH_2CH_2S\overset{O}{\overset{\|}{C}}CH_3 + \text{excess } NH_3 \xrightarrow{-33^\circ} HN(SiMe_2CH_2CH_2SH)_2 + 2NH_4Cl + 2CH_3\overset{O}{\overset{\|}{C}}NH_2 \quad (2)$$

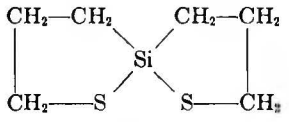
ratio of $-Me_2SiS-$ to $-Me_2SiHN-$ to be about one, corresponding approximately to a compound such as $HN(SiMe_2CH_2CH_2SSiMe_2CH_2CH_2SH)_2$ (I).

Product I was used to prepare silylalkanethiols. Compound I with glacial acetic acid formed 2-dimethylacetoxysilylethanethiol and with anhydrous hydrogen chloride I formed 2-dimethylchlorosilylethanethiol. Hydrolysis of an equal molar mixture of I and 2-dimethylacetoxysilylethanethiol gave 2-dimethylhydroxysilylethanethiol. Compound I decomposed at approximately 240° to produce a 77% yield of 1,1,3,3-tetramethyl-1,3-disila-2,4-dithiacyclohexane ($Me_2SiSSiMe_2CH_2CH_2S$). At 175° I gave a polymer having the structure $+SiMe_2CH_2CH_2S+_x$ and a small amount of the above cyclic compound.

Ammonolysis of bis(3-thiolacetoxypropyl)dichlorosilane gave the unique 1,6-dithia-5-silaspiro[4.4]-nonane (eq 3).

$$Cl_2Si(CH_2CH_2CH_2SAc)_2 \xrightarrow{NH_3} +HNSi(CH_2CH_2CH_2SH)_2+_x + 2AcNH_2 \quad (3)$$

$$\xrightarrow{\Delta}$$



The reaction of vinylsilanes with ethanethiolic acid was investigated further to determine the influence of structure upon the reactivity of vinylsilanes. The results of this study with ethanethiolic acid were then compared with similar results using 1-butanethiol and benzenethiol. The reactivities of compounds of the formula $RR'R''SiCH=CH_2$ relative to the reactivity of hexene-1 were determined by permitting each of the vinylsilanes to compete with hexene-1 for an insufficient amount of the thiols. The results of these competitive reactions are shown in Table I.

The reactivity of thiols with vinylsilanes of the formula $RR'R''SiCH=CH_2$ is not strongly influenced by the structures of R, R', and R''. The most reactive vinylsilane was $Me_3SiCH=CH_2$; the least reactive was $Cl_3SiCH=CH_2$. The difference in reactivity between these was only slightly greater than one order of magnitude. A regular change in the log of the relative rate constant in each series, $Me_nX_{3-n}SiCH=CH_2$ was observed which suggested that a linear free energy correlation might be made.

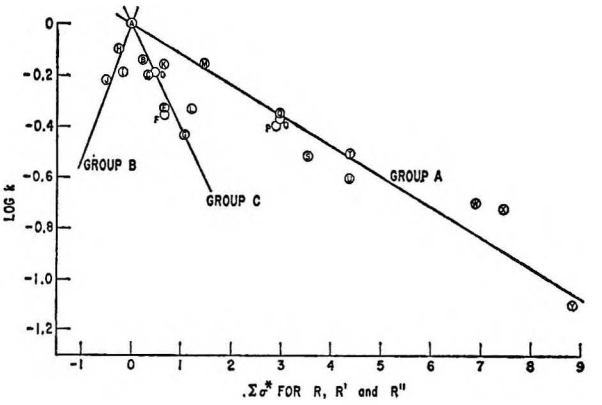


Figure 1.—Log k *vs.* $\Sigma\sigma^*$ for $RR'R''SiCH=CH_2 + AcSH \rightarrow RR'R''SiCH_2CH_2CH_2SAc$; rate k relative to $k_{hexene} = 1$; lettered points refer to compounds shown in Table I.

TABLE I

REACTIVITIES OF $RR'R''SiCH=CH_2$ RELATIVE TO *n*-$BuCH=CH_2$ = 1 TOWARD ETHANETHIOLIC ACID, BENZENETHIOL, AND *n*-BUTANETHIOL

	RR'R''	AcSH k/k_o	PhSH k/k_o	BuSH k/k_o
A.	Me_3	1.00	6.8	4.5
B.	$PhCH_2Me_2$	0.73	5.4	
C.	$(F_3CCH_2CH_2)Me_2$	0.63	2.2	
D.	$(PhCH_2)_2Me$	0.64		
E.	$(PhCH_2)_3$	0.47		
F.	$(F_3CCH_2CH_2)_2Me$	0.44		
G.	$ClCH_2Me_2$	0.37		
H.	$Me_3SiCH_2Me_2$	0.80	6.2	
I.	i-$PrMe_2$	0.64	4.7	
J.	$(Me_3SiCH_2)_2Me$	0.60		
K.	$PhMe_2$	0.69	4.0	
L.	Ph_2Me	0.47		
M.	$MeOMe_2$	0.69	3.9	2.8
N.	Me_3SiOMe_2	0.59	3.1	2.7
O.	$(EtO)_2Me$	0.44	2.5	2.6
P.	$(MeO)_2Me$	0.40	2.2	1.8
Q.	$ClMe_2$	0.45		
R.	$(Me_3SiO)_2Me$	0.36	2.4	1.8
S.	PhClMe	0.30		
T.	$(EtO)_3$	0.31		
U.	$(MeO)_3$	0.25	1.4	1.3
V.	$(Me_3SiO)_3$	0.21	1.4	1.5
W.	Cl_2Me	0.20		
X.	$PhCl_2$	0.19		
Y.	Cl_3	0.08		

Figure 1 shows the results of an attempt to correlate the data of Table I with a modified form of the Taft equation.[9]

$$\log k/k_{hexene} = \Sigma\sigma^*\rho^*$$

The correlation shown in Figure 1 is poor. However, vinylsilanes bearing at least one substituent having an unshared electron pair adjacent to silicon seem to correlate reasonably well (group A in Figure 1). Three vinylsilanes (H, I, and J of Table I) form a separate group. They may be displaying steric effects of branching in the isopropyl and trimethylsilylmethyl

(9) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp 556–675.

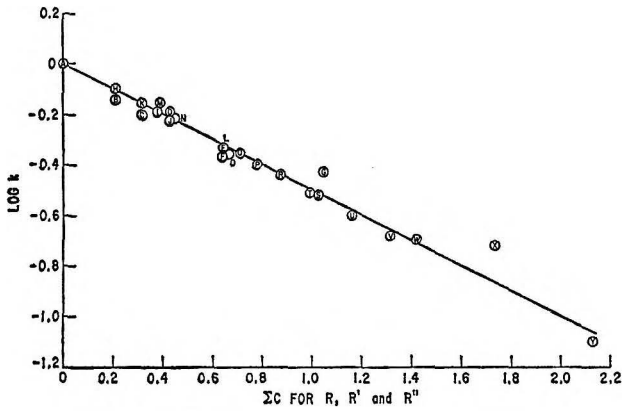


Figure 2.—Log k *vs.* ΣC for $RR'R''SiCH{=}CH_2$ + AcSH → $RR'R''SiCH_2CH_2SAC$; log $k = -0.517C$; lettered points refer to compounds shown in Table I.

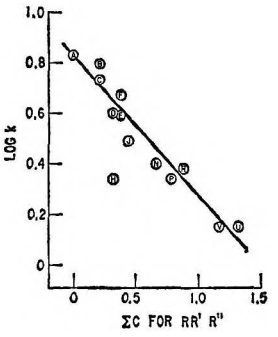


Figure 3.—Log k *vs.* ΣC for $RR'R''SiCH{=}CH_2$ + PhSH → $RR'R''SiCH_2CH_2SPh$; log $k = -0.57C$; lettered points refer to compounds shown in Table I.

groups. The rates of reaction for the other vinylsilanes correlate with a third line (group C). The compounds of group C have unbranched R groups with no unshared electrons adjacent to silicon. Two vinylsilanes (K and L) have phenyl and methyl substituents and seem to fall midway between groups A and C of Figure 1.

These observations suggested that the modified Taft equation fails to correlate the data of Table I because of steric effects and effects due to dative bonding of groups with unshared or π electrons adjacent to silicon. An empirical constant C for each R group on silicon was found which leads to a correlation with all the relative rate data of Table I. The Taft σ^* value was accepted as C for the methyl (0.0), 3,3,3-trifluoropropyl (0.32), benzyl (0.215), and chloromethyl (1.05) substituents. The value of C for other substituents was then calculated from the equation $\log k/k_{hexene} = -0.517\Sigma C$. By this method the following values were assigned: phenyl, 0.32; chlorine, 0.71; trimethylsiloxy, 0.44; methoxy, 0.39; ethoxy, 0.33; trimethylsilylmethyl, 0.21; and isopropyl, 0.38.

These new values for the substituents on silicon allowed us to make the surprisingly linear correlation shown in Figure 2. The values of C for the three groups on silicon are very nearly additive and the sum of the three values apparently represents the total of inductive, steric, and dative bonding effects of substituents on silicon for the addition of ethanethiolic acid to the vinyl group. The values of C obtained in this way were found to be equally useful to correlate

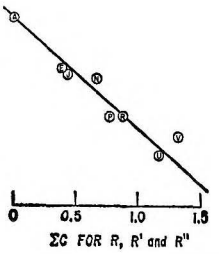


Figure 4.—Log k *vs.* ΣC for $RR'R''SiCH{=}CH_2$ + n-BuSH → $RR'R''SiCH_2CH_2S$-Bu-n; log $k = -0.46C$; lettered points refer to compounds shown in Table I.

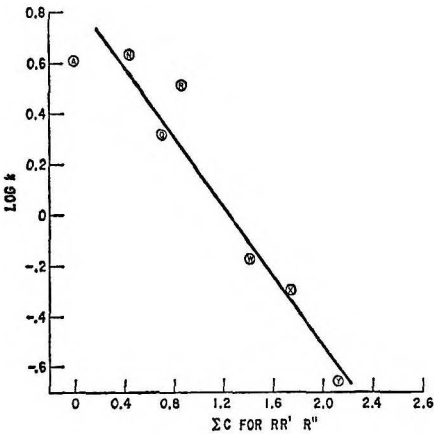


Figure 5.—Log kv *s.* ΣC for $RR'R''SiCH{=}CH_2$ + $MeHSiCl_2$ → $RR'R''SiCH_2CH_2SiMeCl_2$; log $k = 0.69C$; lettered points refer to compounds in Table I.

relative reactivities with benzenethiol and 1-butanethiol. These correlations are shown in Figures 3 and 4.

Data for the rates of reaction of a series of $RR'R''SiCH{=}CH_2$ compounds could be found only for one other reaction. These data were gathered by M. C. Musolf in this laboratory some time ago. He studied the relative rates of $RR'R''SiCH{=}CH_2$ relative to n-hexene-1 in the addition of $MeCl_2SiH$ catalyzed by chloroplatinic acid.[10] In his study an insufficient amount of $MeCl_2SiH$ and an equimolar mixture of $RR'R''SiCH{=}CH_2$ and hexene-1 reacted in the presence of a trace of chloroplatinic acid. The ratio of the two products $RR'R''SiC_2H_4SiCl_2Me$ and n-$HexMeSiCl_2$ was determined by vpc and the relative rates were calculated. The calculation was carried out by the method described in the Experimental Section for the thiols.

The platinum-catalyzed addition of silicon hydrides to aliphatic double bonds has been studied intensively. Reactions such as the above seem to be examples of homogeneous catalysis which give rise to platinum–olefin–silane complexes as highly reactive intermediates during the formation of adducts.[11] Although the mechanisms of free-radical addition of thiols and the platinum-catalyzed addition of silicon hydrides to vinylsilanes seem to be quite different, Musolf's kinetics correlate fairly well with the ΣC values. (See Figure 5.)

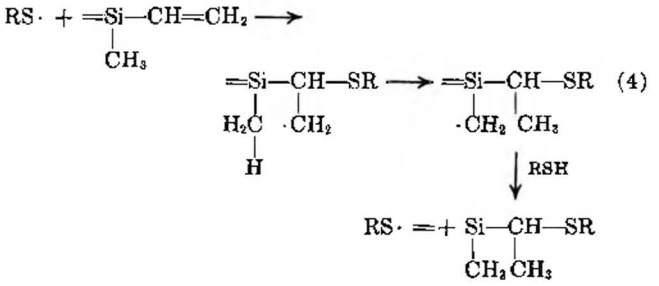
These correlations are sufficiently good and apply to such a variety of R groups on silicon that more examples of kinetic data or other kinds of data for series of silicon compounds would be valuable to assist in an

(10) M. C. Musolf, private communication,.

(11) (a) A. J. Chalk and J. F. Harrod, *J. Amer. Chem. Soc.*, **87**, 16 (1965). (b) J. W. Ryan and J. L. Speier, *ibid.*, **86**, 895 (1964).

estimation of how generally valid these C values may be.

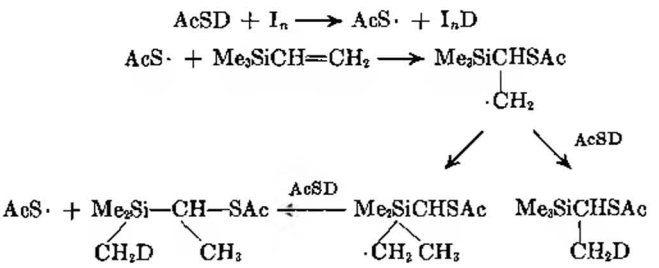
The free-radical addition of thiols to α-olefins leads only to terminal products.[12] Wetterlin[8] found only the terminal adduct from benzenethiol and trimethylvinylsilane when he used trimethylbenzylammonium hydroxide as a catalyst in the presence of hydroquinone. We found that vinyltrimethoxysilane and ethanethiolic acid did not react in the presence of hydroquinone and p-toluenesulfonic acid. All evidence seems to indicate that the vinylsilanes are unique in forming nonterminal adducts with thiols and that only those silanes with alkyl, alkoxy, or trimethylsiloxy groups on the silicon gave the nonterminal adduct. The suggestion arose that perhaps an unusual shift of hydrogen might be occurring in the intermediate radical (eq 4). This postulate was proved incorrect by



(4)

allowing ethanethiolic acid-*d* to react with trimethylvinylsilane (Scheme I). Nmr showed the nonterminal adduct to be $Me_3SiCH(CH_2D)SAc$. Therefore, the intermediate must be $Me_3SiCH(\dot{C}H_2)SAc$. The terminal adduct was the expected $Me_3SiCHDCH_2SAc$.

SCHEME I



The yield of nonterminal adduct is dependent on the substituents on silicon, see Table II. Replacing a methyl group of trimethylvinylsilane with a methoxy, ethoxy, or 3,3,3-trifluoropropyl group does not change the yield of nonterminal adduct significantly. However, a significant decrease in the yield of nonterminal adduct is observed when two methyl groups are replaced by these groups. Replacing only one methyl group with a chlorine atom also reduces the yield of nonterminal adduct significantly. Only a slight change was observed when all the methyl groups were replaced with trimethylsiloxy groups. No correlation between the yield of nonterminal adduct and the relative reactivity of the vinylsilane was observed.

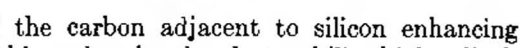
TABLE II

YIELD OF NONTERMINAL ADDUCT FROM THE REACTION OF ETHANETHIOLIC ACID WITH VINYLSILANES

Vinylsilane	% yield by glpc
Me_2Si-	10.0
$Me_2F_3CCH_2CH_2Si$-	10.3
Me_2MeOSi-	9.6
Me_2Me_3SiOSi-	9.5
$Me(Me_3SiO)_2Si$-	8.7
$(Me_3SiO)_3Si$-	7.6
$Me(F_3CCH_2CH_2)Si$-	5.3
$Me(EtO)_2Si$-	5.0
$(EtO)_3Si$-	5.4
$(MeO)_3Si$-	5.2
$Me(Me_2SiCH_2)_2Si$	5.2
Me_2ClSi-	1.3
$MeCl_2Si$-	1.1
Cl_3Si-	0.0

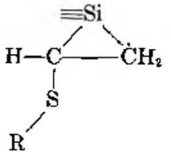
(12) W. A. Hewett, Doctoral Dissertation Series, Publ. No. 15134.

Wetterlin[8] proposed that the nonterminal adduct was formed because of $d\pi$–$p\pi$ bonding between the empty d orbitals of silicon and the π electrons of the double bond (eq 5). This effect should increase the electron

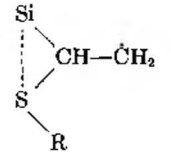


(5)

density of the carbon adjacent to silicon enhancing attack on this carbon by the electrophilic thiol radical. The $\equiv SiCH(SR)CH_2\cdot$ radical may be somewhat stabilized by neighboring group effects of silicon and sulfur similar to that proposed by Readio and Skell.[13]



Or this intermediate could be stabilized by interaction of the nonbonding electrons on sulfur with the d orbitals of silicon.



These types of interaction might be responsible for nonterminal adducts of some vinylsilanes.

Experimental Section

Nuclear magnetic resonance (nmr) spectra were obtained in CCl_4 on a Varian Model A-60 spectrometer using tetramethylsilane as the standard. Infrared spectra were obtained with a Perkin-Elmer Model 221 spectrometer. Gas–liquid partition chromatography (glpc) spectra were obtained with an F & M Model 720 instrument. The columns were 4 or 6 ft lengths of 0.25-in. stainless steel tubing packed with Dow Corning FS 1265 Gum on Chromosorb P (80–100 mesh). The Chromosorb P had been treated with hexamethyldisilazane.

Reagents. Ethanethiolic acid was prepared by the method of Ellingboe[14] in 80% yield.

Acetyl sulfide (bp, 75–76° (40 mm), $n^{25}D$ 1.4805) was prepared in 71% yield by the method of Bonner.[15]

Ethanethiolic acid-*d* was prepared by allowing a mixture of acetyl sulfide (70 g, 0.5 mol), deuterium oxide (10 g, 0.5 mol), and anhydrous sodium acetate (0.05 g, 0.0006 mol) to react at room temperature for 6 days in a nitrogen atmosphere. The mixture was stripped from the catalyst under reduced pressure. The distillate was fractionated to give 32.7 g (87% yield) of ethanethiolic acid-*d*: bp 42–45° (160 mm); $n^{25}D$ 1.4613. Infrared analysis indicated the product to be about 91% ethanethiolic acid-*d*, 3% ethanethiolic acid, and 6% deuterium oxide.

(13) P. D. Readio and P. S. Skell, *J. Org. Chem.*, **31**, 759 (1966).

(14) E. K. Ellingboe in "Organic Synthesis," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 928.

(15) W. Bonner, *J. Amer. Chem. Soc.*, **72**, 427 (1950).

TABLE III
NEW COMPOUNDS

	Compd[a]	Bp, °C (mm)	$n^{25}D$	d^{25}_4	Anal. Found (calcd), %	Neut equiv Found (calcd)
1.	$ClCH_2Me_2SiVi$	119–120	1.4382	0.896		
2.	$Me_2MeOSiVi$	82	1.3920	0.797	—CH=CH_2, 23.4 (23.2); MeO—, 26.4, 26.5 (26.6)	
3.	$Me(MeO)_2SiVi$	104	1.3920	0.884	Si, 21.0 (21.2)	
4.	$Me_2(F_3CCH_2CH_2)SiVi$	113–115	1.3765	0.968	Si, 14.9 (15.4); F, 32.1 (31.2); C, 46.4 (46.2); H, 7.5 (7.2)	
5.	$Me(F_3CCH_2CH_2)_2SiVi$	105 (105)	1.3725	1.130	Si, 11.8 (10.6); F, 42.2 (43.2); C, 41.1 (40.9); H, 5.3 (5.3)	
6.	$Me(Me_3SiCH_2)_2SiVi$	113 (30)	1.4511	0.813	Si, 34.9 (34.4); C, 54.4 (54.1); H, 11.9 (11.5)	
7.	$Me(PhCH_2)_2SiVi$	141 (0.3)	1.5628	0.989	Si, 11.0 (11.1); C, 81.4 (80.8); H, 8.3 (8.0)	
8.	$Cl_3SiCH_2CH_2SAc$	63–66 (1)	1.4940	1.320	Si, 11.8 (11.8); S, 13.6 (13.5)	78.9 (79.2)
9.	$MeCl_2SiCH_2CH_2SAc$	93–94 (8)	1.4898	1.210	Si, 12.9 (12.9); S, 14.3 (14.8)	107 (108.6)
10.	$Me_2ClSiCH(CH_3)SAc$	95–97 (21)	1.4782	1.064	Si, 14.1 (14.3); S, 16.5 (16.3)	194 (193.8)
11.	$Me_2ClSiCH_2CH_2SAc$	101–102 (13)	1.4802	1.069	Si, 14.3 (14.3); S, 17.3 (16.3)	196 (196.8)
12.	$Me_2SiCHDCH_2SAc$	99–100 (30)				
13.	$Me_2SiCH(CH_2D)SAc$	90–95 (35)				
14.	$Me_2SiCH(CH_3)SAc$	81–82 (22)	1.4642	0.927	Si, 15.3 (15.9); S, 18.3 (18.2)	
15.	$Me(MeO)_2SiCH_2CH_2SAc$	75 (1)	1.4579	1.053	Si, 13.8 (13.5); S, 15.2 (15.4)	
16.	$(MeO)_3SiCH(CH_3)SAc$	67–69 (5)	1.4502	1.100	Si, 12.5 (12.5); S, 14.4 (14.4)	
17.	$(MeO)_3SiCH_2CH_2SAc$	95 (5)	1.4512	1.105	Si, 12.3 (12.5); S, 13.9 (14.4)	
18.	$(AcO)_3SiCH_2CH_2SAc$		1.4596	1.219	Si, 9.1 (8.7); S, 10.7 (10.4)	
19.	$Cl_2Si(CH_2CH_2CH_2SAc)_2$	dec	1.5208	1.208	Si, 8.1 (8.4); S, 19.6 (19.2); Cl, 19.1 (21.5)	
20.	$(Me_3SiO)_2SiCH_2CH_2SAc$		1.4270	0.941	Si, 28.1 (28.2); S, 8.0 (8.0)	
21.	$(MeO)_3SiCH_2CH_2SH$	108 (50)	1.4382	1.069	Si, 15.5 (15.4); S, 17.6 (17.6)	
22.	$Me(MeO)_2SiCH_2CH_2SH$	96–98 (50)	1.4462	1.008	Si, 16.7 (16.9); S, 18.7 (19.3)	
23.	$Me_2MeOSiCH_2CH_2SH$	71 (18)	1.4515	0.934		[b]
24.	$Me_2ClSiCH_2CH_2SH$	53 (5)	1.4754	1.027	Si, 18.1 (18.1); S, 20.7 (20.7); Cl, 22.8 (22.9)	
25.	$Me_2AcOSiCH_2CH_2SH$	67–71 (2.5)	1.4556	1.010	Si, 15.9 (15.8); S, 17.8 (18.0)	
26.	$Me_2HOSiCH_2CH_2SH$		1.4742	0.986	Si, 20.3 (20.6); S, 23.0 (23.5)	
27.	$Me_2SiSSiMe_2CH_2CH_2S$	120 (30)	1.5295	1.030	Si, 26.7 (26.9); S, 30.2 (30.7)	
28.	$(Me_2SiCH_2CH_2S)_x$		1.5515		Si, 24.1 (23.8); S, 27.3 (27.1)	
29.	$S(CH_2)_3Si(CH_2)_3S$	85–90[c] (1.0)			Si, 15.4 (15.9); S, 36.1 (36.3)	

[a] Registry no. in descending order are 1, 16709-86-7; 2, 16546-47-7; 3, 16753-62-1; 4, 683-29-4; 5, 16709-89-0; 6, 16709-90-3; 7, 16709-91-4; 8, 16709-92-5; 9, 16709-93-6; 10, 16709-94-7; 11, 16709-95-8; 12, 16720-18-6; 13, 16709-96-9; 14, 16709-97-0; 15, 16709-98-1; 16 16709-99-2; 17, 16720-19-7; 18, 16710-00-2; 19, 16710-01-3; 20, 16710-02-4; 21, 7538-45-6; 22, 14857-98-8; 23, 16710-05-7; 24, 16710-06-8; 25, 16710-64-8; 26, 16710-65-9; 27, 16704-34-0; 29, 16704-32-8. [b] Mercaptan equiv was 150.1 (calcd 150.3). [c] Mp 26–28°.

The S–D (1873 cm^{-1}) and S–H (2580 cm^{-1}) stretching absorptions were used for the analysis. The nmr spectrum showed only one peak at τ 7.64 ($CH_3C(=O)$).

Preparation of Vinylsilanes. Chloromethyldimethylvinylsilane was prepared by adding a slight excess of vinyllithium (Alpha Inorganics, Inc.) to a solution of chloromethyldimethylchlorosilane (163 g, 1.14 mol) in tetrahydrofuran (1000 ml). The mixture was refluxed overnight, distilled free of solvent, and extracted with pentane. The extracts were distilled to give 93.5 g (67% yield) of chloromethyldimethylvinylsilane. The material was judged to contain less than 2% impurities by glpc analysis. Its nmr spectrum showed a characteristic vinyl group absorption at τ 3.7–4.4, (2.9 protons), a singlet at 7.27 (CH_2Cl) (2.0 protons) and a singlet at 9.81 (Me_2Si) (6.1 protons). The physical properties are given in Table III, compound 1.

Dimethylvinylmethoxysilane was prepared in 77% yield from dimethylvinylchlorosilane and trimethylorthoformate by the method of Shorr.[16] Properties and analyses are given in Table III, compound 2.

Methylvinyldimethoxysilane was prepared in 46% yield by treating methylvinyldichlorosilane with methanol. Properties and analyses are given in Table III, compound 3.

3,3,3-Trifluoropropylvinyldimethylsilane was prepared by adding a mixture of dimethylvinylchlorosilane (120.7 g, 1.0 mol) and 1,1,1-trifluoro-3-bromopropane (177 g, 1.0 mol) to magnesium (24.3 g, 1.0 g-atom) in ether (300 ml). The mixture was washed with dilute hydrochloric acid and distilled to obtain 48.4 g (24%) of product having the properties and analyses given in Table III, compound 4.

Bis(3,3,3-trifluoropropyl)vinylmethylsilane was prepared from methylvinyldichlorosilane (141 g, 1.0 mol) and 3,3,3-trifluoropropylmagnesium bromide, prepared from 1,1,1-trifluoro-3-bromopropane (390 g, 2.2 mol) and magnesium (53 g, 2.2 g-atom) in ether (600 ml). Ether was removed until the pot temperature reached 70° before any reaction was observed. The usual work-up with dilute hydrochloric acid gave 97 g (37% yield) of bis(3,3,3-trifluoropropyl)methylvinylsilane. Properties and analyses are given in Table III, compound 5.

Bis(trimethylsilylmethyl)methylvinylsilane was prepared by heating a mixture of methylvinyldichlorosilane (64.5 g, 0.5 mol) and trimethylsilylmethylmagnesium chloride, prepared from chloromethyltrimethylsilane (122.6 g, 1.0 mol), magnesium (24.3 g, 1.0 g-atom), and ether (800 ml) at reflux overnight. The usual work-up with dilute hydrochloric acid gave 26 g of crude product. This material was purified with activated alumina (100 g) to give 15 g (12% yield) of methylbis(trimethylsilylmethyl)vinylsilane. Properties and analyses are given in Table III, compound 6. Impure trimethylsilylmethylmethylvinylsilanol and *sym*-bis(trimethylsilylmethyl)dimethyldivinyldisiloxane were also isolated. These were identified by nmr and infrared analyses.

Dibenzylmethylvinylsilane was prepared from methylvinyldichlorosilane (64.5 g, 0.5 mol) and benzylmagnesium chloride, prepared from benzyl chloride (127.9 g, 1.05 mol), magnesium (24.3 g, 1.0 g-atom), and ether (750 ml). The usual work-up with dilute hydrochloric acid gave 98 g (78% yield) of dibenzylmethylvinylsilane. Properties and analyses are given in Table III, compound 7.

Preparation of Silylethyl Ethanethiolates. 1-Trimethoxysilylethyl ethanethiolate and 2-trimethoxysilylethyl ethanethiolate were prepared by dripping a mixture of ethanethiolic acid (420 g, 5.5 mol) and azobisisobutyronitrile (4.1 g, 0.025 mol) into vinyltrimethoxysilane (740 g, 5.0 mol) at 80–90° with irradiation from an ultraviolet lamp. After 1 hr the mixture was distilled to give 687 g of pure 2-trimethoxysilylethyl ethanethiolate. Properties are given in Table III, compound 17. A

(16) L. M. Shorr, *J. Amer. Chem. Soc.*, **76**, 1390 (1954).

sample of pure 1-trimethoxysilylethyl ethanethiolate was obtained by redistilling the lower boiling fractions. Properties and analyses are given in Table III, compound 16. The ratio of terminal adduct to nonterminal adduct was 95:5 by glpc. The over-all yield of trimethoxysilylethyl ethanethiolates was 954 g (85%).

Air or various peroxides were effective initiators for this reaction. The silylethyl ethanethiolates listed in Table III were prepared from the appropriate vinylsilanes and ethanethiolic acid by procedures similar to the above. The reaction proceeds smoothly only with freshly distilled ethanethiolic acid. The order of mixing the reagents does not appear to affect the reaction. In the preparation of bis(3-thiolacetoxypropyl)dichlorosilane, the diallyldichlorosilane was added to excess ethanethiolic acid.

Preparation of Silylalkanethiols. Base-Catalyzed Methanolysis of 2-Trimethoxysilylethyl Ethanethiolate.—A solution of 2-trimethoxysilylethyl ethanethiolate (95 g, 0.42 mol), methanol (81 ml, 2.0 mol), and sodium (0.1 g, 0.004 g-atom) was refluxed 2 hr and distilled to give 71 g (93% yield) of 2-trimethoxysilylethanethiol. Properties and analyses are given in Table III, compound 21. 2-Dimethylmethoxysilylethanethiol and 2-methyldimethoxysilylethanethiol were prepared in similar manner in 85 and 71% yields, respectively.

Acid-Catalyzed Methanolysis of 2-Trimethoxysilylethyl Ethanethiolate.—A solution of 2-trimethoxysilylethyl ethanethiolate (5.6 g, 0.025 mol), methanol (1.02 g, 0.03 mol), and *p*-toluenesulfonic acid (0.02 g, 0.0001 mol) was refluxed 96 hr. Glpc indicated only 65% conversion of ethanethiolate into thiol.

Ammonolysis of 2-Dimethylchlorosilylethyl Ethanethiolate.—2-Dimethylchlorosilylethyl ethanethiolate (767.0 g, 3.9 mol) was added dropwise to liquid ammonia (1,310 ml, 63 mol). The mixture was stirred for 13 hr at −33° under nitrogen. Hexane (300 ml) was added and the excess ammonia was allowed to escape. A clear liquid and a solid cake of ammonium chloride and acetamide were obtained. The liquid was decanted from the solid and concentrated at room temperature under reduced pressure to give 443 g (80% yield) of crude product (I). Nmr analysis indicated that 40% of the methyl groups were on a silicon attached to sulfur (τ 9.92). The infrared spectrum showed the following absorptions: $\lambda_{max}^{CCl_4}$ 3370 (m) N–H, 2580 (w) SH; $\lambda_{max}^{CS_2}$ 930 (s) SiNHSi.

Anal. Calcd for $C_8H_{23}NS_2Si_2$: Si, 22.1; S, 25.2; N, 5.5. Found: Si, 22.1; S, 25.3; N, 3.5.

2-Dimethylchlorosilylethanethiol was prepared by saturating a solution of the above product I (25.4 g, ~0.1 mol) and hexane (50 ml) with hydrogen chloride. The mixture was filtered free of ammonium chloride and distilled to give 16.4 g (53% yield) of 2-dimethylchlorosilylethanethiol. Properties and analyses are given in Table III, compound 24.

2-Dimethylacetoxysilylethanethiol was prepared by adding acetic acid (18.5 ml, 0.32 mol) to a solution of I (26.9 g, ~0.11 mol) and hexane (25 ml). The mixture was filtered free of ammonium acetate and distilled to give 24.0 g (67% yield) of 2-dimethylacetoxysilylethanethiol. Properties and analyses are given in Table III, compound 25.

2-Dimethylhydroxysilylethanethiol was prepared by adding a solution of 2-dimethylacetoxysilylethanethiol (5.34 g, 0.03 mol) and I (7.6 g, ~0.03 mol) to 5% aqueous ammonium acetate (50 ml). After stirring the mixture for about 1 hr at room temperature hexane (10 ml) was added and two liquid phases formed. The organic phase was washed with distilled water (10 ml) and concentrated at room temperature under reduced pressure to give 9.1 g (86% yield) of 2-dimethylhydroxysilylethanethiol. Its nmr and infrared spectra indicated only traces of water and disiloxane present. Properties and analyses are given in Table III, compound 26.

1,1,3,3-Tetramethyl-1,3-disila-2,4-dithiacyclohexane was prepared by heating I (40.0 g, ~0.16 mol) at 240° (30 mm) until the pot was dry. The distillate was fractionated to give 28 g (77% yield) of 1,1,3,3-tetramethyl-1,3-disila-2,4-dithiacyclohexane. Properties and analyses are given in Table III, compound 27.

$-(-SiMe_2CH_2CH_2S-)-$ was prepared by heating I (50 g, 0.2 mol) at 175° (3 mm) for 48 hr to give 32 g (68% yield) of polymer, viscosity 3700 cSt. Properties and analyses are given in Table III, compound 28. A 10% yield of 1,1,3,3-tetramethyl-1,3-disila-2,4-dithiacyclohexane was obtained also.

Reactions of Thiols and Ethanethiolic Acid with Vinylsilanes. Ethanethiolic Acid-*d* with Trimethylvinylsilane.—Ethanethiolic acid-*d* (14.5 ml, 0.183 mol) was added dropwise to a solution of trimethylvinylsilane (22 g, 0.22 mol) and Lupersol-11 (0.15 g, 0.001 mol) at 50–80°. The mixture was distilled to give 29.6 g (92% yield) of product. Pure nonterminal adduct was obtained by preparative glpc. Pure terminal adduct was obtained from the distillation. The nmr spectrum showed the nonterminal adduct to be $Me_3SiCH(CH_2D)SC(=O)CH_3$ with singlet peaks at τ 9.88 ($Si-CH_3$*) and 7.69 ($(O=)C-CH_3$*), a triplet peak at 7.21 (SiCH*S), and a doublet peak at 8.72 ($CHCH_2$*D). The proton ratios were 8.7:3.0:2.1:1.0, respectively. The nmr spectrum of the terminal adduct showed it to be $Me_3SiCHDCH_2SC(=O)CH_3$ with singlet peaks at τ 9.95 ($Si-CH_3$) and 7.78 ($(O=)CCH_3$), a doublet peak at 7.19 (SCH_2), and a complex peak at 9.18 (SiCHD). The proton ratios were 8.9:3.0:1.9:1.2, respectively.

Nonterminal Adducts from the Reaction of Ethanethiolic Acid with Vinylsilanes.—Ethanethiolic acid (0.5 *M* in benzene) was allowed to react with a slight excess of a vinylsilane at 40 ± 0.5°. The reaction was initiated with about 1 mol % Lupersol-11. The reaction mixture was analyzed for the relative amounts of terminal and nonterminal adducts by glpc. The results are given in Table II.

Relative Reactivities of Vinylsilanes toward Thiols and Ethanethiolic Acid.—Ethanethiolic acid (~0.01 mol) was added in 0.1-ml portions to a solution of hexene-1 (~0.01 mol) and vinylsilane (0.01 mol) in ethylbenzene (10 ml) at 40° in a 2-oz vial. The reaction was initiated with one drop of Lupersol-11. After each addition an exothermic reaction was observed. The reaction mixture was cooled by removing the vial from the bath. Glpc indicated complete reaction a few minutes after the ethanethiolic acid was added. A sample of the original vinylsilane, hexene-1, and ethylbenzene solution was analyzed by glpc and a factor for converting area of the olefin into moles of olefin was obtained (eq 6). A sample of the reaction mixture was analyzed by glpc

$$Z = \frac{(\text{area of olefin})}{(\text{moles of olefin})\,(\text{area of ethylbenzene})} \qquad (6)$$

and the amount of unreacted olefin was obtained as in eq 7.

$$\text{moles of unreacted olefin} = \frac{(\text{area of unreacted olefin})}{(Z)\,(\text{area of ethylbenzene})} \qquad (7)$$

The relative rate (k/k_0) was calculated using the following formula.

$$k/k_0 = \frac{\ln(\text{moles of unreacted vinylsilane/moles of initial vinylsilane})}{\ln(\text{moles of unreacted hexene-1/moles of initial hexene-1})} \qquad (8)$$

The studies with benzenethiol and 1-butanethiol were carried out using the same procedure except the reactions were not exothermic and did not require cooling. The reaction times were about 16–20 hours. No effect on the reactivities of various vinylsilanes was observed when benzene was used as the solvent instead of ethylbenzene. Benzene was used in place of ethylbenzene whenever the retention times of the vinylsilane and ethylbenzene were the same. Hexene-1 and octene-1 were found to react at the same rate. Octene-1 was used instead of hexene-1 whenever hexyl ethanethiolate and the vinylsilane had the same retention times. Several vinylsilanes were allowed to compete with each other to check if the reaction was really competitive. In each case the observed reactivities agreed well with the predicted value obtained from the competition reactions with hexene-1. The approximate range of experimental error was found to be about 10%. Usually the several determinations were well within this range. The results are given in Table I.

Relative Reactivities of Vinylsilanes toward Methyldichlorosilane.—Methyldichlorosilane (1 ml, 0.01 mol), hexene-1 (0.01 mol), the vinylsilane (0.01 mol), and chloroplatinic acid (5×10^{-7} mol) were sealed in 10 mm × 250 mm Pyrex tubes and heated overnight in a boiling water bath. The tubes were opened and the contents were analyzed by glpc methods. The relative reactivity of each vinylsilane was calculated as in the preceding section. The following reactivities were observed (relative to hexene-1): Me_3SiVi, 4.04; $Me_2ClSiVi$, 2.05; $MeCl_2SiVi$, 0.67; Cl_3SiVi, 0.159; $(Me_3SiO)Me_2SiVi$, 4.29; $(Me_3SiO)_2MeSiVi$, 3.24; $C_6H_5Cl_2SiVi$, 0.502.

Registry No.—Ethanethiolic acid-*d*, 16704-33-9; I, 16808-49-4.

Acknowledgments.—We wish to thank Mr. G. A. L. Gant for the preparation of chloromethyldimethylvinylsilane and Miss Anne Moore for the preparation of several other vinylsilanes.

Optical Purity and Optical Rotatory Power of Dehydronorcamphor[1a]

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Received January 25, 1968

The optical properties of dehydronorcamphor have been reinvestigated. The previously reported absolute rotation and ORD amplitude of the n → π* transition have been confirmed by an independent determination of the optical purity by nmr spectroscopy. The circular dichroism has been found to match closely the corresponding values reported for the n → π* transition of dehydrocamphor and dehydroepicamphor.

Bicyclo[2.2.1]hept-5-en-2-one (dehydronorcamphor, **1**) a simple archetype of the dissymmetric β,γ-unsaturated carbonyl chromophore, figures as a key compound in studies of the relationship between optical rotatory power and chemical structure, both from the theoretical[2] and the experimental[3-6] points of view.

It is therefore of interest to note that while (+)-**1** and dehydrocamphor [(−)-**2**] are reported to have similar molecular amplitudes for the Cotton effect of their lowest lying n → π* transition (*a* +780 ± 40[4] and *ca.* −840,[7] respectively), corresponding to similar extinction coefficients [ε 277 (λ_{max} 307.5 mμ) and 308 (λ_{max} 304 mμ) for **1**[2a] and **2**[6]], the corresponding molecular ellipticites are reported to differ significantly ($[\theta]_{max}$ +3.18 × 10[4] and −5.89 × 10[4] for **1**[5] and **2**,[6] respectively). This result is contrary to expectations since, even taking into account that the values cited for **1** and **2** refer to different solvents (hydrocarbon and ethanol, respectively), **1** and **2** do have similar chromophoric geometries and the rotational strengths should clearly manifest parallel behavior in ORD and CD.[2] In terms of the semiquantitative expression relating molecular amplitude and circular dichroism of ketones,[8] $[\theta]_{max}$ values of +6.4 and −6.9 × 10[4] might have been predicted from the *a* values of **1** and **2**, respectively, or, conversely, *a* values of +390 and −720 might have been predicted from the reported $[\theta]_{max}$ values of **1** and **2**, respectively. Whereas calculated and reported values for *a* and $[\theta]_{max}$ of **2** are in reasonable agreement, the corresponding values for **1** are grossly mismatched.



(+)-**1** (−)-**2** (+)-**3**

Similar considerations were advanced by Bays, Cookson, and MacKenzie who pointed out that, given the similarity in the extinction coefficients of the lowest n → π* transition of **1**, **2**, and dehydroepicamphor (**3**) [ε 325 (λ_{max} 310 mμ)], and given the roughly linear relationship of extinction coefficients (log ε) to optical rotatory power (log *a* or log Δε) of ketones,[9] the $\Delta\epsilon_{max}$ values in the CD curves of **1**–**3** would be expected to be closely similar. In fact, reported values for $\Delta\epsilon_{max}$ in hydrocarbon solvents are +9.6, −18.5, and +19.9 for **1**,[5] **2**,[6] and **3**,[6] respectively, once again identifying **1** as the source of the discrepancy. However, because of the close agreement in $\Delta\epsilon_{max}$ values of **2** and **3**, it is the reported circular dichroism of **1** to which the finger of suspicion points, the more so since the $\Delta\epsilon_{max}$ value of **1** calculated[6,8] from the published[4] ORD amplitude is +19.4.

To resolve this discrepancy, we have reinvestigated the ORD and CD of **1**.

Compound **1** was prepared as previously described, *i.e.*, by asymmetric hydroboration of norbornadiene to *exo*-dehydronorborneol (**4**), followed by oxidation to **1**. Use of (−)-α-pinene in the asymmetric hydroboration gave the enantiomer (*i.e.*, (−)-**1**) of the previously studied[4,5] sample.

Since the asymmetric hydroboration furnishes optically impure material, it is crucial to obtain an accurate measure of the optical purity of **1** for purposes of comparison with **2** and **3**, which are obtained from natural sources and are presumed to be optically pure. The optical purity of **1** had previously been estimated[4] by relating **4** and the derived (+)-**1** to *exo*-norborneol, whose optical purity had been established by the isotope dilution method.[10] To be doubly sure, the optical purity of **1** was established in the present work by an entirely independent method, *i.e.*, by nuclear magnetic resonance spectroscopy.[11]

Reaction of racemic dehydronorborneol (*exo/endo* ratio 87:13) with an equimolar amount of racemic O-methylmandelyl chloride gave a mixture of esters whose nmr spectrum at 60 MHz in benzene solution showed

(1) (a) This work was supported by the Air Force Office of Scientific Research under Grant No. AF-AFOSR-1188-67; (b) National Aeronautics and Space Administration Fellow, 1965–1968.

(2) (a) A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Amer. Chem. Soc.*, **84**, 1945 (1962); (b) R. E. Ballard, S. F. Mason, and G. W. Vane, *Trans. Faraday Soc.*, **59**, 775 (1963); (c) A. Moscowitz, A. E. Hansen, L. S. Forster, and K. Rosenheck, *Biopolymers, Symp.*, **1**, 75 (1964); (d) A. Moscowitz, *Proc. Roy. Soc.*, **A297**, 16, 40 (1967); (e) E. G. Höhn and O. E. Weigang, Jr., *J. Chem. Phys.*, **48**, 1127 (1968).

(3) (a) K. Mislow, *Ann. N. Y. Acad. Sci.*, **93**, 457 (1962); (b) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965, pp 235–236; (c) R. C. Cookson, *Proc. Roy. Soc.*, **A297**, 27 (1967); (d) G. Snatzke, *ibid.*, 43 (1967).

(4) K. Mislow and J. G. Berger, *J. Amer. Chem. Soc.*, **84**, 1956 (1962).

(5) E. Bunnenberg, C. Djerassi, K. Mislow, and A. Moscowitz, *ibid.*, **84**, 2823, 5003 (1962).

(6) D. E. Bays, R. C. Cookson, and S. MacKenzie, *J. Chem. Soc., Sect. B*, 215 (1967).

(7) P. J. Mälkönen and R. Frostell, *Suomen Kemistilehti, Sect. B*, **40**, 84 (1967).

(8) Reference 3b, p 19, gives $a = 0.0122[\theta]_{max}$; $a = 40.28$ ($\Delta\epsilon_{max}$).

(9) S. F. Mason, *J. Chem. Soc.*, 3285 (1962); S. F. Mason, *Quart. Rev.* (London), **17**, 20 (1963).

(10) J. A. Berson and S. Suzuki, *J. Amer. Chem. Soc.*, **81**, 4088 (1959).

(11) (a) M. Raban and K. Mislow, "Topics in Stereochemistry," Vol. 2, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, Inc., New York, N. Y., 1967, p 216 ff; (b) M. Raban and K. Mislow, *Tetrahedron Lett.*, 3961 (1966); J. Jacobus, M. Raban, and K. Mislow, *J. Org. Chem.*, **33**, 1142 (1968), and references cited therein.

the following relevant features: the diastereotopic methoxymethine protons (CH_3OCH) of the diastereomers derived from **4** were not perceptibly anisochronous; the signals of the methoxy protons (CH_3O) of the diastereomers derived from either **4** or *endo*-dehydronorborneol (**5**) were separated by *ca.* 1 Hz; the signals of the methoxymethine protons of the diastereomers derived from **5** were separated by *ca.* 2 Hz. The chemical shift nonequivalence of the diastereotopic methoxymethine protons derived from **5** could therefore be used as the basis for estimating the optical purity by nmr. Reaction of racemic **5** with an excess of optically pure O-methylmandelyl chloride gave a 1:1 mixture of diastereomers, as judged by integration of the methoxymethine proton resonances at 100 MHz.

Sodium borohydride reduction of (−)-**1**, $[\alpha]^{23}D$ −525° (isooctane), gave a mixture of diastereomeric dehydronorborneols, (−)-**5** and (−)-**4**, in a ratio of 91:9. Reaction of this mixture with optically pure (*R*)-O-methylmandelyl chloride gave a mixture of diastereomeric esters. The ratio of esters derived from (−)-**5** was 2.65:1.00 as judged by integration and area measurement of the appropriate methoxymethine proton resonances at 100 MHz.[12] This corresponds to an optical purity of 45.2% in the precursor alcohol (−)-**5**. The starting ketone was therefore also 45.2% optically pure, and the absolute rotation of (−)-**1**, *i.e.*, the rotation of the pure enantiomer, is calculated to be $[\alpha]D$ −1160° (isooctane). This value is in satisfactory agreement with the value of $[\alpha]D$ +1140° (isooctane) which may be calculated from the previously reported[4] rotation ($[\alpha]D$ +548° (isooctane)) and optical purity (48.0%). To our knowledge, this is the first example in which the absolute rotation of a compound has been independently established by isotope dilution and nmr spectroscopy.

It may be noted in this connection that the elegant approach developed by Pirkle,[13] in which the chemical shift nonequivalence of corresponding nmr signals in diastereomerically solvated enantiomers (*i.e.*, enantiomers dissolved in a chiral medium) affords a measure of optical purity which is absolute in the sense that no reference to a standard of optical purity is required, is inconvenient to apply in the present instance where the substances whose optical purities are to be determined (*i.e.*, **1**, **4** or **5**) show complex spin–spin coupling.

The ORD of (−)-**1** in isooctane was found to be substantially the same in shape and amplitude as the one previously reported[4] for the enantiomer. The molecular amplitude, corrected to optical purity, was a −840 ± 20 for the transition centered near 308 mμ, in satisfactory agreement with the previous determination,[4] a +780 ± 40, and identical with the value found[7] for **2** in ethanol. However, the CD intensity of (−)-**1** in isooctane differed substantially in magnitude from that previously reported[5] for the enantiomer. The molecular ellipticity of (−)-**1**, corrected to optical purity, was found to be $[\theta]_{max}$ −6.80 × 10^4 for the transition centered at 308 mμ, in excellent agreement with the value of $[\theta]_{max}$ −6.9 × 10^4 calculated[8] from the measured amplitude of the ORD curve, but in poor agreement with the earlier measurement[5] on (+)-**1**, $[\theta]_{max}$ +3.18 × 10^4. It must be concluded that the latter value is in error, as had been surmised.[6]

Cookson, *et al.*,[3c,6] have suggested that in β,γ-unsaturated ketones such as **1**–**3**, the rotational strengths of the $n \rightarrow \pi^*$ and short-wavelength ("charge-transfer") transitions should be nearly equal in magnitude and opposite in sign; indeed, the CD curves of **2** and **3** do change sign at shorter wavelengths.[6] However, in the case of (−)-**1** we have been able to record the complete CD curve in isooctane corresponding to the transition near 212 mμ, and have observed a negative Cotton effect with $[\theta]_{max}$ −2.5 × 10^4 at 215 mμ.[14] Consequently, the Cotton effects associated with the long-wavelength and short-wavelength transitions of **1** are of the *same* sign, in contrast to the behavior observed[6] for the closely analogous β,γ-unsaturated ketones **2** and **3**.

Experimental Section[15]

(−)-**Dehydronorcamphor** (**1**) was prepared in the manner previously described,[4] using (−)-α-pinene ($[\alpha]^{23}D$ −39.4° (neat)) for the preparation of (+)-*sym*-tetraisopinocampheyldiborane. Crude **1** was purified by preparative glpc (a 20 ft × 3/8 in. 30% Carbowax 20M on 45–60 mesh Chromosorb W column at 190–200°, helium flow rate 200 cc/min). Under these conditions **1** had a retention time of 12–13 min. The material collected was further purified by distillation (Kugelrohr, 40–60° at 2 mm) to give a colorless liquid which solidified easily on cooling, $n^{25}D$ 1.4840 (lit. $n^{25}D$ 1.4857[16] and $n^{25}D$ 1.4839[17] for racemic **1**, and $n^{25}D$ 1.4834[4] for optically active **1**), $[\alpha]^{23}D$ −525° (*c* 0.169, isooctane). The material was homogeneous by glpc analysis both on a 2-ft 10% Carbowax 20M on 60–80 mesh Chromosorb W column at 130° (helium flow rate 30 cc/min, retention time 4.9 min), and on a 6-ft 10% Carbowax 4000 on 60–80 mesh Chromosorb W column at 150° (helium flow rate 30 cc/min, retention time 9.6 min). The infrared spectrum was indistinguishable from that of the enantiomer.[4] The ultraviolet spectrum in isooctane solution exhibited the following features: λ_{max} mμ (ε) 320 (176), 307.5 (267), 297 (232), 287.5 (156.5), 212 (2550), 204 (2400) [lit.[2a] 319.5 (177), 307.5 (277), 296.5 (242), 287.5 (162); lit.[17] 320, 308 (266), 297; lit.[18] *ca.* 210 mμ]; ORD in isooctane (*c* 0.0752 g/100 ml at λ >230 mμ, *c* 0.00752 at λ<230 mμ, corrected to optical purity), $[\phi]_{321}$ −48,900°, $[\phi]_{315}$ −20,300°, $[\phi]_{309.5}$ −29,000°, $[\phi]_{306}$ 0°, $[\phi]_{300}$ +9560°, $[\phi]_{295}$ +8520°, $[\phi]_{289}$ +30,300°, $[\phi]_{287.5}$ +30,000°, $[\phi]_{280}$ +34,960°, $[\phi]_{275}$ +33,600°, $[\phi]_{225}$ +6740°, $[\phi]_{203}$ +90,000° (lit.[4] corrected to optical purity, $[\phi]_{322}$ +46,350°, $[\phi]_{315}$ +26,500°, $[\phi]_{311}$ +30,800°, $[\phi]_{305}$ −4430°, $[\phi]_{303}$ −3670°, $[\phi]_{292}$ −24,300°, $[\phi]_{289}$ −24,300°, $[\phi]_{281}$ −31,300°, $[\phi]_{270}$ −25,000°); CD in isooctane, corrected to optical purity (*c* 0.094 g/100 ml at λ >230 mμ, *c* 0.0094 at λ <230 mμ), λ_{max}, mμ ($[\theta]$), 340 (0), 318 (−47,300), 306.5 (−68,000), 296 (−55,300), 286 (−34,600), 215 (−25,000), 205 (0), $[\theta] > 0$ below 205 mμ.

Racemic dehydronorcamphor (**1**) was prepared from racemic dehydronorborneol (Aldrich *exo–endo* mixture) in the same manner as the optically active material.

Racemic *endo*-dehydronorborneol (**5**) was prepared by sodium

(12) The methoxymethine proton resonance of the O-methylmandelates of **4** appears as a signal which is well separated from the signals of the esters derived from **5**.

(13) W. H. Pirkle, *J. Amer. Chem. Soc.*, **88**, 1837 (1966); T. G. Burlingame and W. H. Pirkle, *ibid.*, 4294 (1966); W. H. Pirkle and T. G. Burlingame, *Tetrahedron Lett.*, 4039 (1967); W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, **89**, 5485 (1967).

(14) In the previous CD measurement[5] carried out on (+)-**1**, the beginnings of a positive Cotton effect at shorter wavelengths could be discerned, but the maximum could not be reached.

(15) Elemental analyses by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Nmr spectra were measured on a Varian A-60A or Varian HA-100 spectrometer in *ca.* 10% benzene solution. Chemical shifts in the 60-MHz spectra are reported in hertz upfield from internal benzene, and those in the 100-MHz spectra are reported in parts per million downfield from internal tetramethylsilane. We thank the National Science Foundation for providing the funds for the purchase of the Varian HA-100 spectrometer. ORD measurements were taken on a Cary 60 spectropolarimeter and CD measurements were taken on a Cary 6001 CD accessory.

(16) N. J. Toivonen and J. Kaila, *Suomen Kemistilehti, Sect. B*, **28**, 91 (1955).

(17) P. D. Bartlett and B. E. Tate, *J. Amer. Chem. Soc.*, **78**, 2473 (1956).

(18) C. A. Grob and A. Gagneux, unpublished work, cited by H. Labhart, and G. Wagniere, *Helv. Chim. Acta*, **42**, 2219 (1959).

borohydride reduction of racemic 1.[19a] Sodium borohydride (0.91 g, 24 mmol) was stirred in isopropyl alcohol (5 ml) at 0°. Racemic 1 (2.0 g, 18.5 mmol) in isopropyl alcohol (5 ml) was added over a period of 10 min, and the mixture was stirred overnight at room temperature. Water and saturated ammonium chloride were added to decompose excess borohydride. The ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated to give an oily residue whose infrared spectrum indicated the absence of a carbonyl band. The residue was purified by Kugelrohr distillation to give 0.42 g (21%) of a white solid, mp 104.5–113° (lit.[19b] mp 109.4–110.8°), which had an infrared spectrum in satisfactory agreement with the reported[19b] spectrum of 5.

(−)-*endo*-**Dehydronorborneol** (5) was prepared from (−)-1 in a manner analogous to that described above for the racemic compound. The product was purified by distillation (Kugelrohr, 30–50° at 0.005 mm) to give 0.36 g (39%) of a white solid: mp 105–111°; $[\alpha]^{23}D$ −73.4° (*c* 2.62, chloroform). Analysis by glpc on a 2-ft 10% Carbowax 20 M on 60–80 mesh Chromosorb W column at 131° (helium flow 30 cc/min) indicated an *endo/exo* ratio of 91:9; retention time of the *endo* and *exo* isomers were 5.2 and 6.5 min, respectively.

Anal. Calcd for $C_7H_{10}O$: C, 76.31; H, 9.16. Found: C, 75.98; H, 9.05.

Racemic dehydronorborneol was prepared as previously described.[20] The product was a white solid, mp 60–84° (lit.[20] mp 92–93° for racemic *exo*-dehydronorborneol), which was shown to have an *exo/endo* ratio of 87:13 by glpc analysis, as for 5, above.

Dehydronorbornyl O-Methylmandelate.—Racemic O-methylmandelyl chloride, prepared[11b] from O-methylmandelic acid (1.09 mmol) was stirred magnetically in benzene solution. Pyridine (0.98 g, 12.4 mmol) was added and a precipitate formed. Racemic dehydronorborneol (*exo/endo* ratio 87:13, 0.12 g, 1.09 mmol) in benzene solution was added, and the mixture was stirred at room temperature for 45 min. The work-up was carried out as described for the O-methylmandelamides.[11b] Since impurities were indicated in the nmr spectrum of the crude ester, the product was chromatographed on florisil and eluted with 75:25 v/v benzene–hexane followed by benzene, and 90:10 v/v benzene–ether. The 60-MHz nmr spectrum of the chromatographed material featured a single methoxymethine proton signal at 149 Hz and a single methoxy proton signal at 238 Hz for the mixture of diastereomers from **4**. An analytical sample was collected by glpc (2-ft 10% Carbowax 20M at 210°, helium flow 60 cc/min, retention time 8.2 min).

Anal. Calcd for $C_{18}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.05; H, 6.81.

endo-**Dehydronorbornyl O-Methylmandelate.**—Optically pure O-methylmandelyl chloride, prepared[11b] from (−)-(*R*)-O-methylmandelic acid (1 mmol), was treated with pyridine (0.24 g, 3 mmol) and racemic **5** (0.0539 g, 0.49 mmol) as above, for 13 hr at room temperature. The crude ester mixture was chromatographed on florisil, as above. The 60-MHz nmr spectrum of the chromatographed material featured the following signals. The methoxymethine protons in the mixture of diastereomers derived from the *exo* contaminant appeared as a singlet at 149 Hz, and the corresponding protons in the diastereomers derived from **5** appeared at 152.5 and 154.5 Hz. The methoxy protons appeared at 238 (shoulder) and 239 Hz. Electronic integration of the methoxymethine resonances for the diastereomers from **5** in the 100-MHz spectrum indicated a ratio of 1:1. An analytical sample was obtained by distillation (Kugelrohr, 110–115° at 0.02 mm).

Anal. Calcd for $C_{18}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.30; H, 7.16.

Determination of the Optical Purity of (−)-*endo*-**Dehydronorborneol** (5).—Optically pure O-methylmandelyl chloride, prepared[11b] from (−)-O-methylmandelic acid (1.61 mmol), was treated with pyridine (0.40 g, 5.1 mmol) and (−)-**5** (0.0805 g, 0.71 mmol), $[\alpha]^{23}D$ −73.4° (*c* 2.62, chloroform), as above, for 13 hr at room temperature. The sample used for the nmr measurement was collected by chromatography as described above for racemic dehydronorbornyl O-methylmandelate. The 100-MHz spectrum of the mixture of diastereomers featured the following signals. The methoxymethine protons in the mixture of diastereomers derived from **4** appeared as a singlet at δ 4.63, and the corresponding protons in the diastereomers derived from **5** appeared at 4.59 and 4.55, with that at 4.59 being the more intense. The methoxy protons appeared at δ 3.19 and 3.17. Electronic integration and peak area measurements of expanded scale spectra of the resonances at δ 4.59 and 4.55 indicated that the ratio of diastereomers in the O-methylmandelate derived from (−)-**5**, and hence the ratio of enantiomers in (−)-**5** was 2.65:1.00.

Registry No.—(−)-**1**, 16620-79-4; (−)-*endo*-**5**, 16620-80-7; dehydronorbornyl O-methylmandelate, 16620-82-9; *endo*-dehydronorbornyl O-methylmandelate, 16620-81-8.

(19) (a) H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, **88**, 2811 (1966); (b) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett, and R. Armstrong, *ibid.*, **72**, 3116 (1950).

(20) G. Zweifel, K. Nagase, and H. C. Brown, *ibid.*, **84**, 183 (1962).

Multinuclear Ferrocenes. V. Allylic Oxidation of 1-Ferrocenylcyclopentene[1]

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Received December 11, 1967

Allylic oxidations of 1-ferrocenylcyclopentene (**3**) by selenium dioxide, chromium trioxide, mercuric acetate, and lead tetraacetate have been studied with the view toward development of a suitable entry into the syntheses of new multinuclear ferrocenes. All oxidations were attended by fairly high degrees of decomposition, and products were obtained in low yields. In all cases oxidation was shown to take place exclusively α to the side of the double bond bearing the ferrocenyl group. Thus, **2-ferrocenyl-2-cyclopenten-1-one** (**5**), **2-ferrocenyl-3-acetoxy-1-cyclopentene** (**7**), and **2-ferrocenyl-3-ethoxy-1-cyclopentene** (**8**) were the oxidation products. While the unsaturated ketone (**5**) underwent unexpected conjugate hydride addition with sodium borohydride to give the saturated alcohol, **2-ferrocenyl-1-cyclopentanol** (**9**); the unsaturated alcohol, **2-ferrocenyl-2-cyclopenten-1-ol** (**6**), obtained from hydrolysis of **7**, was not reduced upon similar treatment with sodium borohydride.

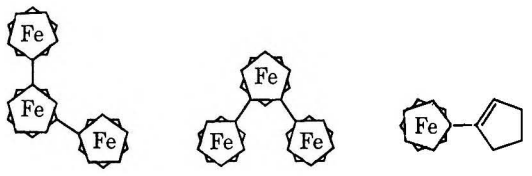
Whereas general methods of synthesis of systems consisting of directly bonded ferrocene nuclei have not been developed to any significant extent, two basic approaches have been used. One, which involves coupling of substituted ferrocenes, has been shown[2] to proceed without rearrangement to substituted biferrocenyls. This approach, however, is attended with serious difficulties at the present time since good general methods of synthesis of a useful range of coupling components is still undeveloped, particularly for appropriately constituted bi- and terferrocenyls.

The second approach lies in the construction of ferrocenylcyclopentadienes, which may then be complexed or "sandwiched" around iron to give the corresponding multinuclear ferrocene systems. The syn-

(1) Previous paper in this series: S. I. Goldberg, W. D. Loeble, and T. T. Tidwell, *J. Org. Chem.*, **32**, 4070 (1967).

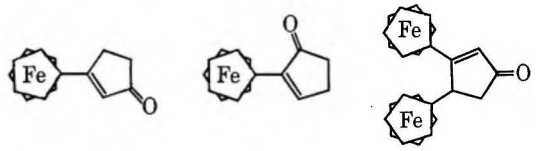
(2) S. I. Goldberg and R. L. Matteson, *ibid.*, **29**, 323 (1964).

theses of 1,1′-terferrocenyl[3] (**1**) and 1,2-terferrocenyl[4] (**2**) provide two examples of that approach; nevertheless, the method is also seriously limited, requiring difficult and numerous steps to achieve the synthesis of a desired cyclopentadiene. Clearly what is needed in this connection is a ready entry into ferrocenylcyclopentadiene systems from which a variety of multinuclear ferrocenes may be obtained. The present study was undertaken to investigate the feasibility of providing such an entry through allylic oxidation of 1-ferrocenylcyclopentene (**3**).



1 **2** **3**

The use of **3** for this purpose appeared to be advantageous, not only for the obvious reason that one ferrocenyl group is directly bonded to a five-membered ring that would become part of a second ferrocenyl group, but also for the practical reason that **3** is obtained in a one-step procedure from ferrocene by treatment of the latter with anhydrous hydrogen fluoride.[5] The question[5,6] of whether the ferrocenylcyclopentene obtained in this way is **3** and/or double bond isomers was easily settled by examination of the nmr spectrum determined from the material. The presence of a low field olefinic proton signal (δ 5.75) which integrated for only one proton clearly showed the structure to be that of the conjugated isomer (**3**).



4 **5** **10**

In principle, allylic oxidation of **3** might be expected to give the two isomeric conjugated ketones, **4** and **5**. These substances could then provide convenient entries into 1,3- and 1,2-disubstituted cyclopentadienes and subsequent conversions into a wide variety of multinuclear ferrocenes. This expectation was not, however, realized experimentally. Oxidation of **3** invariably took place on the more substituted side of the double bond, giving only 3-oxygenated 2-ferrocenyl-1-cyclopentenes. Establishment of this point, which incidentally is in accord with previous observations of relevant allylic oxidations,[7] lay in the chemical correlations made among the various allylic oxidation products obtained during the present study (Table I), and the definitive elucidation of the structure of the ketonic product as that of **5** and not **4**.

TABLE I

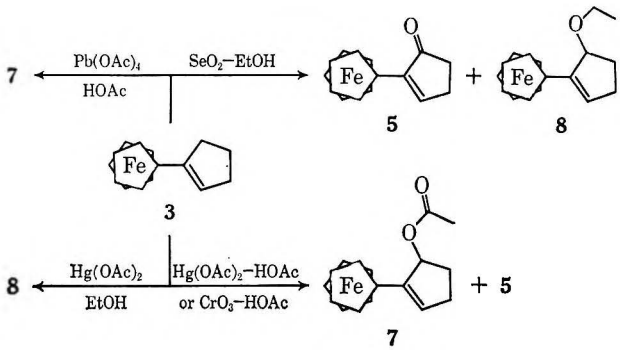
ALLYLIC OXIDATIONS OF 1-FERROCENYLCYCLOPENTENE

Reagent	Reaction time	Temp	Products 3[a]	5[b]	7[b]	8[b]
SeO_2[c]	Overnight	Reflux	4.4	20.3	...	4.4
CrO_3[d]	Overnight	Ambient	7.1	12.9	1.0	...
CrO_3[d]	5 hr	Ambient	25.0	2.7	2.0	...
CrO_3[e]	Overnight	Ambient	35.0	1.5	...	...
$Hg(OAc)_2$[d]	Overnight	Ambient	5.2	4.1	28.1	...
$Hg(OAc)_2$[c]	Overnight	Reflux	16.0	...	...	10.1
$Pb(OAc)_4$[d]	Overnight	Ambient	69.0	...	17.0	...

[a] % recovery. [b] % yield. [c] In 95% aqueous ethanol. [d] In acetic acid. [e] In acetone.

Elementary and spectral analyses of the ketonic product, which was obtained from reaction of **3** with selenium dioxide, chromic anhydride, or mercuric acetate (Table I), was clearly consistent with either structure **4** or structure **5**. The choice in favor of **5** was made by the fact that the chemical shift of the single vinylic proton signal in the nmr spectrum determined from the crystalline substance occurred at δ 7.47. A literature survey of chemical shifts of the α- and β-vinylic protons of conjugated cyclopentenones[8] revealed (20 cases) a range for the α protons to be δ 5.8–6.9 (av = 6.1), while a range of δ 7.2–7.8 (av = 7.6) was found for the β protons. By this criterion the vinylic proton resonance in the nmr spectrum determined from the ketonic product of the present study was attributed to a β proton thus allowing the choice between **4** and **5**.[9] The site of oxygen functions in the acetate (**7**) and the alcohol (**6**) were, therefore, both established by chemical correlation (Scheme II) of these substances with the ketone (**5**). Oppenauer oxidation of **6** gave **5** in 76% yield as the only detectable ketone. The structural relationship of **7** with **5** was established when it was found that hydrolysis of the former gave **6** in 75% yield. While chemical correlation of the remaining oxidation product—the ethoxy compound (**8**)—was not carried out, the site of the oxygen function in this compound was assigned to the same position as in the other oxidation products on the basis of the nmr spectrum obtained from purified compound. Principally, the structural assignment rests on the fact that the chemical shift of

SCHEME I



(3) K. L. Rinehart, Jr., D. G. Ries, C. H. Park, and P. A. Kittle, Abstracts, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan 1964, p 23C.

(4) S. I. Goldberg and J. G. Breland, Jr., Abstracts, 19th Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967, p 308.

(5) V. Weinmayr, *J. Amer. Chem. Soc.*, **77**, 3009 (1955).

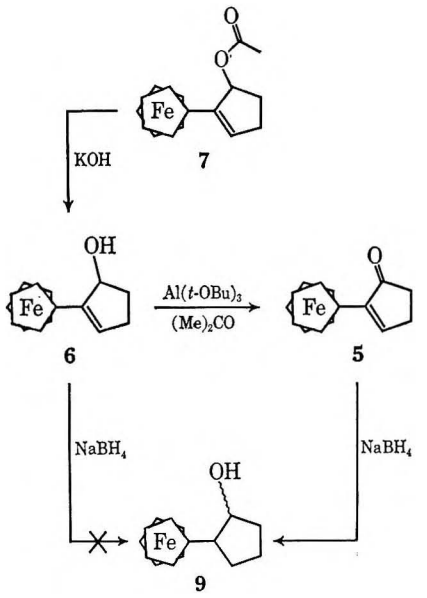
(6) M. Rosenblum, "Chemistry of the Iron Group Metallocenes," Interscience Publishers, Inc., New York, N. Y., 1965, p 161.

(7) K. B. Wiberg and S. D. Nielsen, *J. Org. Chem.*, **29**, 3353 (1964).

(8) W. Herz, S. Rajappa, M. V. Lakshmikantham, D. Raulais, and J. J. Schmid, *ibid.*, **32**, 1042 (1967); Y. Inubushi, Y. Sasaki, Y. Tsuda, and J. Nakano, *Tetrahedron Lett.*, 1519 (1965); R. H. Heck, *J. Org. Chem.*, **30**, 2205 (1965); C. H. DePuy, M. Isaks, K. L. Eilers, and G. F. Morris, *ibid.*, **29**, 3503 (1964); W. Herz, K. Ueda, and S. Inayama, *Tetrahedron*, **19**, 483 (1963); W. G. Dauben, K. Koch, S. L. Smith, and O. L. Chapman, *J. Amer. Chem. Soc.*, **85**, 2616 (1963); and W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *ibid.*, **85**, 19 (1963).

(9) The value of δ 6.26 for the vinylic proton resonance in **4**, communicated to us by Professor K. L. Rinehart,[3] is well within the range of α proton resonances given above.

SCHEME II



the signal due to the single vinylic proton in the ethoxy compound (δ 5.95) was found to be very close to those in the α,β-unsaturated acetoxy and hydroxy (δ 6.09 and 5.91, respectively) products.

An interesting observation made during this work was the conjugate reduction of the α,β-unsaturated ketone (**5**) to the saturated alcohol (**9**) by the action of sodium borohydride. Since sodium borohydride is generally regarded as a reagent whose use does not lead to conjugate hydride addition in α,β-unsaturated carbonyl systems the present example is noteworthy. Perhaps the explanation lies in the close proximity of the ferrocenyl and carbonyl groups in **5**, providing a favorable situation for coordination of the tetrahydroborate anion which is then able to transfer hydride to the olefinic linkage. Something of this sort is indicated by the facts that neither the isomeric α,β-unsaturated ketone (**4**)[3] nor the diferrocenyl-α,β-unsaturated ketone (**10**)[4] undergo conjugate hydride addition with sodium borohydride, but are each reduced to its corresponding unsaturated alcohol. Finally, failure of the allylic alcohol (**6**) to be reduced by the action of sodium borohydride supports the suggestion that reduction of **5** to **9** involves conjugate addition of hydride to the former.

The results of the present study do not indicate allylic oxidation of **3** to be of great practical synthetic utility for entry into new multinuclear ferrocene systems. All of the reactions are attended by fairly high degrees of decomposition and low yields of products. Of the reactions investigated (Table I), the use of selenium dioxide gave the highest direct conversion to **5**. The use of mercuric acetate or lead tetraacetate gave rise to cleaner reactions and provided the acetoxy compound (**7**) in fair yields. Since **7** was converted to the desired ketone (**5**) in a fairly efficient manner, the best route for synthesis of **5** from **3** appeared to be *via* **7**.

Experimental Section

General.—All temperatures were uncorrected. Melting points were determined in capillary tubes. Preparative column chromatography was used throughout this work to separate reaction products. In each case the Merck acid-washed alumina used was carefully packed, as a hexane slurry, into the column. The material to be chromatographed was then placed (in solution) on the top of the alumina column in a narrow band. Each column was then developed and eluted with appropriate solvents which were previously purified. Infrared spectra were determined with a Perkin-Elmer Model 337 recording spectrophotometer. A Varian Model A-60 nuclear magnetic resonance (nmr) spectrometer was used to record nmr spectra at 60 Mc in chloroform-*d* solution with tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in ppm under the δ convention relative to the TMS signal (zero ppm). Electronic spectra were determined with a Perkin-Elmer Model 202 recording spectrophotometer. Combustion analyses were carried out by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

1-Ferrocenylcyclopentene (3).—The procedure used here was based on that originally reported by Weinmayer.[5] Ferrocene (10.0 g, 53.8 mmol) was placed into a 100-ml stainless steel reaction vessel,[10] followed by addition of anhydrous liquid hydrogen fluoride (40.0 g, 2.00 mol). The vessel was closed and slowly heated over a period of 8–9 hr to a final temperature of 95° and then allowed to cool slowly to room temperature overnight. After additional cooling of the reaction vessel in an ice bath for 15 min, the vessel was opened and the contents were poured onto crushed ice (1 l.). Several ice–water rinsings were added, and the total hydrolyzate was allowed to warm to room temperature. The mixture deposited a yellow solid, and the initial green color of the supernatant was discharged within 30 min. The desired solid material was collected in a filter (Celite bed) and copiously washed with water. After the contents of the filter were air-dried, the material was placed in a paper extraction and submitted to continuous extraction by benzene in a Soxhlet apparatus until the extracts were colorless. Evaporation of the benzene left a viscous, dark red oil which solidified after about 30 min. Unchanged ferrocene (640 mg) was sublimed [*ca.* 100° (1 mm)], and the sublimation residue was then fractionated under careful distillation conditions. Crude 1-ferrocenylcyclopentene (**3**) was obtained as an orange-colored crystalline solid: 3.89 g (28.9% yield); bp 113–116° (0.35 mm); mp 50–56°. Recrystallization of the product from ethanol gave material which melted at 64–65° (lit.[6] mp 64–65°): infrared $\nu_{max}^{CCl_4}$ 3045, 1640 (trisubstituted, conjugated double bond), 3095 (ferrocene protons), 1105, and 995 cm^{-1} (unsubstituted ferrocene ring); nmr δ^{CDCl_3} 5.75 (1 H, multiplet, vinyl proton), 4.31 (2 H, triplet, α-ferrocenyl protons), 4.14 (2 H, triplet, β-ferrocenyl protons), 4.06 (5 H, singlet, ferrocenyl protons of unsubstituted ring), and 2.7–1.8 (6 H, complex, remaining cyclopentenyl protons); electronic spectrum $\lambda_{max}^{ethanol}$ 210 mμ (ϵ 23,900), sh 227 (21,000), 276 (9180), and 447 (313) [lit.[5] $\lambda_{max}^{isooctane}$ sh 227 mμ (ϵ 19,400), 276 (8400), sh 325 (424), and 442 (270).

Several larger runs, using 50–100 g of ferrocene, were carried out[11] in a 3-l. stainless steel vessel[10] in order to accumulate sufficient material.

Properties of Products.—Given below is an account of the physical and spectral properties of the new compounds obtained from the experiments carried out during this investigation.

2-Ferrocenyl-2-cyclopenten-1-one (5) was an orange crystalline solid: mp 83–86°; infrared $\nu_{max}^{CCl_4}$ 3040, 1630 (trisubstituted conjugated double bond), 3095 (ferrocene protons), 1715 (conjugated ketone), 1095 and 1000 cm^{-1} (unsubstituted ferrocene ring); nmr δ^{CDCl_3} 7.47 (center, W = 5 cps, 1 H, multiplet, vinyl proton), 4.74 (2 H, triplet, J = 2 cps, α-ferrocenyl protons), 4.25 (2 H, triplet, J = 2 cps, β-ferrocenyl protons), 4.04 (5 H, singlet, ferrocenyl protons of unsubstituted ring), 2.50 and 2.48 (4 H, singlets, remaining cyclopentenone ring protons); electronic spectrum $\lambda_{max}^{ethanol}$ 212 mμ (ϵ 16,900), 258 (8040), 285 sh (6470), 382 (412), and 450 sh (300).

Anal. Calcd for $C_{15}H_{14}FeO$: C, 67.70; H, 5.30. Found: C, 68.04; H, 5.57.

2-Ferrocenyl-2-cyclopenten-1-ol (6) was a yellow-orange crystalline solid: mp 105–106°; infrared $\nu_{max}^{CCl_4}$ 3600, 3550, 1045 (hydroxyl group), 3040, 1640 (trisubstituted conjugated double bond), 3095 (ferrocene protons), 1103, and 995 cm^{-1} (unsubstituted ferrocene ring); nmr δ^{CDCl_3} 5.91 (1 H, triplet, J = 2 cps, vinyl proton), 4.97 (center, W = 16 cps, 1 H, unresolved, hydroxyl proton or carbinol proton), 4.47 (2 H, apparent sextet,

(10) American Instrument Co., Inc., Silver Springs, Md.

(11) We wish to acknowledge our thanks to Mr. M. G. Gergel of Columbia Organic Chemicals Co. through whose courtesy arrangements for carrying out these larger runs were made.

α-ferrocenyl protons), 4.23 (2 H, triplet, J = 2 cps, β-ferrocenyl protons), 4.10 (5 H, singlet, ferrocenyl protons of unsubstituted ring), 2.37 and 2.05 (2 H and 2 H, complex, remaining cyclopentenol ring protons); electronic spectrum $\lambda_{max}^{ethanol}$ 210 mμ (ε 22,000), 228 (18,800), 277 (9300), 336 sh (500), and 450 (250).

Anal. Calcd for $C_{15}H_{16}FeO$: C, 67.19; H, 6.01. Found: C, 67.14; H, 5.89.

2-Ferrocenyl-3-ethoxy-1-cyclopentene (**8**) was yellow-orange oil: infrared ν_{max} 3050, 1640 (trisubstituted, conjugated double bond), 3100 (ferrocene protons), 2950, 2870, 1375, 1120 (ethoxy group), 1100 and 1000 cm^{-1} (unsubstituted ferrocene ring); nmr δ^{CDCl_3} 5.95 (center, W = 6 cps, 1 H, unresolved, vinyl proton), 4.65 (center, W = 8 cps, 1 H, complex, >CH–O), 4.45 (2 H, apparent sextet, α-ferrocenyl protons), 4.18 (2 H, triplet, J = 2 cps, β-ferrocenyl protons), 4.08 (5 H, singlet, ferrocenyl protons of unsubstituted ring), 3.37 (2 H, doublet of quartets, J = 7 and 2 cps, –O–CH_2–), 2.33 and 2.10 (2 H and 2 H, complex, remaining cyclopentene ring protons), 1.25 (3 H, triplet, J = 7 cps, –CH_3); electronic spectrum $\lambda_{max}^{ethanol}$ 235 mμ (ε 19,500), 273 (34,200), 304 sh (480), and 447 (250).

Anal. Calcd for $C_{17}H_{20}FeO$: C, 68.94; H, 6.81. Found: C, 69.32; H, 6.65.

2-Ferrocenyl-3-acetoxy-1-cyclopentene (**7**) was a red-orange crystalline solid: mp 86–88°; infrared $\nu_{max}^{CCl_4}$ 3045, 1640 (trisubstituted conjugated double bond), 2960, 2870, 1730, 1470, 1235 (acetoxy group), 3090, 1100, and 1000 cm^{-1} (ferrocenyl group); nmr δ^{CDCl_3} 6.09 (1 H, apparent triplet, J = 2 cps, vinyl proton), 4.31 (5 H, complex α- and β-ferrocenyl protons and >CH–O–), 4.09 (5 H, singlet, ferrocenyl protons of unsubstituted ring); 2.38 (center, W = 9 cps, 4 H, complex, remaining cyclopentene ring protons), 2.10 (3 H, singlet, CH_3CO).

Anal. Calcd for $C_{17}H_{18}FeO_2$: C, 65.83; H, 5.85. Found: C, 65.84; H, 5.97.

2-Ferrocenylcyclopentan-1-ol (**9**) was yellow crystalline solid: mp 67–68°; infrared $\nu_{max}^{CCl_4}$ 3590, 3500, 1047 (hydroxy group), 3100, 1103, and 998 cm^{-1} (monosubstituted ferrocenyl group); nmr δ^{CDCl_3} 4.13 (10 H, complex, >CH–O and all ferrocenyl protons), 1.78 (center, W = 14 cps, 7 H, unresolved, remain cyclopentanyl protons), and 1.27 (1 H, singlet, hydroxyl protons); electronic spectrum $\lambda_{max}^{ethanol}$ 207 mμ (ε 20,000) and 450 (250).

Anal. Calcd for $C_{15}H_{18}FeO$: C, 66.69; H, 6.72. Found: C, 66.92; H, 6.79.

Allylic Oxidation of 1-Ferrocenylcyclopentene (**3**). **A. Selenium Dioxide in Aqueous Ethanol.**—To a solution of 1-ferrocenylcyclopentene (**3**) (1.00 g, 3.97 mmol) in 30 ml of aqueous ethanol, maintained under gentle reflux and briskly stirred, was added dropwise a solution of selenium dioxide (500 mg, 4.95 mmol) in 25 ml of 95% aqueous ethanol. Reflux heating and stirring was continued overnight (16–18 hr) before the reaction mixture was cooled to room temperature and the precipitated selenium metal separated by filtration. Reduced pressure evaporation of the filtrate to dryness left a residue which was taken up in the minimum volume of methylene chloride and carefully placed onto an alumina column. Development of the column was initially carried out with benzene which eluted unreacted starting material (**3**); 44 mg, 4.4% recovery. The column was then eluted with a 1:1 (v/v) mixture of benzene and ether which produced a yellow band. Collection and evaporation of that material provided 2-ferrocenyl-3-ethoxy-1-cyclopentene (**8**); 40 mg, 4.4% yield. The major band of the chromatogram, which was readily eluted with pure ether, yielded the ketone, **2-ferrocenyl-2-cyclopenten-1-one** (**5**), 197 mg (20.3% yield).

B. Chromic Anhydride. 1. Acetic Acid Solvent.—To a stirred solution of 1-ferrocenylcyclopentene (**3**) (2.00 g, 7.94 mmol) in 40 ml of glacial acetic acid was added dropwise a solution of chromic anhydride (1.50 g, 15.0 mmol) in 20 ml of glacial acetic acid containing 2 ml of water. The reaction mixture was kept at room temperature and stirred overnight (16–18 hr). It was then transferred to a separatory funnel, neutralized with aqueous potassium hydroxide solution, and extracted with ether until a colorless ether extract was obtained. After the combined extracts were washed with three small portions of water, they were dried over anhydrous sodium sulfate and evaporated to dryness. The gummy residue which resulted was taken up in the minimum volume of benzene and carefully washed onto the top of an alumina column. Benzene was used to develop and elute two bands of material. From the faster moving band recovered starting material (140 mg, 7.1% recovery) was obtained, while the slower moving band gave 20 mg (1.0% yield) of **2-ferrocenyl-3-acetoxy-1-cyclopentene** (**7**). A third band developed with the use of 1:1 (v/v) benzene–ether. It yielded 252 mg (12.9% yield) of **2-ferrocenyl-2-cyclopenten-1-one** (**5**).

In another experiment, exactly the same quantities and concentrations of reactants were used. In this case, however, the room temperature reaction was allowed to proceed during only 5 hr. The reaction mixture was worked up as described above, and chromatography again gave the same three substances: starting material **3** (500 mg, 25% recovery), the acetoxy compound **7** (35 mg, 2.0% yield), and the ketone **5** (41 mg, 2.7% yield).

2. Acetone Solvent.—A solution of chromic anhydride (1.00 g, 10.0 mmol) in 25 ml of acetone was added dropwise to a stirred solution of 1-ferrocenylcyclopentene (**3**) (1.00 g, 3.97 mmol). After the reaction mixture was stirred at room temperature overnight (16–18 hr), it was passed through a filter, and the filtrate was evaporated under reduced pressure. The residue, taken up in the minimum volume of benzene, was chromatographed on alumina. Initial elution with 1:1 (v/v) hexane–benzene gave recovered starting material (350 mg, 35.0% recovery). After changing to pure benzene, two additional bands were developed and eluted. The first (faster) gave **2-ferrocenyl-2-cyclopenten-1-one** (**5**) (10 mg, 1.5% yield), and the second band yielded a substance (22 mg) which, on the basis of its infrared and nmr spectra, appeared to be an acetone condensation product of the unsaturated ketone (**5**).

C. Mercuric Acetate. 1. Acetic Acid Solvent.—A solution of mercuric acetate (4.60 g, 14.4 mmol) in 15 ml of glacial acetic acid containing 2 ml of water was allowed to drip into a stirred solution of 1-ferrocenylcyclopentene (**3**) (4.00 g, 15.9 mmol) at room temperature. The dark-colored solution that resulted was stirred overnight and then passed through a filter to remove the metallic mercury that was deposited. The filtrate was diluted with 250 ml of water and then extracted with ether until a colorless ether extract was obtained. The combined extracts were washed with saturated aqueous sodium carbonate solution until evolution of carbon dioxide was no longer apparent. The ethereal residue was then washed with three portions of water, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was carefully placed (minimum benzene solutions) onto an alumina column and chromatographed. Starting material (230 mg, 5.2% recovery) was obtained from a hexane–benzene [1:1 (v/v)] eluate. A second band, eluted with pure benzene, gave **2-ferrocenyl-3-acetoxy-1-cyclopentene** (**7**) (1.27 g, 28.1% yield). Continued elution with benzene produced a third band from which **2-ferrocenyl-2-cyclopenten-1-one** (**5**) (120 mg, 4.1% yield) was isolated.

2. Aqueous Ethanol Solvent.—A mixture of 1-ferrocenylcyclopentene (**3**) (2.00 g, 7.94 mmol) and mercuric acetate (2.30 g, 7.22 mmol), dissolved in 60 ml of 20% (v/v) aqueous ethanol, was stirred and heated under gently reflux overnight (16–18 hr). After the reaction mixture had cooled to room temperature, it was diluted with 100 ml of water and then extracted with benzene until a colorless extract was obtained. The oily residual mass, obtained from evaporation of the combined and dried (anhydrous magnesium sulfate) benzene extracts, was dissolved in the minimum volume of benzene and carefully washed onto a column of alumina. Initial elution with 1:1 (v/v) hexane–benzene gave starting material (320 mg, 16.0% recovery). Continued attempts at column development produced only one more band (eluted with benzene) which yielded **2-ferrocenyl-3-ethoxy-1-cyclopentene** (**8**); 180 mg, 10.1% yield.

D. Lead Tetraacetate.—A solution of lead tetraacetate (5.50 g, 12.4 mmol) in 25 ml of glacial acetic acid was allowed to drip into a stirred solution of 1-ferrocenylcyclopentene (2.00 g, 7.94 mmol) in 35 ml of glacial acetic acid. After the reaction mixture was stirred at room temperature overnight (16–18 hr) and then diluted with 300 ml of water, it was exhaustively extracted with ether. The combined ether extracts were first washed with saturated aqueous sodium carbonate solution to neutralize the acetic acid and then washed with three portions of water. The ethereal residue was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to a residue which was dissolved in the minimum volume of benzene and chromatographed on alumina in the usual way. Only starting material (1.38 g, 69.0% recovery) and **2-ferrocenyl-3-acetoxy-1-cyclopentene** (**7**) (130 mg, 17.0% yield) were obtained [1:1 (v/v) hexane–benzene and pure benzene elution, respectively].

Hydrolysis of 2-Ferrocenyl-3-acetoxy-1-cyclopentene (**7**) **to 2-Ferrocenyl-2-cyclopenten-1-ol** (**6**).—A mixture of potassium

hydroxide (997 mg, 17.8 mmol), the acetoxy compound (7) (1.27 g, 4.10 mmol), and 125 ml of water was stirred and heated on a steam bath overnight. After the reaction mixture had cooled to room temperature, it was exhaustively extracted with ether. Evaporation of the combined and dried (anhydrous magnesium sulfate) ether extracts gave residual material which was placed onto a column of alumina in benzene solution. Elution of the column with benzene gave only a trace of the starting ester. Elution with pure ether provided 820 mg (74.6% yield) of 2-ferrocenyl-2-cyclopenten-1-ol (6).

Oxidation of 2-Ferrocenyl-2-cyclopenten-1-ol (6) to 2-Ferrocenyl-2-cyclopenten-1-one (5). A. Oppenauer Procedure.—A reaction mixture of 2-ferrocenyl-2-cyclopenten-1-ol (6) (243 mg, 0.907 mmol), aluminum isopropoxide (3.50 g, 17.2 mmol), acetone (10 ml), and toluene (50 ml) was stirred and heated under reflux for 18 hr. After the mixture had cooled to room temperature, it was washed with two portions of 50% aqueous acetic acid and then with three portions of water. The residual toluene solution was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to a residue which was placed (benzene solution) on an alumina column for chromatographic separation. Development and elution of the column with benzene gave two bands. An odoriferous, yellow oil (130 mg), which was not identified, was obtained from the eluate of the faster moving band. The slower moving band gave 182 mg (75.5% yield) of 2-ferrocenyl-2-cyclopenten-1-one (5).

B. Activated Manganese Dioxide.—A solution of the alcohol (6) (210 mg, 0.784 mmol) in 50 ml of methylene chloride was stirred overnight at room temperature in the presence of activated manganese dioxide[12] (1.50 g, 17.1 mmol). All of the solid material was then collected in a filter and washed with small portions of methylene chloride until a colorless wash was obtained. The washes were combined with the original filtrate, and the whole was evaporated to a residue which was chromatographed on alumina in the usual way. Elution with benzene gave the ketone (5) (9 mg, 7% yield), while unchanged starting alcohol (6) (70 mg, 30% recovery) was obtained from ether eluates.

Reduction of 2-Ferrocenyl-2-cyclopenten-1-one (5) to 2-Ferrocenyl-1-cyclopentanol (9).—A solution of 2-ferrocenyl-2-cyclopenten-1-one (5) (114 mg, 0.429 mmol) in 25 ml of methanol was stirred and maintained at 0° while sodium borohydride (1.00 g, 26.5 mmol) was added. After addition was complete, the mixture was stirred for an additional 10 min and then diluted with 250 ml of water. The combined ether extracts, obtained from exhaustive extraction of the diluted reaction mixture, were dried and evaporated to a residue which was chromatographed on alumina. Elution with ether gave 73 mg (63% yield) of the saturated alcohol, 2-ferrocenyl-1-cyclopentanol (9).

Failure of Sodium Borohydride to Effect Reduction of 2-Ferrocenyl-2-cyclopenten-1-ol (6).—Sodium borohydride (67 mg, 1.8 mmol) was added to 25 ml of a cold (0°) methanolic solution of 2-ferrocenyl-2-cyclopenten-1-ol (165 mg, 0.557 mmol) while the latter was stirred vigorously. The stirring was continued for 10 min after the addition was complete, and then the reaction mixture diluted with 250 ml of water. The hydrolyzate was exhaustively extracted with ether, which extracts were combined, dried, and evaporated to yield only unchanged starting material—the unsaturated alcohol (6)—identified by means of its infrared spectrum, 150 mg (91% recovery).

Registry No.—**3**, 12260-67-2; **5**, 12260-661-; **6**, 12260-68-3; **7**, 12260-71-8; **8**, 12260-72-9; **9**, 12260-69-4.

(12) Beacon Chemical Industries, Inc., Cambridge, Mass.

Synthesis of Macrocyclic o-Phthalate Esters from the Corresponding Polyesters[1]

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Received August 11, 1967

The esterification of phthalic anhydride with selected glycols in the presence of suitable catalysts (*e.g.*, tetrabutyl *o*-titanate) yields polyesters, from which can be distilled, at 220–260° (0–4 mm), the respective macrocyclic *o*-phthalate esters 1–11. The *o*-phthalate polyesters of diethylene, triethylene, 1,5-pentylene, and 1,6-hexylene glycols can be converted into the respective macrocycles 1–4 in nearly quantitative yields. Macrocyclic esters 5–11 distill from the corresponding polyesters in relatively poor yields. Saponification of the macrocycles 10a and 10b produced the two diastereoisomers of 2-(2-hydroxypropoxy)-1-propanol which have been characterized as their bis-*p*-nitrobenzoates.

Prior to 1930, it was believed that condensations of difunctional compounds always gave rise to cyclic products. Carothers and coworkers[2] established that the condensation of difunctional compounds produces *linear polymers* unless five- or six-membered rings are possible. It was also found, however, that both "monomeric" and higher order macrocycles can often be obtained by thermolysis of these linear polymers *in vacuo*. In fact, cyclic esters of aliphatic dicarboxylic acids, with 11- to 36-membered rings, were obtained in yields of up to 65% by thermolysis of catalyzed polyesters at 270°.[2,3] Small amounts of macrocyclic esters apparently exist in equilibrium with polyester and one another and as one or more of the macrocycles is removed by distillation, more is formed in an attempt to maintain this equilibrium. Although Carothers, *et al.*,[2] suggested that thermolysis of condensation polymers should be a rather general preparative method for macrocycles with practical advantages over high dilution techniques, it appears to have received little subsequent attention.[4-6] The only reference to *o*-phthalate macrocycles is a patent[3] giving melting points of the "monomeric" and "dimeric" macrocyclic ethylene *o*-phthalates (**5** and **6**); however, no other specific information was disclosed. This paper reports on the preparation of *o*-phthalate macrocycles by the polyester thermolysis method.

Polyester Preparation.—Because *o*-phthalic acid is eliminated from carboxy terminated chains as phthalic anhydride, which sublimes and clogs the apparatus, it is expedient to prepare polyesters with acid numbers of less than about five before subjecting them to thermolysis (Chart I).

Although *o*-phthalic acid is relatively difficult to esterify completely, such polyesters have been obtained in 2–6 hr by a melt polymerization technique which employs efficient esterification catalysts, a 20–40% molar excess of the glycol, and precautions to minimize

(1) Presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

(2) W. H. Carothers, *et al.*, in "Collected Papers of Wallace H. Carothers on Polymerization," H. Mark and G. S. Whitby, Ed., Interscience Publishers, Inc., New York, N. Y., 1940.

(3) E. W. Spanagel U. S. Patent 2,092,031 (1937).

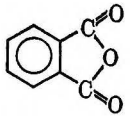
(4) L. I. Belenkii, *Russ. Chem. Rev.*, **33**, 551 (1964).

(5) C. E. Berr, *J. Polym. Sci.*, **16**, 591 (1955).

(6) S. D. Ross, E. R. Coburn, W. A. Leach, and W. B. Robinson, *ibid.*, **13**, 406 (1954).

TABLE I

ESTERIFICATION AND THERMOLYSIS CONDITIONS

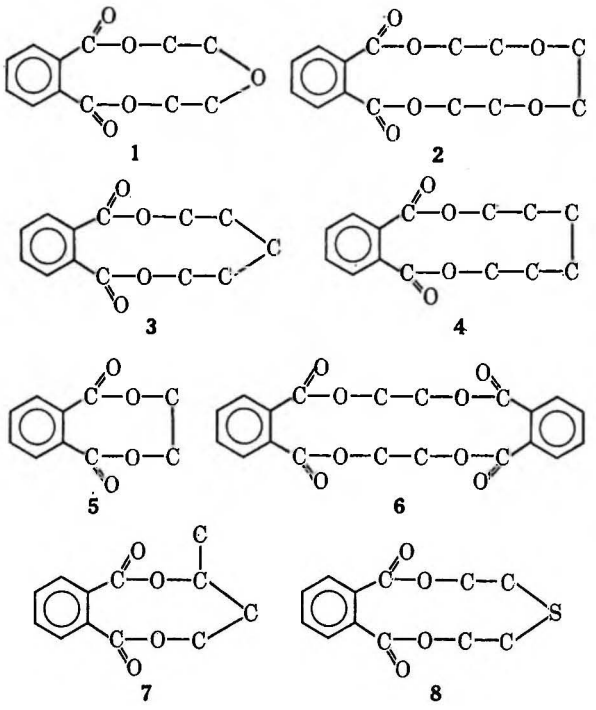


+ 1.2HOROH $\xrightleftharpoons{-H_2O}$ hydroxy terminated polyester $\rightleftharpoons$ macrocyclic esters(s) + 0.2HOROH

	Esterification[a]		Thermolysis				
R	Max temp, °C	Time, hr	Temp, °C	Pressure, mm	Time, hr	Product(s)	Yield, % (theoretical)
$-(CH_2)_2O(CH_2)_2-$	220	3.0	220–230	1–2	6.5	1	89
$-(CH_2)_2O(CH_2)_2O(CH_2)_2-$	220	3.7	250–260	1–2	5.0	2	90
$-(CH_2)_5-$	235	1.3	235–260	1–2	5.25	3	94
$-(CH_2)_6-$	235	1.3	235–260	1–2	8.5	4	88
$-(CH_2)_2-$	235	4.2	235–275	1–2	4.2	5, 6	3, 0.5
$-CH(CH_3)CH_2CH_2-$	225	4.0	240	2–5	7.0	7	5
$-(CH_2)_2S(CH_2)_2-$	200	*a*	220–240	2–5	1.1	8	2

[a] Reactions catalyzed by 0.36% $Ti(OBu)_4$. Fusion cooks using molar ratio of glycol to anhydride of 1.2/1.0 for all but the last example. This was a solvent (xylene) cook using a 1.4:1.0 ratio of glycol to anhydride and refluxed 4 hr (temp 145–200°). Xylene was removed prior to thermolysis.

CHART I



glycol loss. Catalysts used serve subsequently as thermolysis catalysts. Specific esterification data are included in Table I.

Thermolysis of *o*-Phthalate Polyesters of "Simple" Glycols.—Tables I and II summarize those thermolyses conducted on *o*-phthalate polyesters of "simple" glycols. Preliminary thermolyses were conducted in most cases to find the appropriate temperature range. Distillation was always rapid until most of the excess glycol was removed. As the distillation subsided the temperature was generally raised further in an attempt to maintain a reasonable rate. The occurrence of side reactions dictated against going above 240° in the last two thermolyses. In the first four reactions listed, conversion of the respective polyesters into 1,3,4,6,7,9-hexahydro-2,5,8-benzotrioxacycloundecin-1,9-dione (**1**), 1,3,4,6,7,9,10,12-octahydro-2,5,8,11-benzotetraoxacyclotetradecin-1,12-dione (**2**), 1,4,5,6,7,9-hexahydro-3(H)-2,8-benzodioxacycloundecin-1,9-dione (**3**) and 1,3,4,5,6,7,8,10-octahydro-2,9-benzodioxacyclododecin-1,10-dione (**4**) was essentially quantitative. The higher thermolysis temperature required for **3**, as compared to that required for **1**, may be due to the additional nonbonded interactions incurred when oxygen is replaced by methylene in the ring. Lower volatilities and statistical probabilities of formation may explain why a higher temperature had to be employed to obtain **2** than was needed for **1** and why **4** was obtained more slowly than **3** under the same conditions. In the case of poly(ethylene *o*-phthalate), after most of the excess glycol had distilled, the distillation practically stopped and raising the temperature to 275° did not noticeably accelerate it. The distillate did, however, contain small amounts of 1,3,4,6-tetrahydro-2,5-benzodioxacyclooctin-1,6-dione[3] (**5**) and 5,7,8,10,15,17,18,20-octahydrodibenzo[*c*,*k*]-1,6,9,14-tetraoxacyclohexadecin-5,10,-15,20-tetrone[3] (**6**). Compound **6** was the only "dimer" detected in this study, perhaps because the other dimers are too high boiling to distill under the conditions employed. Unlike the larger ring compounds, **5**, which has an eight-membered ring, could be constructed with Fisher–Taylor–Hirschfelder atomic models only by twisting the carbonyl groups well out of the plane of the benzene ring. This provides a rationale for the poor yield. 3-Methyl-1,4,5,7-tetrahydro-3(H)-2,6-benzodioxacyclononin-1,7-dione (**7**) and 1,3,4,6,7,9,-hexahydro-2,8-benzodioxa-5-thiacycloundecin-1,9-dione (**8**) were obtained only in poor yield and were accompanied by other decomposition products.

Tetrabutyl *o*-titanate reacts with water and/or end groups during the esterification (*n*-butyl alcohol is evolved) so that the active esterification and thermolysis catalyst is titanium in some other form (probably a complex polymeric structure).

Thermolysis of "Poly(dipropylene *o*-phthalate)."—Commercial dipropylene glycol (DPG) is reported to be a mixture of the three positional isomers 1-(2-hydroxypropoxy)-2-propanol (A), 2-(2-hydroxypropoxy)-1-propanol (B), and 2-(1-hydroxypropoxy)-1-propanol (C).[7–10]

Each positional isomer is composed of two diastereoisomers. Havlik and Lawson[9,10] have separated Union Carbide Corp. DPG into four significant frac-

(7) British Patent 835,717 (1960); *Chem. Abstr.*, **55**, 2696*f* (1961).

(8) A. J. Havlik and A. F. Hildebrandt, *J. Polym. Sci.*, **41**, 533 (1959).

(9) A. J. Havlik and D. D. Lawson, Research Summary 36-14 (B), 145–8, Jet Propulsion Laboratory, Pasadena, 1962.

(10) D. D. Lawson and A. J. Havlik, Space Programs Summary 37-22 (D), 94–6, Jet Propulsion Laboratory, Pasadena, 1963.

TABLE II

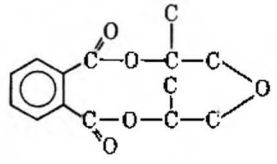
PRODUCT CHARACTERIZATION[a]

Compd	Recrystn solvents[b]	Mp, °C	Calcd C	Calcd H	Calcd Sapon equiv	Calcd Mol wt	Found C	Found H	Found Sapon equiv[c]	Found Mol wt
1[d]	1.33 e:p	61.5–62.5	61.01	5.12	118.1	236	60.83	5.06	121.0	232
2[e]	1 b:n, 1.5 m:w	119.5–121.0	59.99	5.76	140.7	280	59.78	5.58	143.0	275
3	4 h:b, n	100.8–102.3	66.66	6.02	117.1	234	66.90	6.16	117.4	230
4	m, e	63.7–64.5	67.73	6.50	124.2	248	67.76	6.56	125.5	239
5	10 e:p	59.5–61.8[f]								
6	1.5 n:a	193.0–195.0[f]								
7	n, 10 h:b	78.6–78.8	65.45	5.49	110.1	220	65.18	5.30	112.6	217
8[g]	e, 2 h:b, m	107.2–107.7	57.13	4.79	126.2	252	56.98	4.69	127.2	250

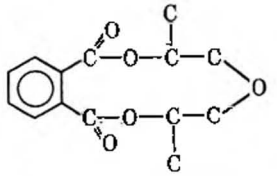
[a] The ir spectra of 1–8 all had strong bands near 5.77, 7.85, 8.90, 9.35, and 13.45 μ typical of *o*-phthalate esters and no OH bands. [b] Solvents: p = petroleum ether; m = methanol; n = naphtha (bp 160–200°); w = water; h = hexane; b = benzene; e = ether; a = acetone; 4 h:b = four volumes of h to one of b; etc. [c] Phthalic acid and the parent glycol were isolated upon saponification of all the new macrocycles by the method of J. F. Shay, S. Skilling, and R. W. Stafford, *Anal. Chem.*, 26, 652 (1954). Identification by comparison of ir spectra with spectra of authentic samples. [d] Nmr signals ($CDCl_3$) at δ 3.89 (4 H half of $A_2'B_2'$ pattern, 2 (CCH_2O)), at 4.43 (4 H half of $A_2'B_2'$ pattern, 2 ($COOCH_2C$)), at 7.65 (4 H $A_2'B_2'$ pattern, aromatic protons). [e] Nmr signals ($CDCl_3$) at δ 3.58 (4 H single peak, $O(CH_2)_2O$), at 3.77 (4 H half of $A_2'B_2'$ pattern, 2(CCH_2O), at 4.47 (4 H half of $A_2'B_2'$ pattern, 2 ($COOCH_2C$)), at 7.62 (4 H $A_2'B_2'$ pattern, aromatic protons). [f] Lit.[3] mp of 5 is 55° and 6 is 198°. [g] *Anal.* Calcd for 8: S, 12.71. Found: S, 12.50.

tions by glpc. From their assignments for these fractions and the relative peak areas the approximate composition is deduced to be 43% A, 47% B, 5.7% C, and 4.5% unknown. Whether or not the 5.7 and the 4.5% fractions which have similar retention times could be the individual diastereoisomers of positional isomer C is not clear. We have repeated this work and obtained the same four fractions in similar percentages.

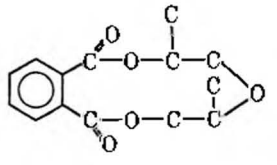
Thermolysis of "poly(dipropylene *o*-phthalate)" gave an alkali insoluble liquid–crystal paste believed to be a mixture of the six macrocyclic *o*-phthalates **9a–11b**.



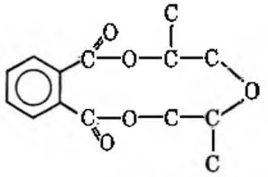
meso cis (**9a**)



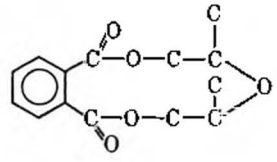
racemic *trans* (**9b**)



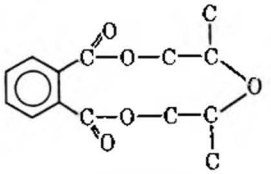
racemic *cis* (**10a**)



racemic *trans* (**10b**)



meso cis (**11a**)



racemic *trans* (**11b**)

The crystalline portion of this mixture was separated from the oil and a combination of fractional crystallization and chromatography separated this portion into two pure isomers. These have been shown to be the diastereoisomers of 3,6-dimethyl-1,3,4,6,7,9-hexahydro-2,5,8-benzotrioxacycloundecin-1,9-dione (**10a** and **10b**); however, differentiation between them has not been accomplished.

Saponification of **10a** and **10b** produced the two diastereoisomers of 2-(2-hydroxypropoxy)-1-propanol (B) which have been characterized for the first time as their bis-*p*-nitrobenzoate derivatives. Glpc assay of the isomeric mixture of glycols obtained upon saponification of the total macrocyclic mixture indicated that **10a** and **10b** comprise about 65% of this mixture.

Experimental Section

General.—Melting points were determined in a capillary using a Laboratory Devices Mel-Temp apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Nmr spectra were obtained by Nuclear Magnetic Resonance Specialties, Inc., using a Varian Model A-60 spectrometer operating at 60 Mc. Chemical shifts are expressed in parts per million from the internal standard tetramethylsilane (δ). Molecular weights were determined using a Mechrolab vapor pressure osmometer, Model 301 (solvent, benzene). Infrared spectra were determined with a Perkin-Elmer Infracord spectrophotometer, Model 137. Nujol mulls were prepared for solids and liquids were used neat except for the dipropylene glycols (1% carbon disulfide solutions).

Materials.—The following materials were purchased from the indicated suppliers in the purest available grades and used, without further purification: phthalic anhydride, Koppers Co., Inc.; tetrabutyl *o*-titanate, E. I. du Pont de Nemours and Co.; 1,3-butanediol and 1,6-hexanediol, Celanese Chemical Co.; 1,5-pentanediol, ethylene glycol, diethylene glycol, triethylene glycol, dipropylene glycol, and bis(2-hydroxyethyl sulfide), Union Carbide Corp.

Preparation and Thermolysis of "Simple" Poly(*o*-phthalates).—Into a 3-l., five-necked flask was placed 2200 g of a 1.2:1.0 *M* mixture of the respective glycol and phthalic anhydride along with 8.0 g of tetrabutyl *o*-titanate.

The flask was equipped with a heating mantle, mechanical stirrer, thermometer, temperature controller, gas inlet tube, and a vacuum jacketed fractionating column (length = 47 cm, i.d. = 1.5 cm) filled with $^1/_8$ in. i.d. glass helices.[11] A still head with thermometer and take-off condenser was mounted on the fractionating column. Carbon dioxide was bubbled through the mixture at a rate of 1.8 l./min. The temperature was raised to that indicated in Table I as fast as possible without driving the temperature of the distilling vapors at the top of the column above about 100°. This temperature was held for the indicated time (Table I) during which the acid number had dropped to <5. The gas inlet tube was then replaced by a hose adapter (with stopcock) to which was attached a McLeod gauge and the fractionating column by a still head and short air condenser leading to a receiver (a 3-l. two-necked round-bottom flask) in an ice–water bath. The flask and still head were insulated and

(11) This type of partial condenser proved ideal as it allows water to escape easily, returns glycol and anhydride almost quantitatively to the vessel, and resists clogging in most cases.

the system was evacuated[12] to 1–4 mm. When the initial thermolysis temperature, as given in Table I, is higher than the maximum esterification temperature, the initial thermolysis temperature was approached rapidly. Once reached, this temperature was held for a time and then gradually increased to the maximum indicated in an effort to maintain a reasonable distillation rate.

In the preparation of 1–4 the distillations were continued until the polyester was practically gone. In the preparation of 5 and 6 the distillation essentially stopped after the excess glycol distilled and was terminated when the rate could not be increased by gradually raising the temperature to 275°. In the preparation of 7 and 8 the reactions were stopped arbitrarily as it became evident that side reactions were predominating. The distillates were melted and poured into water (vigorous agitation) and sodium carbonate was added to bring the pH to 9–10. Compounds 1–4 were isolated by filtration, washing, and drying. The white crystals thus obtained had melting points only 1–4° lower than those of the subsequent analytical samples and the yields reported are based on these materials. Compounds 5 and 6 were isolated by ether extraction of the aqueous suspension (partial evaporation of the ether extract caused precipitation of 6 and evaporation to near dryness gave 5). Compound 7 was isolated by filtration, followed by recrystallization from methanol. Compound 8 was isolated by chloroform extraction, evaporation of the chloroform, and recrystallization of the residue from methanol. Analytical samples of 1–8 were obtained by recrystallization to constant melting point using the solvents indicated in Table II.

Preparation and Thermolysis of "Poly(dipropylene *o*-phthalate)."—Using the same apparatus and procedure as described above, a polyester of acid number <3 was prepared (maximum temperature 225°, 5.5 hr) from 1080 g (7.3 mol) of phthalic anhydride, 1205 g (9.0 mol) of dipropylene glycol (DPG), and 6.0 g of stannous oxalate. The system was modified and evacuated to 1–2 mm; the temperature was raised gradually to and kept at 235° for 3.8 hr. The distillate (577 g) was melted, poured into ice water in a Waring Blendor, and neutralized with sodium carbonate. The aqueous phase was decanted from an oil. This oil was washed with two 2.8-l. portions of ice water which resulted in its partial crystallization. The sludge was dissolved in 500 ml of chloroform. This solution was distilled and a 289 g (15%) fraction boiling at 130–135° (0.15 mm) was collected. This became predominantly crystalline upon cooling. Its origin, saponification equivalent (134.0; calcd 132.2), ir spectrum,[13] and chromatographic behavior[14a] suggest that it is a mixture of the isomeric macrocycles 9a–11b. A portion of this mixture (140 g) was triturated with 3:1 DPG–methanol. Filtration produced 105 g of white crystals, mp 82–112°. Recrystallization from 3:2 petroleum ether–benzene gave a 42-g fraction (F_1) melting at 125–130°. Evaporation of the mother liquor produced an oily crystalline mass. This was triturated with petroleum ether and the crystals were collected by filtration, washed with a little ether, and recrystd from 4:1 methanol–water to give 31 g of another fraction (F_2) melting at 96–99°. Further recrystallization of F_1 (twice from 3:2 petroleum ether–benzene and once from naphtha (bp 160–200°) afforded an analytical sample, mp 134.5–136.5°. Further recrystallization of F_2 (from 4:1 methanol–water and 4:3 ether–petroleum ether) raised its mp to a constant 99.3–101.3°. Efforts to resolve F_1 into additional fractions failed; however, F_2 (a solid solution or molecular complex) was separated into two fractions by preparative glpc and by elution from a column of neutral alumina with benzene. One of these fractions (approximately 25% of F_2) was identical with F_1 (mixture melting point and ir) and the other (approximately 75% of F_2) was a new substance, F_3, that melted at 106.6–107.9° after recrystallization from hexane–ether. The nmr spectra ($CDCl_3$) of F_1 and F_3 are complex; however, both have single proton multiplets (δ 5.5 and 5.03, respectively) which could be assigned only to methine protons adjacent to ester linkages. Since isomers 9a and 9b would have two such protons each and since isomers 11a and 11b would have none, isomers 10a and 10b are the only compatible structures.

Anal. of F_1 and F_3 Calcd for $C_{14}H_{16}O_5$ (10a or 10b): C, 63.62; H, 6.10; sapon equiv, 132.2; mol wt, 264. Found (F_1): C, 63.56; H, 6.04; sapon equiv, 132.5; mol wt, 270. Found (F_3): C, 63.92; H, 6.12; sapon equiv, 130.0; mol wt, 254.

There was isolated, upon saponification of F_1 and saponification of F_3, phthalic acid and a glycol which formed bis-*p*-nitrobenzoate derivatives D_1 (mp 110–111°) and D_2 (mp 99.8–100.8°), respectively. The glycols obtained by saponification of F_1 and F_3 had almost identical infrared spectra, essentially identical with the published spectrum[15] of DPG positional isomer B (mixed diastereoisomers). They also exhibited identical glpc retention times[16] which corresponded to that of the 47% peak of DPG, reported by Havlik and Lawson[9] to be DPG isomer B (mixed diastereoisomers). A 1:1 mixture (by weight) of the glycol derivatives (D_1 and D_2) was recrystallized from ethanol yielding a solid solution or molecular complex melting at 83.1–85.3° (identical with that reported[15] for the ethanol recrystallized bis-*p*-nitrobenzoate of DPG positional isomer B).

Anal. of D_1 and D_2 Calcd for $C_{20}H_{20}N_2O_9$ (D_1 or D_2): C, 55.55; H, 4.66; N, 6.48. Found for D_1: C, 55.66; H, 4.76; N, 6.45. Found for D_2: C, 55.76; H, 4.66; N, 6.35.

The bis-*p*-nitrobenzoates of the diastereoisomers of DPG positional isomer A melt at 119–120 and 148.5–149.5°[10,17] (different from D_1 and D_2 above).

Another DPG polyester was prepared and thermolyzed in a similar manner to that above except that 8.0 g of tetrabutyl *o*-titanate was used as catalyst and the thermolysis was conducted for 12 hr at 225–240°. The chloroform solution obtained upon work-up of the distillate (as before) was simply washed with water and evaporated giving a 44% yield of mixed isomers. Glpc of this mixture and of the glycols isolated upon its saponification revealed no impurities and indicated that it also contained about 65% 10a and 10b.

Registry No.—1, 13988-26-6; 2, 16709-48-1; 3, 16709-49-2; 4, 16709-50-5; 5, 4196-98-9; 6, 16709-52-7; 7, 16720-20-0; 8, 16709-53-8; 10a, 16709-54-9; 10b, 16709-55-0; 2-(2-hydroxypropoxy)-1-propanol bis-*p*-nitrobenzoate (a), 16709-56-1; 2-(2-hydroxypropoxy)-1-propanol bis-*p*-nitrobenzoate (b), 16709-57-2.

Acknowledgment.—The author is indebted to Mr. Clarence Rohrer for the molecular weight determinations, helpful suggestions and general assistance with the work; to Mr. Robert Nash for the gas chromatography; to Mr. Frank Byers for the infrared spectra; and to Mrs. Charlotte Gottschalk for the saponifications.

(12) It is important that the system be evacuated gradually, that the vacuum train is free of narrow restrictions, and/or that the McLeod gauge be connected directly to the flask. These precautions tend to prevent and/or allow the detection of clogging.

(13) Strong bands were at 5.78, 7.76, 8.77, 9.33, and 13.34 μ, consistent with *o*-phthalate ester; there was no OH absorption.

(14) (a) The mixture of macrocycles 9a–11b was eluted from an Aerograph Autoprep gas chromatograph as five overlapping peaks and shoulders. Conditions were as follows: sample size, 0.10 ml of a 25% benzene solution; column, 30 ft × 3/8 in. aluminum, packed with 15% Carbowax 20M-TPA on acid-washed Chromosorb W; carrier gas rate, 170 ml/min; column temperature, 255°. (b) The diastereoisomers 10a and 10b were separated on a preparative scale using the same apparatus and conditions as in a, except that the column used was only 18 ft long. Retention times were 69 (mp 134.5°) and 75 min (mp 106.6°).

(15) A. R. Sexton and E. C. Britton, *J. Amer. Chem. Soc.*, **75**, 4357 (1953).

(16) The isomeric dipropylene glycols were resolved on an F & M Scientific Model 500 gas chromatograph using a 2.5 ft × 0.25 in. o.d. stainless-steel column packed with 10% Carbowax 20M-TPA on 60–80 mesh Chromosorb W (acid washed) at 150°.

(17) R. K. Summerbell, D. M. Jerina, and R. J. Grula, *J. Org. Chem.*, **27**, 4433 (1962).

Molecular Rearrangements. VI.[1] A Study of the Rearrangements of 2-Chlorobicyclo[2.2.1]hept-2-ene *exo*-Oxide

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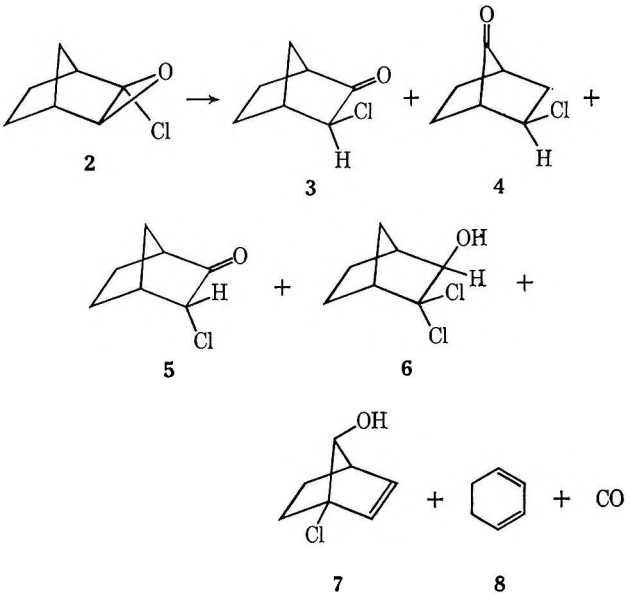
Received January 23, 1968

The synthesis of 2-chlorobicyclo[2.2.1]hept-2-ene *exo*-oxide (**2**) is reported. Neat, thermal rearrangement of **2** gives rise to two major products, *exo*-3-chlorobicyclo[2.2.1]heptan-2-one (**3**, 37.4%) and *exo*-2-chlorobicyclo-[2.2.1]heptan-7-one (**4**, 34.9%), in addition to seven minor products. Acetolysis of **2** gives a ratio of **4**/**3** of 2.7 along with acetoxy ketone product resulting from the addition of acetic acid to **2**. Reaction of **2** with anhydrous hydrogen chloride in ether leads to the unexpected addition product 3,3-dichlorobicyclo[2.2.1]heptan-*exo*-2-ol. Possible mechanistic pathways for these reactions are considered.

Our previous work in the rearrangements of 1-chloro-*cis*- and -*trans*-4-methylcyclohexene oxide led us to conclude that an α-ketocarbonium ion–chloride ion pair was produced as a common intermediate which yields *trans*-2-chloro-4-methylcyclohexanone exclusively.[1] To expand our knowledge of the rearrangements of α-chloro epoxides and, hopefully, substantiate further the ion pair intermediacy, we initiated an investigation into the synthesis and rearrangements of 2-chlorobicyclo-[2.2.1]hept-2-ene *exo*-oxide (**2**). It was felt that **2** served experimental purposes well for at least two reasons: (1) the rearrangements would be starting with a single epoxide rather than a mixture, and (2) the literature holds a wealth of information on the carbonium ion chemistry of this bicyclic system.[3]

2-Chlorobicyclo[2.2.1]hept-2-ene (**1**) was prepared by the Diels–Alder reaction of cyclopentadiene and *trans*-1,2-dichloroethylene, hydrogenation,[4] and the product dehydrochlorinated in good yield with potassium *t*-butoxide in *t*-butyl alcohol.[5] Epoxidation of **1** gave **2** in 65% yield. The assignment of the *exo* configuration to the epoxide is based upon the analogous epoxidation of bicyclo[2.2.1]hept-2-ene[6] and the observation that the nuclear magnetic resonance (nmr) spectrum of the epoxide shows a one-proton doublet at high field (τ 9.18) for the *anti*-7 hydrogen.[7]

A slow, neat, thermal rearrangement of the α-chloro epoxide **2** was conducted in a manner analogous to the thermal rearrangement of 1-chloro-4-methylcyclohexene oxide.[1] Analysis of the rearrangement mixture by gas chromatography (gc) with integration of the areas under the peaks showed two major components in addition to 11% of unrearranged epoxide and seven minor components. The two major components of the rearrangement were identified as *exo*-3-chlorobicyclo-[2.2.1]heptan-2-one (**3**, 37.4%) and *exo*-2-chlorobicyclo[2.2.1]heptan-7-one (**4**, 34.9%). Several minor products were as follows: *endo*-3-chlorobicyclo[2.2.1]-heptan-2-one (**5**, 4.3%), a saturated alcohol whose nmr spectrum suggests the structure 3,3-dichlorobicyclo[2.2.1]heptan-*exo*-2-ol (**6**, 2.9%), a liquid unsaturated alcohol which from its infrared and nmr spectra is believed to be 1-chlorobicyclo[2.2.1]hept-2-en-*syn*-7-ol (**7**, 2.7%), 1,3-cyclohexadiene (**8**, 3.0%), and carbon monoxide (1.6%). The other two minor components (2.0% of total) were not identified.



Diene **8** and carbon monoxide were found to be arising from the thermal decomposition (during the gc analysis) of bicyclo[2.2.1]hept-2-en-7-one (**9**) present in the rearrangement mixture. The photolytic cleavage of **9** to give **8** and carbon monoxide has been reported.[8]

The isomeric chloro ketones **3** and **5** were identified by their gc retention times, and by collection and comparison of their infrared spectra with authentic samples. The *exo* isomer **3** was prepared independently by sulfuryl chloride chlorination of bicyclo[2.2.1]heptan-2-one. The *endo* isomer **5** was then obtained by base equilibration of the *exo* isomer.[9]

No report on the preparation of the chloro ketone **4** could be found in the literature. Walborsky and Loncrini[10] have reported that the major product upon treat-

(1) For paper V in this series, see R. N. McDonald and T. E. Tabor, *J. Amer. Chem. Soc.*, **89**, 6573 (1967).

(2) NDEA Fellow, 1962–1965. This represents a portion of a dissertation presented by R. E. Tabor to the Graduate School of Kansas State University in partial fulfillment of the requirements for the Ph.D. Degree.

(3) Some recent reviews on this subject are (a) P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965; (b) G. D. Sargent, *Quart. Rev.* (London), **20**, 301 (1966); (c) J. A. Berson, "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 111.

(4) J. D. Roberts, F. O. Johnson, and R. A. Carboni, *J. Amer. Chem. Soc.*, **76**, 5692 (1954).

(5) N. A. LeBel, *ibid.*, **82**, 623 (1960).

(6) H. Kwart and T. Takeshita, *J. Org. Chem.*, **28**, 670 (1963).

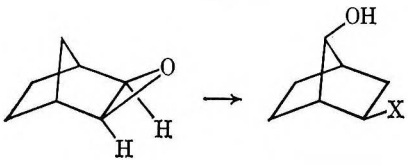
(7) K. Tori, K. Kitahonoki, Y. Takano, H. Tanida, and T. Tsuji [*Tetrahedron Lett.*, 559 (1964)] report this proton appears as a doublet at τ 9.30 in bicyclo[2.2.1]hept-2-ene *exo*-oxide.

(8) D. I. Shuster, F.-T. Lee, A. Padwa, and P. G. Gassman, *J. Org. Chem.*, **30**, 2262 (1965).

(9) (a) J. Meinwald, Y. C. Meinwald, and T. N. Baker, *J. Amer. Chem. Soc.*, **86**, 4074 (1964); (b) E. Tobler, D. E. Battin, and D. J. Foster, *J. Org. Chem.*, **29**, 2834 (1964).

(10) H. M. Walborsky and D. F. Loncrini, *ibid.*, **22**, 1117 (1957).

ment of bicyclo[2.2.1]hept-2-ene *exo*-oxide (**10**) with 48% hydrobromic acid is *exo*-2-bromobicyclo[2.2.1]-heptan-*syn*-7-ol (**11a**). In the present study it was found that treatment of **10** with concentrated hydrochloric acid gave the corresponding chloro alcohol, *exo*-2-chlorobicyclo[2.2.1]heptan-*syn*-7-ol (**11b**). The prop-



10 **11a**, X = Br
b, X = Cl

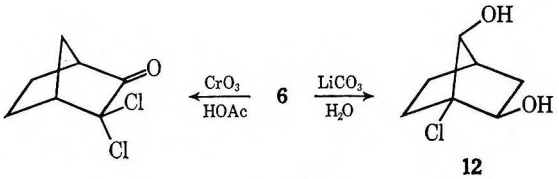
erties of **11b** differed from those of *exo*- and *endo*-3-chlorobicyclo[2.2.1]heptan-*exo*-2-ol,[9b] *endo*-3-chlorobicyclo[2.2.1]heptan-*endo*-2-ol,[9b] and *syn*- and *anti*-7-chlorobicyclo[2.2.1]heptan-*exo*-2-ol.[4] The infrared and nmr spectra were in agreement with the structure **11b**.[11]

Oxidation of the chloro alcohol **11b** with chromium trioxide in acetic acid gave the desired chloro ketone **4**. This oxidation product was identical with the chloro ketone formed in 34.9% yield in the thermal rearrangement of **2**. The infrared spectrum of **4** showed carbonyl absorptions at 5.43 (m) and 5.62 (s) μ which are quite characteristic of bicyclo[2.2.1]heptan-7-ones.[12] In the nmr spectrum of **4** the *endo*-2 hydrogen appeared as a multiplet at τ 5.25 (1 H). This oxidation product also gave further support for the 7 position of the hydroxyl group in **11b**. Additional evidence for the 7-keto structure of **4** was afforded by conversion into its ethylene ketal, dehydrochlorination, and hydrolysis to the known bicyclo[2.2.1]hept-2-en-7-one (**9**).[12,13] Gc analysis of **9** gave 1,3-cyclohexadiene (**8**) and carbon monoxide.

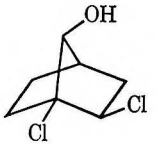
The combined data for the solid dichloro alcohol, assigned structure **6**, obtained as a minor product (2.9%) in the rearrangement of chloro epoxide **2** initially made a structural assignment somewhat perplexing. The alcohol was found to correspond to the molecular formula $C_7H_{10}Cl_2O$ as determined by its molecular weight and elemental analysis. This indicated that the alcohol was arising by addition of a molecule of hydrogen chloride to the α-chloro epoxide **2**. It was subsequently found that the dichloro alcohol was the major product (27.1%) when **2** was treated with hydrogen chloride in ether.

When the dichloro alcohol was oxidized with chromium trioxide in acetic acid, a solid ketone was obtained whose infrared spectrum showed carbonyl absorptions at 5.48 (m) and 5.62 (s) μ. These absorptions suggested that this ketone was a bicyclo[2.2.1]heptan-7-one, in view of the similar absorptions observed for *exo*-2-chlorobicyclo[2.2.1]heptan-7-one (**4**). However, Krieger[14] has reported that the carbonyl absorption of 3,3-dibromobicyclo[2.2.1]heptan-2-one appears at 1772 cm^{-1} (5.64 μ) compared to 1761 (5.68 μ) and 1758 cm^{-1} (5.69 μ) for *endo*- and *exo*-3-bromobicyclo[2.2.1]-heptan-2-one, respectively. This then allowed for the possibility that the oxidation product was 3,3-dichlorobicyclo[2.2.1]heptan-2-one.

Hydrolysis of the dichloroalcohol with aqueous lithium carbonate gave 1-chlorobicyclo[2.2.1]heptane-*exo*-2,*syn*-7-diol (**12**). Diol **12** would be the expected hydrolysis product from either 1-*exo*-2-dichlorobicyclo[2.2.1]heptan-*syn*-7-ol (**13**)[15] or **6**, with the latter involving Wagner–Meerwein rearrangement.



12



13

The nmr spectrum allows a differentiation between **6** and **13**. In the latter structure two carbon-bound downfield protons should be observed since chlorine and hydroxyl have similar effective shielding constants;[16] only one is observed. The spectrum (CCl_4, TMS internal standard) can be reasonably interpreted in terms of structure **6** with the *endo*-C_2 proton as a singlet at τ 6.17 (indication of some splitting), the hydroxyl proton as a broad singlet at τ 6.83 (concentration dependent), the bridgehead C_4 proton as broad adsorption at τ 7.26,[17] and the bridgehead C_1 proton as a broad singlet at τ 7.77, which is not completely separated from the complex absorption from τ 7.8 to 9.0 for the six methylene protons.

The liquid unsaturated alcohol obtained as a minor product (2.7%) in the rearrangement of **2** was assigned the structure of 1-chlorobicyclo[2.2.1]hept-2-en-*syn*-7-ol (**7**) on the basis of its nmr spectrum. The complex absorption centered at *ca.* τ 4.0 was assigned to the two vinyl protons. The *anti*-7 proton appeared as a singlet at τ 6.29 and the hydroxyl proton appeared as a singlet at 7.10 (concentration dependent). The broad singlet at τ 7.23 was assigned to the lone bridgehead proton and the remaining four methylene protons gave rise to complex absorption in the region of τ 7.9–9.3. The assignments agree quite well with those reported for bicyclo-[2.2.1]hept-2-en-*syn*-7-ol.[18]

As was mentioned previously, the dichloro alcohol **6** was the major product (27.1%) when the α-chloro epoxide **2** was treated with hydrogen chloride in ether. This reaction also gave rise to the chloro ketones **3** and **4** in 13.0 and 23.2% yields, respectively. Four other products (32.8% total) remain unidentified. Another component observed in the gc analysis of the reaction mixture integrated as 3.9%, and was indicated by its retention time to be unreacted epoxide. *endo*-3-Chloro-

(11) The nmr spectral assignments agree with those of the acetate of **11b** reported by W. C. Baird [*J. Org. Chem.*, **31**, 2411 (1966)].

(12) P. G. Gassman and P. G. Pape, *ibid.*, **29**, 160 (1964).

(13) R. K. Bly and R. S. Bly, *ibid.*, **28**, 3165 (1963).

(14) H. Krieger, *Suomen Kemistilehti*, **31B**, 112 (1958); *Chem. Abstr.*, **52**, 13423e (1958).

(15) Reference 11 describes the analogous hydrolysis of *exo*-2-chloro-*syn*-7-acetoxybicyclo[2.2.1]heptane to bicyclo[2.2.1]heptane-*exo*-2,*syn*-7-diol.

(16) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p 59.

(17) The fact that this proton absorption is at lower field than is normally observed for bicyclo[2.2.1]heptanes (*ca.* τ 7.8) is explained as due to the deshielding effect of the two chlorines on C_3.

(18) R. R. Sauers and R. M. Hawthorne, *J. Org. Chem.*, **29**, 1685 (1964).

bicyclo[2.2.1]heptan-2-one (**5**) was indicated to be present in only a trace amount.

The reaction of α-chloro epoxide **2** with anhydrous acetic acid was carried out by the dropwise addition of **2** to a relatively large volume of acetic acid in order to determine whether any acetoxy ketone products as well as chloro ketone products would be formed. Gc analysis of the crude product of this reaction showed the presence of at least 14 products. The major product of the reaction was found to be a hydroxyacetate whose structure is indicated to be 1-chloro-*exo*-2-acetoxybicyclo[2.2.1]heptan-*syn*-7-ol (**14**, 24.5% by integration). Other products of this reaction are given in Table I. In addition, there were seven other minor components (18.3% total) which were unidentified, except that one of these (1.7%) was indicated by its retention time to be unreacted epoxide.

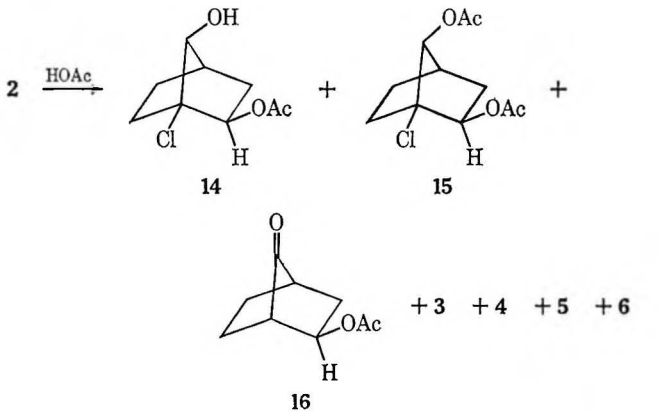


TABLE I

Compound	% yield
1-Chloro-*exo*-2-*syn*-7-diacetoxybicyclo[2.2.1]heptane (**15**)	14
exo-2-Acetoxybicyclo[2.2.1]heptan-7-one (**16**)	12.6
exo-2-Chlorobicyclo[2.2.1]heptan-7-one (**4**)	13.3
exo-3-Chlorobicyclo[2.2.1]heptan-2-one (**3**)	5.0
endo-3-Chlorobicyclo[2.2.1]heptan-2-one (**5**)	3.5
3,3-Dichlorobicyclo[2.2.1]heptan-*exo*-2-ol (**6**)	8.9

Compounds **3**–**6** were identified by their retention times and by collection of each component from the gas chromatogram and comparison of their infrared spectra with those of known samples. The acetoxy ketone **16** was collected from the gas chromatogram and identified by comparison of its infrared spectrum with that of a known sample.[19]

The major product of the acetolysis, **14**, was collected from the gas chromatogram. The elemental analysis and molecular weight were in agreement with the formula $C_9H_{13}ClO_3$. Its structural assignment as **14** is based on the interpretation of its nmr spectra and conversion into a known compound. The placement of the acetoxyl group at C-2 is argued from mechanistic considerations. The diacetate **15** likewise was collected from the gas chromatogram and could also be prepared by acetylation of **14**.

Attempted reduction of **14** with lithium aluminum hydride gave only recovered starting material probably due to the initial formation of an insoluble alkoxide intermediate. Reduction of the diacetate **15** with lithium aluminum hydride proceeded readily at room temperature to yield 1-chlorobicyclo[2.2.1]heptane-*exo*-2,*syn*-7-diol (**12**). No ketal formation was realized by treating **12** with acetone and *p*-toluenesulfonic acid in benzene. However, using the ketal exchange method by reaction of **12** with 2,2-dimethoxypropane and *p*-toluenesulfonic acid catalyst in benzene gave a small amount of material believed to be the cyclic ketal in addition to considerable recovered diol. Both the infrared and nmr spectra indicated the presence of the geminal dimethyl group in this product. Molecular models indicate that there are considerable steric interactions involved in the ketal, which might explain the difficulties in its preparation and its apparent ease of cleavage during purification attempts. The indication that the ketal could be formed, however, was added support for the *exo-syn* relationship of the hydroxyl groups in the diol **12**.

To establish completely the structure of the diol as **12**, it was first treated with sodium in refluxing glyme followed by reaction with dimethyl sulfate. Three major products were isolated from this reaction mixture and all were dimethyl ethers. The mass and nmr spectral data and mechanistic considerations suggest that these products are 1-chloro-*exo*-2,*syn*-7-dimethoxybicyclo[2.2.1]heptane (33%), *exo*-2,*syn*-7-dimethoxybicyclo[2.2.1]heptane (**17**, 20%), and 1-methyl-*exo*-2,*syn*-7-dimethoxybicyclo[2.2.1]heptane (43%). Compound **17** was identified by comparison of its infrared spectrum with that of a known sample prepared by a similar treatment of bicyclo[2.2.1]heptane-*exo*-2,*syn*-7-diol.[20]

Although neither *exo*-3-acetoxybicyclo[2.2.1]heptan-2-one nor its *endo* isomer was isolated from the acetolysis of α-chloro epoxide **2**, the presence of these compounds could not be excluded since seven minor products of this reaction were not isolated and identified. Several unsuccessful attempts were made to prepare these compounds.[2]

Discussion

The formation of products in the rearrangements of α-chloro epoxide **2** can be interpreted by the two different sets of processes shown in Scheme I. No data are available to allow one to say if and where equilibrating classical carbonium ions or their nonclassical counterparts are involved in these pathways.

Some criticism of the process on the right-hand half of Scheme I can be offered. It does not involve chlorine as the migrating group to form α-chloro ketone product, which is contrary to our previous finding[1,21] and those of others,[22] and requires a 3,2-*endo* hydride shift to produce *exo*-3-chlorobicyclo[2.2.1]heptan-2-one. A rebuttal to the first part of this criticism might be that the bicyclo[2.2.1]heptane system is so prone to Wagner–Meerwein rearrangements that this takes precedence over the normal processes found in acyclic and alicyclic α-chloro epoxides. The C_{1-6} or C_{4-5} σ

(19) The infrared spectra of **16** and the *endo* isomer were kindly furnished by Professor P. G. Gassman.

(20) K. Alder, F. H. Flock, and H. Wirtz, *Chem. Ber.*, **91**, 609 (1958).

(21) (a) R. N. McDonald and P. A. Schwab, *J. Amer. Chem. Soc.*, **85**, 4004 (1963); (b) *J. Org. Chem.*, **29**, 2459 (1964).

(22) A. Kirrman, P. Duhamel, and R. Nouri-Bimorghi, *Bull. Soc. Chim. Fr.*, 3264 (1964); *Ann.*, **691**, 33 (1966); R. Nouri-Bimorghi, *C. R. Acad. Sci.* (Paris), *Ser. C*, **262**, 759 (1966); G. A. Razuvaev, V. S. Etlis, and N. N. Trofimov, *Zh. Org. Khim.*, **1**, 2128 (1964) [*Chem. Abstr.*, **64**, 11145e (1966)].

orbitals appear from models to be spatially well arranged in 2 for participation in C–O bond fissions as has been argued for bicyclo[2.2.1]hept-*exo*-2-yl tosylate. Such an argument, however, should also lead to the conclusion that the rearrangements of 2 and bicyclo-[2.2.1]heptene *exo*-oxide should occur with similar facility. This is obviously *not* the case when the present work is compared with that of Crandall.[23]

The second part of the criticism is possibly the more serious since most reactions which could involve 3,2-*endo* shifts of hydrogen or other atoms or groups take alternate paths in this bicyclic ring system.[24] Such a 3,2-*endo* migration appears as an attractive possibility for the formation of bicyclo[2.2.1]heptan-2-one as a major product during attempted gc purification of bicyclo[2.2.1]heptene *exo*-oxide.[23] No proof of such a process has, however, been offered.

The yield of *exo*-3-chlorobicyclo[2.2.1]heptan-2-one is somewhat larger than that of *exo*-2-chlorobicyclo-[2.2.1]heptan-7-one and much greater than that of any products formed by 6,2-hydride shift (not established as even present) in the neat thermal rearrangement of 2. This would then mean that the rate of *endo*-3,2 hydride shift is essentially equal to that of Wagner–Meerwein rearrangement and far greater than that of 6,2-hydride shift. This is exceedingly difficult to accept in light of the nmr study of the norbornyl cation by Saunders, Schleyer, and Olah[25a] in mixed SbF_5–SO_2–SO_2F_2 solvent who calculated that at $-120°$ the 3,2-hydride shift is slower than 6,2-hydride shift and Wagner–Meerwein rearrangement by a minimum of $10^{8.8}$. Berson and coworkers[25b] have found that the *exo*-3-methylbicyclo[2.2.1]hept-2-yl cation does not undergo the *endo*-3,2 hydride shift despite the large thermodynamic driving force for such a process. However, such an *endo*-3,2 hydride shift has recently been established in the pinacol rearrangement of *endo*-3-phenyl-2,3-*exo*,*cis*-bornanediol.[26,27]

The authors believe that a concerted *endo*-3,2 hydride shift with epoxide ring opening is ruled out from strain and stereoelectronic considerations just as a concerted 1,2-chlorine shift was argued unreasonable in certain other α-chloro epoxide rearrangements[21a] and would not account for the stereospecificity in product formation in the neat thermal rearrangement of 1-chloro-*cis*- and -*trans*-4-methylcyclohexene oxide.[1]

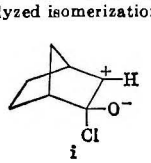
(23) J. K. Crandall, *J. Org. Chem.*, **29**, 2830 (1964).

(24) D. C. Kleinfelter and T. E. Dye, *J. Amer. Chem. Soc.*, **88**, 3174 (1966).

(25) (a) M. Saunders, P. von R. Schleyer, and G. A. Olah, *ibid.*, **86**, 5680 (1964); (b) J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *ibid.*, **89**, 2590 (1967).

(26) A. W. Bushell and P. Wilder, *ibid.*, **89**, 5721 (1967).

(27) Referees have suggested that **3** may be formed by *endo* capture of chloride by the α-ketocarbonium ion, or possibly by an *endo*-2,3 chloride shift from i, followed by acid-catalyzed isomerization. That this does not occur



i

is shown by the fact that **3** is almost completely uneffected when placed in a rearrangement of **2**, as well as by itself or in the presence of hydrogen chloride when placed in sealed tubes at 5 mm of pressure and heated in a bath at 80° for the same length of time as a rearrangement: R. N. Steppel, unpublished results. A maximum of about 2% of **3** might be produced by this route. It is also interesting to note that the same products in about the same distribution are produced on "gc analysis" of **2** with the injection port at 250°; some unrearranged **2** is evident under these conditions.

The significant difference between the right and left hand sides of Scheme I is that each side yields a different enantiomer of *exo*-3-chlorobicyclo[2.2.1]heptan-2-one if optically active α-chloro epoxide 2 is used. Such studies are presently underway and should allow us to determine the extent to which both C_2–O and C_3–O bond fissions occur.

Experimental Section[28]

***trans*-5,6-Dichlorobicyclo[2.2.1]hept-2-ene.**—The Diels–Alder adduct from cyclopentadiene and *trans*-1,2-dichloroethylene was obtained in 67% yield: bp 80.0–76.6° (17.0–14.5 mm); $n^{20}D$ 1.5123 (lit.[4] 34%, bp 76–78° (18 mm), $n^{25}D$ 1.5101).

***trans*-2,3-Dichlorobicyclo[2.2.1]heptane.**—Hydrogenation of *trans*-5,6-dichlorobicyclo[2.2.1]hept-2-ene according to the published procedure,[4] except using palladium on carbon rather than platinum oxide as the catalyst, gave *trans*-2,3-dichlorobicyclo-[2.2.1]heptane in 96% yield: bp 85° (17.5 mm), $n^{20}D$ 1.5040 (lit.[4] 85% yield, bp 85–86° (18 mm), $n^{25}D$ 1.5015).

2-Chlorobicyclo[2.2.1]hept-2-ene (1).—Dehydrochlorination of *trans*-2,3-dichlorobicyclo[2.2.1]heptane was carried out using the procedure of LeBel[5] with potassium *t*-butoxide in *t*-butyl alcohol. 2-Chlorobicyclo[2.2.1]hept-2-ene was obtained in 60% yield: bp 69.5–71.5° (67.5–68.0 mm), $n^{21}D$ 1.4896 (lit.[4] bp 64–66° (52 mm), $n^{25}D$ 1.4880).

2-Chlorobicyclo[2.2.1]hept-2-ene *exo*-Oxide (2).—A solution of 40.0 g (0.311 mol) of 2-chlorobicyclo[2.2.1]hept-2-ene in 25 ml of methylene chloride was treated with a solution of 72.0 g of *m*-chloroperbenzoic acid (82% minimum purity) in 700 ml of methylene chloride for 10 hr. After work-up, vacuum distillation through a short path column gave 34.9 g (77.7%) of crude epoxide containing a small amount of methylene chloride. Redistillation (semimicro spinning-band column) gave 29.4 g (65.4%) of pure 2-chlorobicyclo[2.2.1]hept-2-ene *exo*-oxide: bp 52.2–53.4° (5.1–5.2 mm), $n^{26}D$ 1.4886. The epoxide could be stored under Dry Ice for periods of several weeks with little or no rearrangement, but samples left at room temperature and atmospheric pressure soon underwent a violent exothermic rearrangement with evolution of hydrogen chloride fumes. Elemental analysis was not attempted because of this facile decomposition.

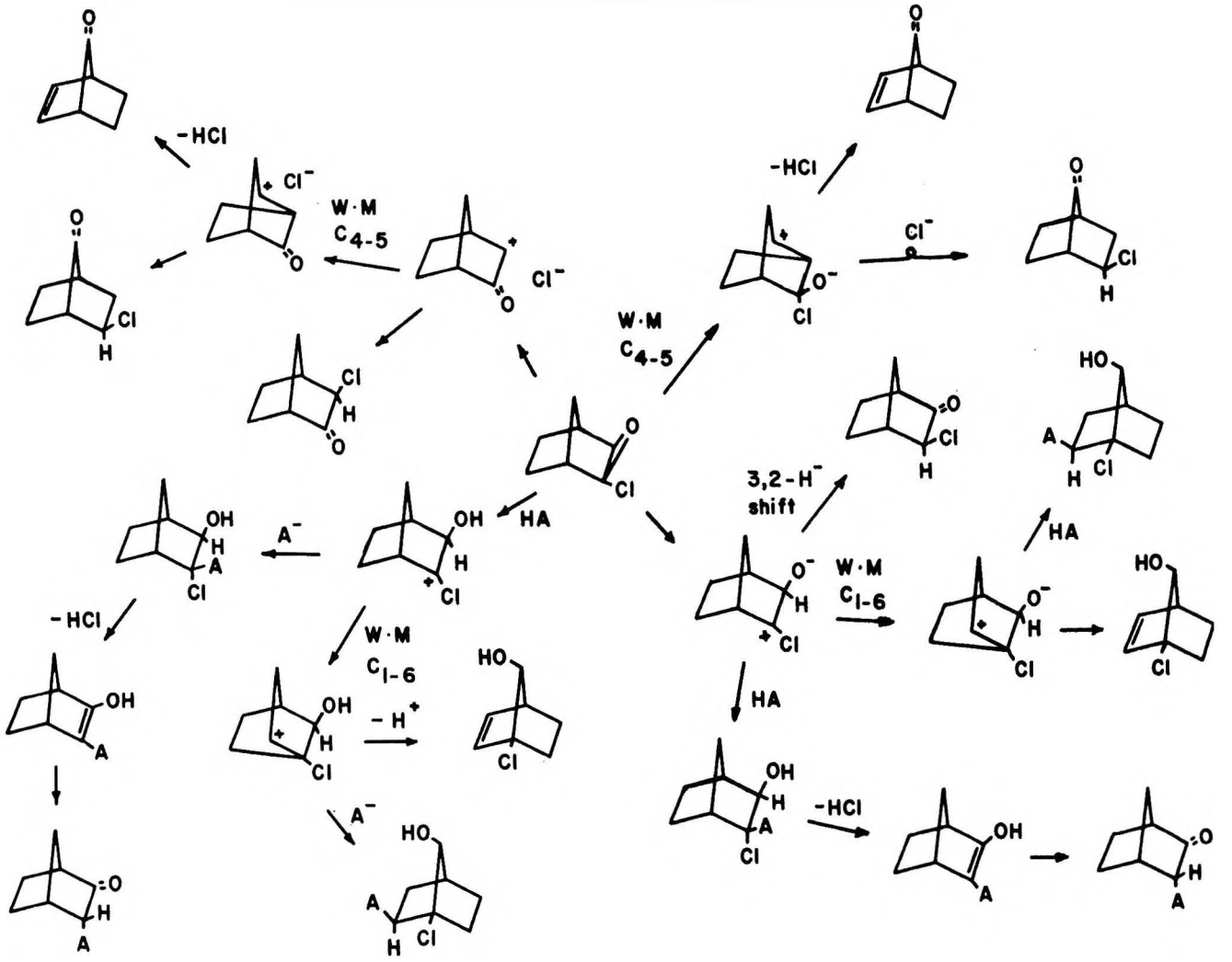
A strong band at 11.54 μ was observed in the infrared spectrum and is believed to be due to the epoxide ring vibration. The nmr spectrum (CCl_4, TMS internal standard) exhibited absorptions at τ 6.86 (singlet, 1, epoxide ring), 7.38 (multiplet, 1, bridgehead C_1), 7.53 (multiplet, 1, bridgehead C_4), 8.2–8.9 (multiplet, 5, C_5, C_6, and *syn*-C_7), and 9.18 (broad doublet, 1, *anti*-C_7).

Neat Thermal Rearrangement of 2-Chlorobicyclo[2.2.1]hept-2-ene *exo*-Oxide.—A 4.1-g sample of epoxide 2 was placed in a 10 ml distillation flask connected to a semimicro spinning-band column and brought to reflux at reduced pressure, bp 51.0° (4.9 mm), with a wax bath maintained at 80°. These conditions are essentially those used for distillation of the epoxide in which only slight rearrangement occurred over a period of several hours. After heating for 46 hr the sample was still refluxing at 51.0° (4.9 mm). At the end of 187.5 hr the head temperature had decreased to 39.5° (4.9 mm) and refluxing had slowed considerably. After a total of 260.5 hr refluxing had completely ceased and the head temperature had dropped to 30.0° (4.9 mm). At this point heating was discontinued, and the flask was cooled, removed, and stored under Dry Ice.

During the rearrangment the sample had slowly discolored and by the end of the rearrangement had become dark red. About 60% of the mixture is volatile, the remaining 40% being polymeric material. The infrared spectrum of the rearrangement mixture showed intense carbonyl absorption at 5.63, weak carbonyl absorption at 5.41 and weak hydroxyl absorption at 2.87 μ. Also, a weak epoxide absorption at 11.52 μ indicated that the rearrangement still had not proceeded to completion.

(28) All melting points were taken on a Kofler hot stage and are corrected. Boiling points are uncorrected. Infrared spectra were determined on a P-E Model 137 or 237 spectrophotometer; nmr spectra were determined on a Varian A-60 spectrometer, and mass spectra were determined with a Bendix time-of-flight mass spectrometer. Molecular weights were obtained either mass spectrometrically or with an osmometer, Model 301A. Gc analyses were performed using an F & M Model 500 gas chromatograph. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

SCHEME I
POSSIBLE MECHANISTIC PATHWAYS FOR THE REARRANGEMENTS OF 2



Gc analysis of the volatile portion of the rearrangement mixture using a 0.25 in. × 6 ft 20% Carbowax 20M on 60/80 Chromosorb W column at 200° showed the presence of ten major components. The peak numbers, retention times, and integrated percentages were as follows: no. 1, 0.23 min, 1.6%; no. 2, 0.41 min, 3.0%; no. 3, 1.70 min, 1.2%; no. 4, 2.04 min, 11.0%; no. 5, 3.15 min, 0.8%; no. 6, 4.20 min, 2.7%; no. 7, 4.80 min, 37.4%; no. 8, 5.66 min, 34.9%; no. 9, 6.16 min, 4.3%; and no. 10, 9.68 min, 2.9%.

Peak no. 4 was indicated to be unrearranged epoxide by comparison of retention times and also by the fact that this peak had essentially disappeared after the rearranged sample had been standing for several weeks. The component could not be collected for identification as the epoxide, because the epoxide was found to undergo rearrangement in the detector block under these conditions.

Peaks no. 7 and 9 had retention times corresponding to *exo*- and *endo*-3-chlorobicyclo[2.2.1]heptan-2-one, respectively. Collection of each of these components from the gc and comparison of the infrared spectra with authentic samples confirmed the assignments.

Collection of peak no. 8 from the gc followed by infrared analysis showed this component to be identical with *exo*-2-chlorobicyclo[2.2.1]heptan-7-one prepared independently by the oxidation of *exo*-2-chlorobicyclo[2.2.1]heptan-*syn*-7-ol.

When collections were attempted on peak no. 1, it was found that no material would condense in the Dry Ice–isopropyl alcohol cooled receiver. Peak no. 2 was obtained as a volatile, colorless liquid whose nmr spectrum was found to be identical with that of an authentic sample of 1,3-cyclohexadiene. This suggested that peak no. 1 might be carbon monoxide. When investigated, peak no. 1 did give a positive test for carbon monoxide using a U. S. Safety Service Co., No. CO-100 indicating tube for SAF-CO-METER carbon monoxide indicator.

The infrared spectrum of a low boiling fraction obtained by distillation of another sample of the rearrangement mixture strongly indicated the presence of bicyclo[2.2.1]hept-2-en-7-one by the intense carbonyl absorption at 5.62, a medium intense carbonyl absorption at 5.42, a weak carbon–carbon double bond absorption at 6.18, and vinyl hydrogen absorption at 3.23 (w) and 14.27 μ (s), in good agreement with the report of Bly and Bly.[13] A 2,4-dinitrophenylhydrazone recrystallized twice from 95% ethanol, melted at 136.0–137.5° (lit.[12] mp 136–137°). When the sample containing this ketone was subjected to gc analysis under the conditions employed above, two components were observed at the same retention times as peaks no. 1 and 2 in the rearrangement mixture and were identified as carbon monoxide and 1,3-cyclohexadiene.

Collection of peak no. 10 from the gc gave a white crystalline solid, which melted at 104–107° after vacuum sublimation. An osmometric molecular weight in ethanol gave a value of 182.8, which indicated the addition of a molecule of hydrogen chloride to the epoxide. The structure of this solid is assigned as 3,3-dichlorobicyclo[2.2.1]heptan-*exo*-2-ol.

Anal. Calcd for $C_7H_{10}Cl_2O$: C, 46.44; H, 5.77; mol wt, 181.06. Found: C, 46.75; H, 5.60.

Peak no. 6 was collected as a clear, colorless liquid and assigned the structure of 1-chlorobicyclo[2.2.1]hept-2-en-*syn*-7-ol on the basis of its spectral data and mechanistic considerations.

Insufficient quantities of peaks no. 3 and 5 were obtained for determination of their structures.

***exo*-3-Chlorobicyclo[2.2.1]heptan-2-one (3).**—A 25.0-g (0.227 mol) sample of bicyclo[2.2.1]heptan-2-one was placed in a 100-ml, three-necked flask equipped with a condenser, an addition funnel, and a magnetic stirrer. The flask was heated until all of the solid ketone melted, and then 30.7 g (0.227 mol) of sulfuryl chloride was added dropwise. A vigorous gas evolution ensued, and heating was continued until the evolution ceased. After

cooling, the light yellow reaction mixture weighed 34.8 g. Gc analysis using a 0.25 in. × 6 ft 20% Carbowax 20M on 60/80 Chromosorb W column at 225° showed the presence of six peaks. The yield of **3** was 77%. Distillation (semimicro spinning-band column) gave pure *exo*-3-chlorobicyclo[2.2.1]heptan-2-one: bp 85.3° (4.8 mm); n^{20}D 1.4976 (lit.[9a] bp 88–89° (4.5 mm), $n^{28.5}$D 1.4941). The infrared and nmr spectra were in agreement with those reported.[9]

***endo*-3-Chlorobicyclo[2.2.1]heptan-2-one (5).**—A mixture of 6.02 g (0.0417 mol) of *exo*-3-chlorobicyclo[2.2.1]heptan-2-one, 12.0 g of potassium carbonate, and 50 ml of water was heated under reflux for 20 hr. After cooling, the reaction mixture was extracted continuously with ether overnight. The ether extract was dried and the ether was removed under reduced pressure leaving 5.5 g of a light brown liquid residue. Gc analysis using a 0.25 in. × 6 ft 20% Carbowax 20M on 60/80 Chromosorb W column at 225° showed two major components which were identified as *exo*-3-chlorobicyclo[2.2.1]heptan-2-one (40.8%) and *endo*-3-chlorobicyclo[2.2.1]heptan-2-one (59.2%), respectively. Gc collections gave the *endo* isomer as a waxy solid, mp 55.5–60.5° (lit. mp 53–56°,[9a] lit. mp 50–53° [9b]). The infrared and nmr spectra were in agreement with the reported data.[9]

Bicyclo[2.2.1]hept-2-ene *exo*-Oxide (10).—A solution of 25.0 g (0.265 mol) of bicyclo[2.2.1]hept-2-ene in 25 ml of methylene chloride was treated with a solution of 61.3 g of *m*-chloroperbenzoic acid (82% minimum purity) in 650 ml of methylene chloride for 8 hr. After work-up, vacuum distillation through a short path column gave 21.2 g (72.6%) of crude epoxide as a white crystalline solid. After recrystallization twice for hexane, the epoxide showed mp 139–142° in a sealed capillary (lit.[29] mp 125.5–126.5°).

***exo*-2-Chlorobicyclo[2.2.1]heptan-*syn*-7-ol (11b).**—This compound was prepared in a manner quite similar to that described by Walborsky and Loncrini[10] for the preparation of *exo*-2-bromobicyclo[2.2.1]heptan-*syn*-7-ol. To 50 ml of concentrated hydrochloric acid cooled to below 10° was added 12.96 g (0.117 mol) of bicyclo[2.2.1]hept-2-ene *exo*-oxide at such a rate that the temperature did not rise above 15°. The mixture was allowed to stir for an additional 1 hr with cooling and then was added to 100 ml of water. The aqueous mixture was extracted with four 50-ml portions of ether, and the combined ether extracts were washed with 25 ml of 10% sodium carbonate solution and 25 ml of water, and dried. Removal of the ether under reduced pressure gave 12.6 g of a light yellow liquid residue. Gc analysis using a 0.25 in. × 6 ft 20% Carbowax 20M on 60/80 Chromosorb W column at 190° showed the presence of three peaks. The center peak (50.7%) was collected as a white crystalline solid, which after recrystallization from hexane had mp 52.2–53.2°.

Anal. Calcd for $C_7H_{11}ClO$: C, 57.34; H, 7.56. Found: C, 57.45; H, 7.72.

In the infrared spectrum the hydroxyl group exhibited strong absorption at 3.07 μ, while in the nmr spectrum (CCl_4, TMS internal standard) absorptions occurred at τ 6.0 (complex, 2, *endo*-C_2 and *anti*-C_7), 7.07 (singlet, 1, hydroxyl), 7.8 (complex, 4, bridgeheads and C_3), and 8.0–9.1 (complex, 4, C_5 and C_6).

***exo*-2-Chlorobicyclo[2.2.1]heptan-7-one (4).**—To a solution of 0.860 g (5.87 mmol) of *exo*-2-chlorobicyclo[2.2.1]heptan-*syn*-7-ol in 4 ml of glacial acetic acid was added slowly a solution of 0.464 g (4.6 mmol) of chromium trioxide in 12 ml of glacial acetic acid. The exothermic reaction was moderated with a water bath at room temperature. After stirring at room temperature for 2 hr, the reaction mixture was added to 20 ml of water, followed by extraction with four 20-ml portions of pentane. The combined pentane extracts were washed with 10 ml of 10% sodium carbonate solution, 10 ml of water, and dried. Removal of the pentane under reduced pressure left a light yellow liquid residue. The infrared spectrum of the crude product showed carbonyl absorptions at 5.44 (m), 5.64 (s), and 5.77 (s) μ. A medium intense hydroxyl absorption at 2.94 μ indicated the presence of some starting material. Column chromatography using Woelm acid-washed alumina, activity grade 1, gave a clear liquid, eluted with methylene chloride, which showed carbonyl absorptions at 5.43 (m) and 5.62 (s) μ, but no hydroxyl absorption.

Purification by gc collections using a 0.25 in. × 6 ft 20% Carbowax 20M on 60/80 Chromosorb W column at 175° gave pure *exo*-2-chlorobicyclo[2.2.1]heptan-7-one in low yield.

Anal. Calcd for C_7H_9ClO: C, 58.14; H, 6.27. Found: C, 58.09; H, 6.40.

The nmr spectrum (neat, TMS external standard) exhibited absorptions at τ 5.25 (multiplet, 1, *endo*-C_2) and 6.8–8.3 (complex, 8).

This ketone gave a 2,4-dinitrophenylhydrazone which melted at 140.0–142.0°.

***exo*-2-Chlorobicyclo[2.2.1]heptan-7-one Ethylene Ketal.**—The procedure of Meinwald, Meinwald, and Baker[9a] was employed, using ethylene glycol, benzene solvent, and *p*-toluenesulfonic acid catalyst. A 0.805-g (5.57 mmol) sample of *exo*-2-chlorobicyclo[2.2.1]heptan-7-one gave 0.778 g of the crude ketal after distillation through a short path column. The yield of the ketal based on gc integration was 63.5%.

Bicyclo[2.2.1]hept-2-en-7-one Ethylene Ketal.—To a refluxing solution of potassium *t*-butoxide in *t*-butyl alcohol, prepared from 0.675 g (0.173 g-atom) of potassium and 10 ml of dry *t*-butyl alcohol, was added a solution of 0.778 g (85.7% pure, 3.54 mmol) of *exo*-2-chlorobicyclo[2.2.1]heptan-7-one ethylene ketal in 10 ml of dry *t*-butyl alcohol. The reaction mixture immediately began to turn cloudy and after refluxing for an additional 28 hr a white solid had precipitated. The reaction mixture was cooled, added to 50 ml of water, and extracted continuously with ether overnight. After drying, the ether solution was concentrated by distillation at atmospheric pressure, leaving 1.26 g of a light yellow liquid residue. Gc collection of the product gave 0.408 g (76%). The nmr spectrum (neat, TMS external standard) exhibited absorptions at τ 3.48 (triplet, 2, vinyl), 5.78 (multiplet, 4, dioxolane), 7.13 (quintet, 2, bridgeheads), 7.66 (multiplet, 2, *exo*-C_5 and *exo*-C_6), and 8.65 (multiplet, 2, *endo*-C_5 and *endo*-C_6).

Bicyclo[2.2.1]hept-2-en-7-one (9).—A 0.400-g (0.00263 mol) sample of bicyclo[2.2.1]hept-2-en-7-one ethylene ketal was hydrolyzed with 5% sulfuric acid according to the method of Gassman and Pape.[12] After work-up, there was obtained 0.550 g of a clear, colorless liquid containing some solvent (pentane). The infrared spectrum of this crude product was in agreement with that reported[12,13] for bicyclo[2.2.1]hept-2-en-7-one, showing carbonyl absorptions at 5.36 (m) and 5.60 (s), carbon double bond absorption at 6.17 (w), and vinyl carbon hydrogen absorptions at 3.28 (w) and 14.27 μ (s).

Gc analysis using a 0.25 in. × 7.5 ft 20% Carbowax 20M column at 100° showed decomposition of the ketone to give carbon monoxide and 1,3-cyclohexadiene. The ketone could be converted into its 2,4-dinitrophenylhydrazone, which melted at 138.5–139.2° (lit.[12] mp 136–137°).

Reaction of 2-Chlorobicyclo[2.2.1]hept-2-ene *exo*-Oxide with Hydrogen Chloride in Ether.—Anhydrous hydrogen chloride gas was bubbled through 25 ml of anhydrous ether at room temperature for *ca.* 15 min. A solution of 2.067 g (0.0143 mol) of 2-chlorobicyclo[2.2.1]hept-2-ene *exo*-oxide in 10 ml of anhydrous ether was added slowly and the mixture allowed to stir at room temperature for 3.5 hr. The solution was then concentrated under reduced pressure to give 2.293 g of a clear, colorless liquid which developed a light pink color upon standing.

Gc analysis using a 0.25 in. × 6 ft 20% Carbowax 20M on 60/80 Chromosorb W column at 200° showed the presence of eight major components. The retention times and integrated percentages were as follows: peak no. 1, 1.71 min, 3.9%; peak no. 2, 3.35 min, 7.9%; peak no. 3, 3.60 min, 3.2%; peak no. 4, 3.90 min, 13.0%; peak no. 5, 4.59 min, 23.2%; peak no. 6, 4.98 min, 12.4%; peak no. 7, 7.54 min, 27.1%; and peak no. 8, 13.27 min, 9.3%.

Peak no. 1 was indicated to be unreacted epoxide by its retention time only. Peaks no. 2 and 3 were not identified. Peak no. 4 was identified as *exo*-3-chlorobicyclo[2.2.1]heptan-2-one (**3**) by its retention time. Peak no. 5 was identified as *exo*-2-chlorobicyclo[2.2.1]heptan-7-one (**4**) by its retention time and by collection and comparison of its infrared spectrum with that of an authentic sample. The retention time of peak no. 6 suggested it to be *endo*-3-chlorobicyclo[2.2.1]heptan-2-one (**5**), but after collection of this component the infrared spectrum showed only a weak, sharp carbonyl absorption at 5.66 and a strong hydroxyl absorption at 2.90 μ. Thus, this peak from the gc is an unknown compound probably containing a small amount of **5**.

Peak no. 7 was identified as 3,3-dichlorobicyclo[2.2.1]heptan-*exo*-2-ol (**6**) by its retention time and by collection and comparison of its infrared spectrum with that of the same material obtained in the thermal rearrangement of the epoxide. A collected sample, after vacuum sublimation and recrystallization from hexane, melted at 103.0–109.0° (sealed capillary). The melting points of samples of this alcohol appeared to vary somewhat depending upon length of exposure to the atmosphere.

(29) S. B. Soloway and S. J. Cristol, *J. Org. Chem.*, **25**, 327 (1960).

Collection of peak no. 8 gave a tan waxy solid. Vacuum sublimation of the collected material gave a white waxy solid, which melted at 85–92°. This material was not identified, but the infrared spectrum showed major absorptions at 2.98 (s), 5.73 (m), and 6.15 (w) μ.

Reaction of 3,3-Dichlorobicyclo[2.2.1]heptan-*exo*-2-ol with Chromium Trioxide in Acetic Acid.—The method described previously for the oxidation of *exo*-2-chlorobicyclo[2.2.1]heptan-*syn*-7-ol was employed. A 0.119-g (0.657 mmol) sample of the dichloro alcohol in 2 ml of glacial acetic acid was treated with a solution of 0.064 g (0.64 mmol) of chromium trioxide in 6 ml of glacial acetic acid for 7 hr at room temperature. After work-up there was obtained 0.116 g of a tan solid whose infrared spectrum showed no hydroxyl absorption, but did show carbonyl absorptions at 5.48 (m) and 5.62 (s) μ, initially suggesting a 7-keto structure. Recrystallization of the crude product from hexane followed by vacuum sublimation gave 0.032 g (27.2%) of a white crystalline solid, mp 101.5–102.5°, which is indicated to be 3,3-dichlorobicyclo[2.2.1]heptan-2-one. Repeated attempts to prepare an ethylene ketal by the method of Meinwald, Meinwald, and Baker[9a] were unsuccessful.

The infrared spectrum had absorptions at 5.48 (m) and 5.62 (s) μ for the carbonyl group while the nmr spectrum (CCl_4, TMS internal standard) exhibited absorptions at τ 6.94 (multiplet, 1, C_4), 7.18 (multiplet, 1, C_1), and 7.4–8.5 (complex, 6).

Hydrolysis of 3,3-Dichlorobicyclo[2.2.1]heptan-*exo*-2-ol.—This compound was hydrolyzed according to the procedure described by Baird.[11] A mixture of 0.108 g (0.596 mmol) of 3,3-dichlorobicyclo[2.2.1]heptan-*exo*-2-ol, 0.238 g of lithium carbonate, and 10 ml of water was heated to reflux for 32 hr. After cooling, the reaction mixture was filtered, and the filtrate was extracted continuously with ether for 12 hr. The ether extract was dried and concentrated to give 0.060 g of a light yellow liquid residue. In addition to a strong hydroxyl absorption at 3.00 μ the infrared spectrum showed fairly strong absorption in the carbonyl region at 5.74 μ.

The crude product was taken up in ether and washed with 10 ml of 40% sodium bisulfite solution. After drying and removal of the ether under reduced pressure, 0.023 g of a viscous, yellow-brown liquid remained. Vacuum sublimation gave a white semisolid material, which was recrystallized from cyclohexane to give a low yield of 1-chlorobicyclo[2.2.1]heptane-*exo*-2,*syn*-7-diol (12) as a white crystalline solid, mp 170–192° (sealed capillary). The melting point of the diol varied somewhat upon exposure to the moist atmosphere. The infrared spectrum of this product was identical with that of the diol (mp 200–202°) obtained by the lithium aluminum hydride reduction of 1-chloro-*exo*-2,*syn*-7-diacetoxybicyclo[2.2.1]heptane (15).

Reaction of 2-Chlorobicyclo[2.2.1]hept-2-ene *exo*-Oxide with Anhydrous Acetic Acid.—A 6.97-g (0.0482 mol) sample of 2-chlorobicyclo[2.2.1]hept-2-ene *exo*-oxide in a Dry Ice cooled addition funnel was added dropwise with stirring to 75 ml of anhydrous acetic acid at room temperature. The temperature of the reaction mixture increased to 32.3° during the addition and then gradually decreased again. After stirring for a total of 18 hr, the reaction mixture was taken up in ether and cooled in an ice bath while the acetic acid was neutralized by the addition of a cold saturated sodium bicarbonate solution. The ether layer was separated, washed with water, and dried. Concentration under reduced pressure gave 6.59 g of a light yellow liquid residue.

Gc analysis of the crude product using a 0.25 in. × 6 ft 20% Carbowax 20M on 60/80 Chromosorb W column at 200° showed the presence of fourteen major components besides some solvent. The retention times and integrated percentages were as follows: peak no. 1, 0.99 min, 0.7%; peak no. 2, 1.70 min, 1.7%; peak no. 3, 2.98 min, 2.7%; peak no. 4, 3.33 min, 3.0%; peak no. 5, 3.59 min, 0.6%; peak no. 6, 3.88 min, 5.0%; peak no. 7, 4.56 min, 13.3%; peak no. 8, 4.95 min, 3.5%; peak no. 9, 6.09 min, 12.6%; peak no. 10, 6.90 min, 4.1%; peak no. 11, 7.52 min, 8.9%; peak no. 12, 13.20 min, 5.5%; peak no. 13, 14.66 min, 24.4%; and peak no. 14, 15.97 min, 14.0%. These integrated percentages are only approximate owing to the overlap of some of the peaks.

Peak no. 2 was indicated to be unreacted epoxide by its retention time. Peaks no. 6 and 8 were identified as *exo*- and *endo*-3-chlorobicyclo[2.2.1]heptan-2-one, respectively, by comparison of retention times, and by collection of the components and comparison of their infrared spectra with those of known samples. Peak no. 7 was identified as *exo*-2-chlorobicyclo[2.2.1]heptan-7-one by its retention time and by the infrared spectrum of a collected sample. In the same manner peak no. 11 was identified as 3,3-dichlorobicyclo[2.2.1]heptan-*exo*-2-ol. Peak no. 9 was collected and identified as *exo*-2-acetoxybicyclo[2.2.1]heptan-7-one by comparison of its infrared spectrum with that of an authentic sample.[19]

Collection of peak no. 13 from the gc gave a white crystalline solid, which after recrystallization from hexane melted at 70.7–71.7°. An osmometric molecular weight determination in ethanol gave a value of 196.8, suggesting the addition of a molecule of acetic acid to epoxide 2. The infrared spectrum exhibited absorptions at 3.03 (s) (O–H), 5.75 (s) and 8.12 μ (s) (acetate). The nmr spectrum (CCl_4, TMS internal standard) exhibited absorptions at τ 5.14 (triplet, 1, *endo*-C_2), 6.17 (multiplet, 1, *anti*-C_7), 7.45 [doublet (J = 4.5 cps), 1, hydroxyl], and 7.5–9.1 (multiplet, 10) with an intense singlet at τ 7.97 due to the methyl of the acetoxyl substituent. After treatment of the sample with deuterium oxide, the doublet at τ 7.45 was gone and the multiplicity at 6.17 was simplified. From mechanistic considerations the structure 1-chloro-*exo*-2-acetoxybicyclo[2.2.1]-heptan-*syn*-7-ol (14) is assigned.

Anal. Calcd for $C_9H_{13}ClO_3$: C, 52.82; H, 6.40; mol wt, 204.66. Found: C, 52.57; H, 6.37.

Collection of peak no. 14 from the gc also gave a white crystalline solid, which after recrystallization from hexane melted at 92.5–93.0°. An osmometric molecular weight determination in ethanol gave a value of 250.7. The infrared spectrum contained absorptions at 5.73 (s) and 8.00 μ (s) for the acetates and the nmr spectrum (CCl_4, TMS internal standard) exhibited absorptions at τ 5.13 (complex, 2, *endo*-C_2 and *anti*-C_7) and 7.5–8.8 (complex, 13, methyl absorptions at τ 7.96 and 8.00). These data are in accord with the structure of 1-chloro-*exo*-2,*syn*-7-diacetoxybicyclo[2.2.1]heptane (15).

Anal. Calcd for $C_{11}H_{13}ClO_4$: C, 53.56; H, 6.13; mol wt, 246.69. Found: C, 53.85; H, 6.21.

Owing to poor separation for collections, insufficient quantities of the remaining peaks (no. 1, 3, 4, 5, 10, and 12) could be obtained for identification. These six components account for a total of 16.6% of the products. No further attempts were made to identify these peaks.

Acetylation of 1-Chloro-*exo*-2-acetoxybicyclo[2.2.1]heptan-*syn*-7-ol.—A mixture of 0.062 g (0.303 mmol) of 1-chloro-*exo*-2-acetoxybicyclo[2.2.1]heptan-*syn*-7-ol, 1 ml of pyridine, and 0.5 ml of acetic anhydride was allowed to stir at room temperature for several days. The mixture was then added to *ca.* 25 ml of water, and, while cooling in an ice bath, 10% hydrochloric acid was added dropwise until the pyridine odor had nearly disappeared. The resulting mixture was extracted with four 6-ml portions of pentane, and the combined pentane extracts were washed with two 10-ml portions of 5% hydrochloric acid and 10 ml of water and dried. Removal of the pentane by distillation left 0.076 g (100%) of a tan crystalline solid, mp 91.0–92.5°. Gc analysis of an ether solution of the solid showed only one component (besides ether) whose retention time was identical with that of 1-chloro-*exo*-2,*syn*-7-diacetoxybicyclo[2.2.1]heptane (15). Recrystallization from hexane gave 0.035 g of white crystals, mp 91.5–92.0°, whose infrared spectrum was identical with that of 15.

Reduction of 1-Chloro-*exo*-2,*syn*-7-diacetoxybicyclo[2.2.1]heptane with Lithium Aluminum Hydride.—To a well-stirred mixture of 0.335 g (8.83 mmol) of lithium aluminum hydride in 8 ml of anhydrous ether was added dropwise a solution of 0.400 g (1.62 mmol) of 1-chloro-*exo*-2,*syn*-7-diacetoxybicyclo[2.2.1]heptane in 4 ml of ether. After stirring at room temperature for 1 hr, the excess lithium aluminum hydride was destroyed by the cautious addition of water followed by moist sodium sulfate. The mixture was extracted with ether and the ether extracts were dried and concentrated to give 0.302 g of a light yellow, gummy, solid residue. Vacuum sublimation yielded 0.221 g of a white crystalline solid, which after recrystallization from hexane gave 0.180 g (68.3%) of 1-chlorobicyclo[2.2.1]heptane-*exo*-2,*syn*-7-diol (12), mp 200–202° (sealed capillary) with prior sublimation. The infrared spectrum showed strong absorption at 2.97 μ while the nmr spectrum ($CDCl_3$, TMS internal standard) exhibited absorptions at τ 6.1 (complex, 4, hydroxyls, *endo*-C_2, *anti*-C_7) and 7.5–9.1 (complex, 7).

O-Isopropylidene Derivative of 1-Chlorobicyclo[2.2.1]heptane-*exo*-2-*syn*-7-diol.—A mixture of 0.270 g (1.66 mmol) of the diol, 0.587 g (5.64 mmol) of 2,2-dimethoxypropane, 10 ml of anhydrous benzene, and several small crystals of *p*-toluenesulfonic acid

monohydrate was heated under reflux. Then the benzene was distilled off very slowly through a 12-cm, vacuum-jacketed Vigreux column until *ca.* 5 ml of a brown liquid remained. Then several milliliters of a solution of sodium methoxide in methanol was added which turned the mixture to an intense yellow color. Distillation was then continued until the volume had been reduced to about 3 ml. The residue was dissolved in 25 ml of ether, washed with three 10-ml portions of water, and dried. Concentration of the ether solution gave 0.336 g of a yellow-orange liquid residue. The infrared spectrum of the crude product showed absorptions at 3.01 (m), 6.23 (m), 7.25 (s), 7.34 μ (s), and bands in the 8.0-9.5-μ region characteristic of ketals. The absorptions of 7.25 and 7.34 μ are suggestive of a geminal dimethyl group.

The crude product, insoluble in Skellysolve B, was dissolved in a small amount of benzene and chromatographed through a column of Woelm basic alumina, activity grade 1. The major portion of the sample was eluted in the second fraction with benzene as a solvent. Concentration of this fraction gave 0.082 g of a light yellow oil, whose infrared spectrum was very similar to the crude product except that the hydroxyl absorption at 3.01 μ had disappeared. Elution of the column with methanol gave 0.055 g of recovered diol. An additional 0.059 g of the diol was recovered after extraction of the above aqueous wash with ether. The nmr spectrum of the chromatographed product indicated the sample to be quite impure, but it did show a pair of methyl singlets at τ 8.48 and 8.54, and the complex absorption at *ca.* 6.0 expected for the *endo*-2 and *anti*-7 protons of the desired product.

In another reaction, gc collections were attempted on the crude product using a 0.25 in. × 6 ft 20% Carbowax 20M on 60/80 Chromosorb W column at 200°. The results indicated that cleavage of the product was occurring on the column. From 0.092 g of crude product was isolated 0.004 g of a waxy white solid, mp 37.5–47.5°, whose infrared spectrum was essentially identical with that of the crude product. No further attempts were made at isolation or purification of the product of this reaction.

Bicyclo[2.2.1]heptane-*exo*-2-*syn*-7-diol.—This compound was prepared according to the procedure of Walborsky and Loncrini.[30] Performic acid oxidation of a 10.0-g (0.106 mol) sample of bicyclo-[2.2.1]hept-2-ene, followed by basic hydrolysis of the intermediate hydroxyformate, gave 10.6 g (77.7%) of crude diol as a yellow, sticky solid. Attempted purification by the method of Crandall[23] gave 6.0 g (44%) of a white crystalline solid as the carbon disulfide soluble fraction. A portion of this material was recrystallized from cyclohexane and sublimed under vacuum to give bicyclo[2.2.1]heptane-*exo*-2,*syn*-7-diol, mp 178–184.5° (sealed capillary), with prior sublimation (lit.[23] mp 175.5–181°).

To check the purity of the carbon disulfide soluble material, a sample was converted into the diacetate using acetic anhydride and pyridine. Gc analysis of the crude diacetate, using a 0.25 in. × 6 ft 20% Carbowax an 60/80 Chromosorb W column at 200°, showed three components besides ether and some acetic anhydride. The retention times and integrated percentages of these three peaks were as follows; peak no. 1, 4.37 min, 1.9%; peak no. 2, 5.20 min, 14.7%; and peak no. 3, 5.78 min, 83.4%. The 14.7% impurity is most likely the diacetate of bicyclo[2.2.1]-heptane-*exo*-2,*anti*-7-diol.[23]

***exo*-2-*syn*-7-Dimethoxybicyclo[2.2.1]heptane (17).**—To a refluxing mixture of 0.440 g (0.0191 g-atom) of sodium metal and 20 ml of dry 1,2-dimethoxyethane was added a solution of 0.511 g (3.99 mmol) of bicyclo[2.2.1]heptane-*exo*-2,*syn*-7-diol (of *ca.* 83% purity) in 10 ml of dry 1,2-dimethoxyethane. A tan solid soon began to precipitate, and after heating under reflux for an additional 1 hr, the excess sodium was still present. Then a solution of 2.0 g (15.8 mmol) of dimethyl sulfate in 5 ml of 1,2-dimethoxyethane was added dropwise, and the tan solid present largely disappeared and was finally replaced by a white solid precipitate. After another 4 hr of heating, the mixture was cooled and treated with 10 ml of dilute ammonium hydroxide to destroy the excess dimethyl sulfate. Then an additional 10 ml of water and 20 ml of ether were added, the mixture was stirred well, and the layers were separated. The aqueous layer was extracted with three 20-ml portions of ether, and the combined ether solutions were dried. Concentration under reduced pressure left 0.517 g of a yellow-orange liquid residue.

Gc analysis of the crude product using a 0.25 in. × 6 ft 20% Carbowax 20M on 60/80 Chromosorb W column at 150° showed two major components. The first of these was collected as a colorless liquid (64% of product). The infrared spectrum showed an ether linkage at 8.96 μ (s), while the nmr spectrum ($CDCl_3$, TMS internal standard) exhibited absorptions at τ 6.51 (multiplet, 2, *endo*-C_2 and *anti*-C_7), 6.72 (singlet, 6, methoxyl), 7.65 and 7.82 (broad singlets, 2, C_1 and C_4), and 8.1–9.2 (complex, 6). This shows its identity to be the dimethyl ether 17.

The second major gc component (25% of product) is one of the monomethyl ethers of the starting diol as evidenced by infrared absorptions at 2.90 (m) (OH) and 9.02 μ (s) (ether). The nmr spectrum (CCl_4, TMS internal standard) also agreed with this assignment of structure exhibiting absorptions at τ 6.15–6.59 (complex, 2, *endo*-C_2 and *anti*-C_7), 6.59 (singlet, 3, methoxyl), 7.36 (singlet, 1, hydroxyl), 7.6–8.1 (complex, 2, C_1 and C_4), 8.1–9.2 (complex, 6). It is, of course, reasonable that both possible monomethyl ethers are present in this single gc fraction.[30]

Reaction of 1-Chlorobicyclo[2.2.1]heptane-*exo*-2-*syn*-7-diol with Sodium and Then Dimethyl Sulfate.—This reaction was conducted in the same manner as described above for the preparation of *exo*-2,*syn*-7-dimethoxybicyclo[2.2.1]heptane. To a mixture of 0.422 g (0.0184 g-atom) of sodium metal and 20 ml of dry 1,2-dimethoxyethane heated under reflux was added a solution of 0.320 g (1.97 mmol) of 1-chlorobicyclo[2.2.1]heptane-*exo*-2,-*syn*-7-diol in 10 ml of dry 1,2-dimethoxyethane. A white solid precipitated and gradually turned to a tan color. After refluxing for an additional 1 hr, a solution of 2.0 g (15.8 mmol) of dimethyl sulfate in 5 ml of 1,2-dimethoxyethane was added dropwise. The tan precipitate nearly disappeared during the addition, but was soon replaced by a white precipitate. After refluxing for another 4 hr, the mixture was cooled and worked up as described above to give 0.434 g of crude product as a light yellow liquid. Gc analysis of this material showed three major peaks. One of these (20% of product) was identified as dimethyl ether 17 by collection and comparison of its infrared spectrum with that of authentic material.

The second major peak (33% of product) was collected as a clear, colorless liquid. Its infrared spectrum contained absorptions at 8.94 (s) (ether) and 13.44 μ (m) (carbon–chlorine) with none for hydroxyl. The nmr spectrum (CCl_4, TMS internal standard) exhibited absorptions in the region of τ 6.7 (complex, 8, methoxyls, *endo*-C_2, and *anti*-C_7) (with the methyl singlets at τ 6.58 and 6.65) and 7.7–9.3 (complex, 7). The mass spectrum of this compound (mol wt 190.67) did not show a parent ion, but the peak *m/e* 158 indicates the loss of methanol to give the parent ion of the corresponding olefin.[31] These data lead one to conclude that the structure of this compound is 1-chloro-*exo*-2,*syn*-7-dimethoxybicyclo[2.2.1]heptane.

The third major component was collected as a colorless liquid. Its infrared spectrum also showed absorption at 9.08 μ (s) (ether). The nmr spectrum (CCl_4, TMS internal standard) exhibited absorptions at τ 6.75 and 6.84 (singlets, 6, methoxyls), 7.00 (complex, 2, *endo*-C_2 and *anti*-C_7), 7.84 (broad singlet, 1, C_4), 8.1–9.1 (complex, 6, C_3, C_5, and C_6), and 8.95 (singlet, 3, methyl at C_1). The mass spectrum of this compound (mol wt 170.25) likewise did not show a parent ion, but the peak at *m/e* 138 again indicated fragmentation with loss of methanol to give the parent ion of the olefin.[29] These data lead one to conclude that the structure of this compound is 1-methyl-*exo*-2,*syn*-7-dimethoxybicyclo[2.2.1]heptane.

Registry No.—**2**, 16709-75-4; **4**, 16031-39-3; **6**, 16808-48-3; **11b**, 16709-78-7; **12**, 16720-16-4; **14**, 16709-79-8; **15**, 16709-80-1; **17**, 13921-80-7; bicyclo[2.2.1]hept-2-en-7-one ethylene ketal, 1491-12-9; 3,3-dichlorobicyclo-[2.2.1]heptan-2-one, 16720-17-5; *o*-isopropylidene derivative of 1-chloro[2.2.1]heptane-*exo*-2-syn-7-diol, 16709-84-5; 1-chloro-*exo*-2-*syn*-7-dimethoxybicyclo[2.2.1]heptane, 16709-85-6; 1-methyl-*exo*-2-*syn*-7-dimethoxybicyclo[2.2.1]heptane, 16709-83-4.

Acknowledgments.—The authors wish to express their gratitude to the U. S. Army Research Office (Durham) (DA-ARO-D-31-124-G584) for their support of this research.

(30) H. M. Walborsky and D. F. Loncrini, *J. Amer. Chem. Soc.*, **76**, 5396 (1954).

(31) Such ether cleavages are known to occur; see K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc. New York, N. Y., 1962, p 116.

Syntheses and Diels–Alder Reactions of Two Dimethyl 10-Methoxyanthryl Phosphates

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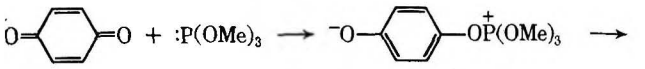
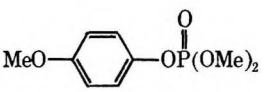
Received December 7, 1967

Dimethyl 10-methoxy-9-anthryl phosphate (**3**) and dimethyl 4,5-dichloro-10-methoxy-9-anthryl phosphate (**5**) were synthesized by treating anthraquinone and 1,8-dichloroanthraquinone with trimethyl phosphite. The structure of **5** was shown by its conversion into 1,8-dichloro-9-anthrone on treatment with a hydriodic acetic acid mixture and by its formation of 4,5-dichloro-10-methoxyanthrone in aqueous sodium hydroxide. The formation of **5** indicates that steric rather than electronic factors controlled the initial nucleophilic attack of phosphite on the unsymmetrical 1,8-dichloroanthroquinone. The acid cleavage showed that the ether link was cleaved more rapidly than that of an anthryl phosphate. Both **3** and **5** condensed readily with maleic anhydride to give adducts whose nmr spectra showed the phosphoryl methoxy doublet was further split by a long range action of an asymmetric environment. Reductive cleavage of these adducts with hydriodic acid gave (10-keto-9,10-dihydro-9-anthryl)succinic acid. In a similar fashion (1,8-dichloro-10-keto-9,10-dihydro-9-anthryl)succinic acid was prepared from 1,8-dichloro-9-methoxyanthracene. The condensation of acrylic acid with **5** and the condensation of acrylic acid and acrylonitrile with 1,8-dichloro-9-methoxyanthracene gave adducts in which the carboxyl or nitrile group was shown to be vicinal to the ether group.

Methyl Phosphite-Quinone Condensations.—Trimethyl phosphite has been reported[2] to react with *p*-benzoquinone and symmetrically substituted *p*-benzoquinones to yield dimethyl *p*-methoxyaryl phosphates. The pathway proposed involves nucleophilic attack of phosphite at the carbonyl center to form an intermediate quaternary phosphonium salt, **1**, which undergoes intermolecular methyl group transfer to form the product, **2**.[2a] The driving force in this reaction is due to the formation of a P–O bond and the resonance stabilization of a benzene ring.



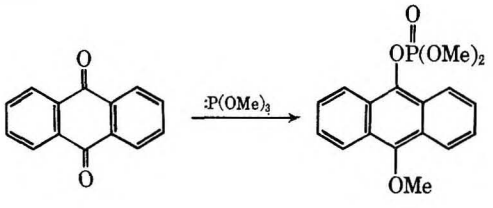
1



2

Since the reaction had not been reported for anthraquinones or unsymmetrically substituted quinones and the reaction with anthraquinones would lead to 9,10-disubstituted anthracenes that would be of interest to us as dienes in orientation studies in the Diels–Alder reaction, the extension of the quinone–phosphite condensation was investigated.

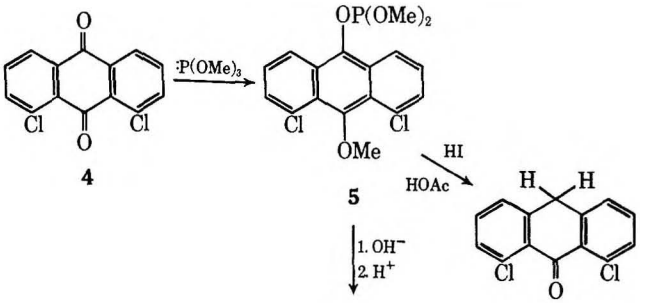
The resonance energy released in condensing anthraquinone with methyl phosphite would be less than that with a *p*-benzoquinone, but anthraquinone reacted readily to give dimethyl 10-methoxy-9-anthryl phosphate (**3**).[3]



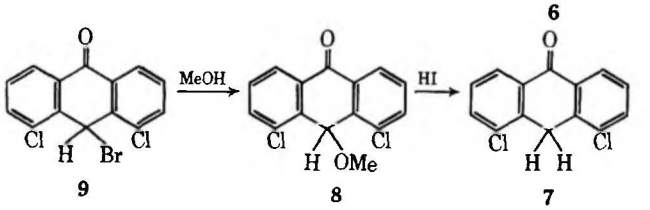
3

1,8-Dichloroanthraquinone was chosen as an unsymmetrically substituted quinone. Theoretically it could lead to two different phosphates. Since chloranil is reported[2b] to react more vigorously than *p*-benzoquinone, one might expect attack to occur more readily on the 9-carbonyl group, but if steric factors play a significant part, then the less-hindered 10-carbonyl group would form the phosphate linkage.

The phosphite reaction appeared to proceed more readily with quinone **4** than with anthraquinone as judged by the more rapid development of a red color,[4] but this may be due to the greater solubility of **4** in trimethyl phosphite, since it is the lower melting of the two quinones. A crystalline dimethyl dichloro-10-methoxy-9-anthryl phosphate (**5**) was isolated. Only traces of a second isomer were detected in an nmr spectrum of the mother liquor. In order to prove conclusively the position of the chlorine atoms, compound **5** was hydrolyzed under acidic and basic conditions. When the phosphate was refluxed in a hydriodic–acetic acid mixture, 1,8-dichloro-9-anthrone (**6**) was formed.



4 **5** **6**



9 **8** **7**

This anthrone was obtained by Barnett and Matthews from the reduction of quinone **4** by aluminum powder in concentrated sulfuric acid.[5] Since chlorine atoms *ortho* to a carbonyl group should protect it from

(1) National Institutes of Health, Predoctoral Fellow, 1965–1967.

(2) (a) F. Ramirez and S. Dershowitz, *J. Amer. Chem. Soc.*, **81**, 587 (1959); (b) F. Ramirez, E. H. Chen, and S. Dershowitz, *ibid.*, 4338 (1959).

(3) After this paper was submitted the preparation of **3** was reported by F. Ramirez, S. B. Bhatia, A. V. Patwardhan, E. H. Chen, and C. P. Smith [*J. Org. Chem.*, **33**, 20 (1968)].

(4) A transient red color was noted previously in this sort of reaction and was ascribed to a charge transfer complex.[2b] Later work indicates phosphonium substituted semiquinones may be involved: E. A. C. Leuchen, *J. Chem. Soc.*, 5123 (1963). For a discussion of the subject see R. F. Hudson, "Structure and Mechanisms in Organophosphorus Chemistry," Academic Press Inc., New York, N. Y., 1965, p 188.

(5) E. B. Barnett and M. A. Matthews, *J. Chem. Soc.*, 123, 2549 (1923).

reduction, they felt that isomer **6** was the more likely structure. Later, they and Cook[6] prepared the isomeric anthrone **7** from 1,8-dichloroanthracene by a six-step synthesis where the structure assigned the key intermediate was logical but not rigorously proven.

However, their assignments of structures for the two isomers are correct and **6** and **7** can be distinguished by nmr spectroscopy since *peri* protons on anthracene and naphthalene derivatives are deshielded by substituents *peri* to them.[7] An nmr spectrum ($CDCl_3$) of 4,5-dichloro-9-anthrone (**7**) exhibited a quartet at 8.15–8.3, a complex multiplet at 7.25–8.00 and a sharp singlet at 4.12 ppm for the two *peri*-aromatic protons, the remaining aromatic protons, and the two methylene protons, respectively. The downfield quartet is characteristic of anthrone derivatives having protons *peri* to a carbonyl group and are absent in derivatives having halo substituents in these positions. The quartet results from coupling of the *peri*-hydrogen nuclei with aromatic protons *ortho* and *meta* to them.

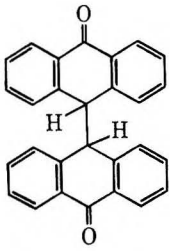
An nmr spectrum of 1,8-dichloro-9-anthrone (**6**) showed only a narrow multiplet at 7.2–7.45 ppm for the six aromatic hydrogen nuclei and a singlet at 4.16 ppm for the two methylene hydrogen nuclei.

Compound **5**, after heating in 20% aqueous sodium hydroxide solution gave, after acidification, a nearly quantitative yield of 4,5-dichloro-10-methoxyanthrone (**8**) previously prepared by methanolysis of 4,5-dichloro-10-bromoanthrone (**9**).[8] An nmr spectrum of compound **8** ($CDCl_3$) exhibited the quartet characteristic of *peri*-deshielded aromatic hydrogen nuclei.

This basic cleavage establishes the structure of phosphate **5** and shows that the hydriodic acid cleaves the methyl ether group faster than it hydrolyzes the phosphate anthryl linkage. If the reverse were true or the rates were equivalent, then anthrone **7** would have been formed.

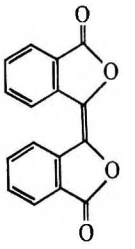
Treatment of compound **8** with hydriodic acid provides a ready route to **7** and the phosphite addition appears to open routes for the selective reduction of either carbonyl group in a 1,8-disubstituted anthraquinone.

In addition to phosphate **4**, a small amount of bianthronyl, **10**, was observed to form in the reaction of



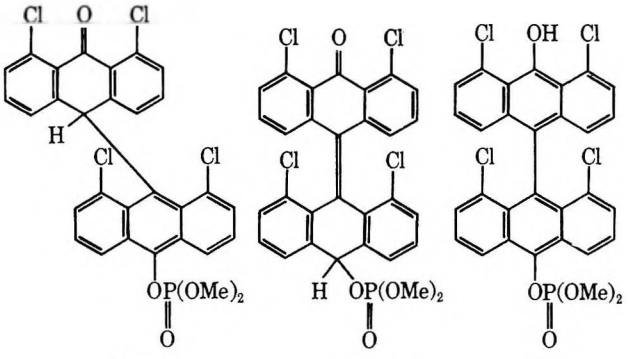
10

anthraquinone with trimethyl phosphite. The only other product observed was trimethyl phosphate. Although nmr analysis of the trimethyl phosphite used showed the presence of only a small amount of trimethyl phosphate as an impurity, it is felt that the large amount observed in the crude product mixture could have formed from air oxidation as well as oxygen abstraction during the reductive coupling of anthraquinone to bianthronyl in the presence of some moisture. A reductive coupling of dibenzoylethylene in ethanolic triethyl phosphite is known to give *meso*-1,2,3,4-tetrabenzoylbutane,[3c,9] and phthalic anhydride is known to be converted into biphthalyl (**11**) by trimethyl phosphite.[10]



11

In the reaction of 1,8-dichloroanthraquinone with trimethyl phosphite to give compound **5**, a high melting phosphate, **12**, was found which was hard to separate from still another by-product, which was probably a tetrachlorobianthronyl. The analysis of the phosphate was consistent with structures **12**, **12a**, and **12b**. The infrared spectrum revealed a carbonyl group which ruled out structure **12b**. The nmr spectrum showed a singlet at 5.12 ppm not split by a ^{31}P nucleus which is consistent with structure **12** and not **12a**. The positions of the chlorine atoms were assigned in part on the basis that the nmr spectrum did not show *peri* protons deshielded by a carbonyl group and in part on the basis that trimethyl phosphite attacked an unhindered carbonyl group in the formation of **5**.



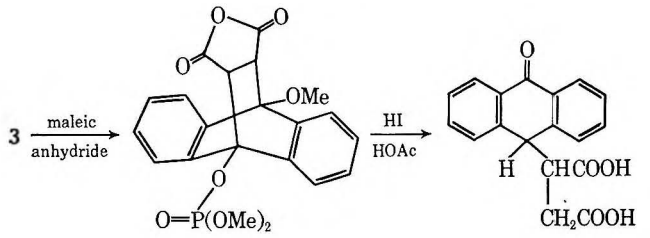
12 **12a** **12b**

Diels–Alder Reactions.—Maleic anhydride condensed readily with phosphates **3** and **5** to give adducts whose nmr spectra indicated normal addition at the 9,10 positions of the anthracene had occurred, since no bridgehead protons could be found. The spectra of the adducts revealed that the methyl groups in the phosphate ester moiety were not equivalent and they appeared as two doublets in contrast to the single doublet of the starting phosphates. This is an example of diasteromeric methyl groups and examples have been reported before.[11] It is due to ring currents of the aromatic rings and carbonyl groups having an asymmetric effect on the methyl protons rather than being

(6) E. B. Barnett, J. Cook, and M. A. Matthews, *Rec. Trav. Chim. Pays-Bas*, **45**, 68 (1926).
(7) V. Balasubramaniyan, *Chem. Rev.*, **66**, 578 (1966).
(8) E. B. Barnett, N. F. Goodway, and J. Wiltshire, *Ber.*, **63B**, 1690 (1930).
(9) R. H. Harvey and E. V. Jensen, *Tetrahedron Lett.*, 1801 (1963).
(10) F. Ramirez, H. Yamanaka, and O. H. Basedow, *J. Amer. Chem. Soc.*, **83**, 173 (1961).
(11) T. H. Siddall, III, and C. A. Prohaska, *ibid.*, **84**, 3467 (1962).

due to restricted rotation in the dimethylphosphato group.

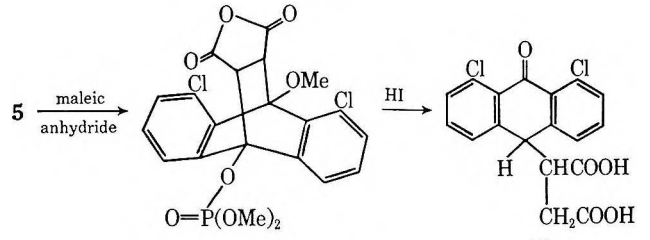
Treatment of the adduct **13** with hydriodic acid in acetic acid gave the succinic acid **14**.[12] This type of



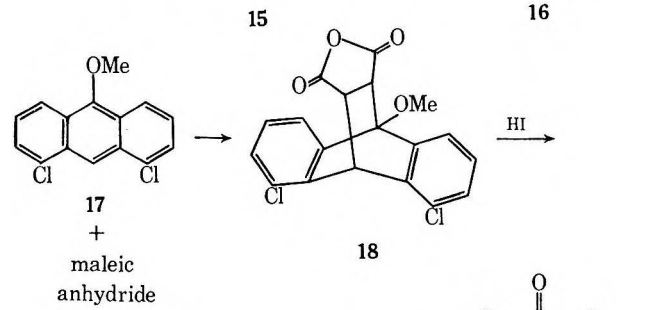
13 **14**

reaction has been discussed previously[12] and a related ring opening has been reported by Sauer and Schroeder.[13] So far, this ring opening has been found only for compounds having a negative group on the bridge vicinal to an ether, ester or amine group on a bridgehead.

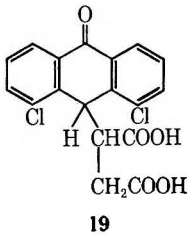
Since compound **5** gave **6** on treatment with hydriodic acid, it was expected that the adduct **15** would likewise have the methyl ether group cleaved and the ring would open before the anthryl phosphate bond was broken. This would lead preferentially to acid **16** and this acid was formed as expected. The isomeric succinic acid **19** was prepared by condensing maleic anhydride with 4,5-dichloro-9-methoxyanthracene (**17**) and treating the adduct **18** with hydriodic acid. In this case the positions of the chlorine atoms are known to be *peri* to the succinic acid moiety.



15 **16**



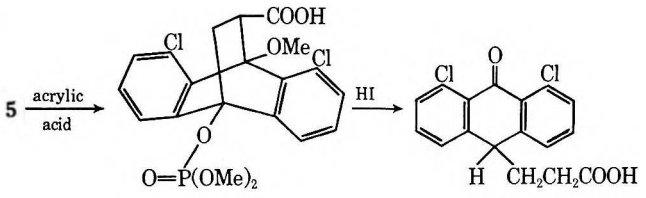
17 + maleic anhydride **18**



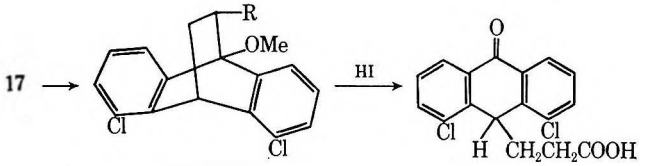
19

When compound **5** was condensed with acrylic acid only one adduct was isolated. This was shown to be **20** since the ring opening occurred with hydriodic acid which led to the keto acid **21**. Similarly, the isomeric keto acid, **23** was prepared from the acrylic acid and acrylonitrile adduct of 4,5-dichloro-9-methoxyanthracene. The bridgehead proton of **22b** appeared as a triplet which is additional proof that the adduct had the vicinal structure.

These results show that the vicinality[14] of a methoxy group is greater than that of a hydrogen atom and presumably more than a dimethylphosphato group.



20 **21**



22a, R = COOH
b, R = CN

23

Experimental Section

All nmr spectra were run on Varian A-50 and A-60-A spectrometers using tetramethylsilane as an internal standard. Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer. Melting points were obtained on a Fisher-Johns melting point block. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Dimethyl 10-Methoxy-9-anthryl Phosphate (3).—Trimethyl phosphite (10 ml) was added to 6 g (28.2 mmol) of anthraquinone; the mixture was corked and placed on a steam bath for 2–3 days. The first day a yellow solution formed which turned red and then green. The solution was concentrated by a stream of air and gave 10.37 g of a dark, viscous oil. By adding ethyl acetate, filtering and reconcentrating the filtrate several times, several crops of yellow crystals of bianthronyl (**10**) were collected which, after washing well with ethyl acetate and pentane, weighed 1.12 g (20%) and decomposed at 250–255° (lit.[15] 256–258° dec). They were identical with an authentic sample obtained from the Aldrich Chemical Company.

The yellow filtrate was then washed with water, alkaline sodium hydrosulfite and again with water, dried over anhydrous magnesium sulfate, filtered, and concentrated to a yellow oil. This procedure was repeated a second time and gave 4.78 g (79%) of a viscous, yellow oil identified as phosphate **3**: nmr ($CDCl_3$) δ 8.4–8.0, 7.6–7.2 (m, 8, aromatic protons), 4.06 (s, 3, C–OCH_3), and 3.38 ppm (d, 6, J = 11.5 Hz, $POCH_3$); ir (NaCl smear), 7.87 (P=O) and 9.65 μ (P–O–C).[3]

Dimethyl 4,5-dichloro-10-methoxy-9-anthryl phosphate (5) was obtained *via* the same procedure as used for phosphate **3**, starting with 6 g (22.2 mmol) of 1,8-dichloroanthraquinone in 10 ml of trimethyl phosphite. A red solution, which formed within 1 hr, turned green and deposited yellow crystals. Crystals (2.5 g) were filtered, washed with chloroform and then pentane. Treatment with Norit followed by crystallization from a large volume of acetone–petroleum ether (bp 60–70°) gave 2 g (29%) of a pale yellow phosphate (**12**). An analytical sample turned yellow at about 240° and decomposed at 250°; nmr (DMSO-d_6), δ 7.8–6.65 (m, 12, aromatic protons), 5.12 (s, 1, benzhydrylic proton), and 3.60 ppm (d, 6, J = 11.5 Hz, $POCH_3$); ir (KBr), 5.9 (C=O), 6.3, 6.9, 6.96 (sh) and 9.6–9.83 μ (d, P–O–C).

Anal. Calcd for $C_{30}H_{19}Cl_4O_5P$: C, 56.99; H, 3.03; Cl, 22.43; P, 4.90. Found: C, 56.76; H, 3.09; Cl, 22.27; P, 4.93.

The yellow filtrate remaining after removal of compound **12** was reduced in volume. Methanol was added and after further

(12) J. S. Meek, P. A. Monroe, and C. J. Bouboulis, *J. Org. Chem.*, **28**, 2572 (1963).

(13) J. Sauer and B. Schroeder, *Ber.*, **100**, 678 (1966).

(14) Vicinality of a group is hereby defined as the ability to polarize a diene so that a negatively monosubstituted dienophile gives the vicinal adduct as the predominant product.

(15) Aldrich Chemical Company.

concentrating, phosphate **5** crystallized. After washing with ethyl acetate and petroleum ether, a yield of 6.38 g (71%), mp 114–116°, was obtained. Crystallization from acetone–petroleum ether gave an analytical sample of bright yellow needles: mp 116–117°; nmr ($CDCl_3$), δ 8.3–8.15 (q, 2), 8.7–7.2 (m, 4), 3.88 (s, 3, C–OCH_3), and 3.85 ppm (d, 6, J = 11 Hz, $POCH_3$); ir (KBr), 7.33, 7.64 (d, P=O) and 9.55 μ (m, P–O–C).

Anal. Calcd for $C_{17}H_{15}Cl_2O_5P$: C, 50.89; H, 3.77. Found: C, 50.95; H, 3.86.

An nmr spectrum ($CDCl_3$) of the oily residue remaining after evaporation of the mother liquors from phosphate **5** showed peaks belonging to its isomer, dimethyl 1,8-dichloro-10-methoxy-9-anthryl phosphate, at δ 3.88 (d, 6, J = 11 Hz) and 3.85 ppm (s, 3, C–OCH_3).

9-Methoxy-10-dimethylphosphato-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic Acid Anhydride (13).—Dimethyl 10-methoxy-9-anthryl phosphate (**3**) (1.7 g, 5.12 mmol) and maleic anhydride (0.49 g, 5.12 mmol) were refluxed in 2 ml of xylene for 4 hr. White needles (1.9 g, 95%) crystallized from the dark solution and melted with decomposition between 205–215° after being filtered and washed with benzene and acetone. The product was purified by treatment with Norit in acetone and recrystallization from acetone petroleum ether (bp 60–70°). The analytical sample of white needles decomposed at 224–229°: nmr (DMSO-d_6), 8.0–7.2 (m, 8), 4.94 (d, 1, J = 15 Hz, H-11), 4.40 (d, 1, J = 15 Hz, H-12), 4.07 (s, 3, $COCH_3$), 4.06 (d, 3, J = 18 Hz, $POCH_3$), and 4.02 ppm (d, 3, J = 18 Hz, $OPCH_3$); ir (KBr), 5.35–5.58 (d, C=O), 6.87, 7.75–8.4 (m, P=O) and 9.3–10.0 (m, P–O–C).

Anal. Calcd for $C_{21}H_{19}O_8P$: C, 58.61; H, 4.45. Found: C, 58.81; H, 4.34.

1,8-Dichloro-9-methoxy-10-dimethylphosphato-9,10-ethanoanthracene-11,12-dicarboxylic Acid Anhydride (15).—Dimethyl 4,5-dichloro-10-methoxy-9-anthryl phosphate (**5**) (3 g, 7.48 mmol) and 0.98 (10 mmol) of maleic anhydride were dissolved in xylene and refluxed for 12 hr. The solvent was removed by distillation under reduced pressure and the resulting solid was washed well with ethyl acetate and pentane. This yielded 3.22 g (86%) of white needles, mp 230–240° dec. Recrystallization from acetone–petroleum ether gave analytically pure white needles, mp 232–241° dec.

Anal. Calcd for $C_{21}H_{17}Cl_2O_8P$: C, 50.52; H, 3.43. Found: C, 50.60; H, 3.57.

An nmr spectrum (DMSO-d_6–acetone-d_6) showed two doublets at 3.95, 3.9 (3 H, J = 11 Hz), one singlet at 3.74 (3 H), and one multiplet at 7.05–7.85 ppm (6 H). The 11,12-CH protons were obscured by the phosphate and solvent peaks. An infrared spectrum showed peaks at λ_{max} 5.35–5.58 (d, C=O), 7.7–8.45 (m), 9.3–9.9 (m, P=O) and 10.4–11.2 μ (m, P–O–C).

1,8-Dichloro-9-methoxy-10-dimethylphosphato-9,10-dihydro-9,10-ethanoanthracene-12-carboxylic Acid (20).—Dimethyl 4,5-dichloro-10-methoxy-9-anthryl phosphate **5** (1 g, 2.49 mmol), and 1.0 g of hydroquinone were refluxed in 2 ml of freshly distilled acrylic acid for 50 min. The resulting hot, viscous solution was decanted, leaving acrylic acid polymer behind. Since the reaction was slow, a longer period of refluxing only gave more polymer, which was difficult to separate from the adduct.

An ethyl acetate–chloroform solution of the product was washed with water, treated with Norit, dried over anhydrous magnesium sulfate, and partially concentrated. After several days at 5°, 0.20 g (24%) of white crystals formed, mp 240–260° dec. Recrystallization from acetone–petroleum ether gave an analytical sample melting at 244–264° dec.

Anal. Calcd for $C_{20}H_{15}Cl_2O_7P$: C, 50.87; H, 3.84. Found: C, 50.78; H, 4.06.

An infrared spectrum showed peaks at λ_{max} 3.85 (broad m, OH), 5.73 (C=O), 7.9–8.23 (t, P=O) and 9.35–9.85 μ (m, P–O–C).

4,5-Dichloro-9-methoxyanthracene (17).—This procedure was adapted from Toji's method.[16] Sodium borohydride (6 g, 159 mmol) was added slowly over a 0.5-hr period to a magnetically stirred solution of 9 g (32.6 mmol) of 1,8-dichloroanthraquinone suspended in 500 ml of absolute methanol at room temperature. The solution turned red after each addition owing to the formation of a side product, but air reoxidized it to the anthraquinone and the final solution was yellow. This solution was evaporated by a stream of air and the resulting semisolid yellow product was stirred with 500 ml of water, filtered, and washed well with water to remove most of a yellow impurity. This gave 8.79 g (96%) of nearly colorless *trans*-1,8-dichloro-9,10-dihydro-9,10-anthradiol which turned yellow at 155° and melted with decomposition between 160–170°. Treatment of an acetone solution of the product with Norit followed by crystallization from acetone–petroleum ether yielded white needles which turned yellow at 160° and decomposed at 170° (lit.[16] turned yellow at 160° and melted with decomposition at 176°).

All reagents used below were boiled or treated with a stream of nitrogen to deoxygenate them. Exclusion of air is critical since the anion of anthrone is readily oxidized to anthraquinone.

To a solution of 7.64 g (26.5 mmol) of the diol in 40 ml of 2-propanol under a nitrogen atmosphere was added 40 ml of 20% sodium hydroxide solution. The resulting dark red solution was boiled while 35 ml of methyl tosylate was added during a 10–20 min period. Refluxing was continued until the solution became pale yellow and the product began to crystallize. Cold water was added; the yellow needles were washed well with water and air dried to give 7.35 g (quantitative yield), mp 140°. One recrystallization from acetone raised the melting point to 144–146° (lit.[17] 145°).

1,8-Dichloro-10-methoxy-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic Acid Anhydride (18).—4,5-Dichloro-9-methoxyanthracene (1 g, 3.7 mmol) ground together with 0.36 g (3.7 mmol) of maleic anhydride was placed in a test tube immersed in a nitrobenzene bath. The bath was refluxed overnight during which time the reaction mixture darkened. The dark semisolid product, **18**, was dissolved in ethyl acetate and treated with Norit which resulted in a yellow solution. After refrigeration, 0.5 g (36%) of white crystals, mp 230–240° dec, was filtered. Recrystallization from acetone–petroleum ether raised the decomposition range to 232–241°: nmr (DMSO-d_6–acetone-d_6), 7.65–7.26 (m, 6), 5.69 (d, 1, J = 3 Hz, H-9), 4.36 (d, 1, J = 16 Hz, H-11), 4.08 (s, 3, OCH_3), and 4.03 ppm (q, 1, J = 3 Hz, 16, H-12); ir, 5.84–5.55 (d, C=O), 6.87–7.03 (d, C=C), 8.05–8.26 (t), 9.3–9.45 (d), 10.65, and 12.85.

Anal. Calcd for $C_{19}H_{12}Cl_2O_4$: C, 60.82; H, 3.22. Found: C, 60.75; H, 3.44.

1,8-Dichloro-9-methoxy-9,10-dihydro-9,10-ethanoanthracene-12-carboxylic Acid (22a).—A solution of 1.6 g (5.78 mmol) of 4,5-dichloro-9-methoxyanthracene with 0.1 g of hydroquinone in 1.8 ml of acrylic acid was refluxed for 40 min. The resulting yellow oil was dissolved in ethyl acetate–acetone and treated with Norit. The solution was partially evaporated and gave 1.26 g (60%) of white crystals, mp 215–230° slight dec. Further recrystallization from methanol did not raise the decomposition range.

Anal. Calcd for $C_{18}H_{14}Cl_2O_3$: C, 62.09; H, 3.76. Found: C, 61.90; H, 4.01.

An infrared spectrum showed peaks at λ_{max} 3.88 (m, OH), 5.83, 6.87–7.02 (d), 7.52–7.74 (d), 7.9–8.7 (m), 10.0 and 12.6–12.75 μ (d). The compound was not soluble enough in DMSO to permit nmr analysis.

1,8-Dichloro-10-methoxy-9,10-dihydro-11-cyano-9,10-ethanoanthracene (22b).—A solution of 5.0 g (18.5 mmol) of 1,8-dichloro-9-methoxyanthracene and 0.1 g of hydroquinone in 25 ml of acrylonitrile was placed in a bomb at 150° for 5 hr. The resulting pale yellow solution was filtered to remove a powdery residue and the filtrate was evaporated by a stream of air to yield 7.4 g of pale yellow crystals, mp 160–190°. Several recrystallizations from methanol of acetone–petroleum ether gave 5 g (87%) of white needles, mp 173–175°. An analytical sample melted at 174–175°: nmr (acetone-d_6) 7.2–6.6 (m, 6), 4.85 (t, 1, J = 3, Hz, H-9), 3.48 (s, 3, OCH_3), 3.3–3.05 (m, 1, H-11), and 2.0–1.3 ppm (m, 2, H-12).

Anal. Calcd for $C_{18}H_{13}Cl_2NO$: C, 65.47; H, 3.97. Found: C, 65.49; H, 4.07.

Attempted Diels–Alder Reaction.—Dimethyl 4,5-dichloro-10-methoxy-9-anthryl phosphate did not form an adduct in any appreciable amount after 3 weeks of refluxing in acrylonitrile.

1,8-Dichloro-9-anthrone (6) and 4,5-Dichloro-9-anthrone (7).—A solution of 1.0 g (2.5 mmol) of dimethyl 4,5-dichloro-10-methoxy-9-anthryl phosphate, **5**, in 5 ml of hydriodic acid (sp gr 1.5) and 10 ml of glacial acetic acid was refluxed for 70 min. The initially colorless solution turned yellow. After cooling, 500 ml of cold water was added which caused precipitation of a bright yellow solid (probably the anthrol tautomer). The

(16) Masuo Toji, Ph.D. Thesis, University of Colorado, 1963.

(17) E. B. Barnett and C. L. Hewlett, *J. Chem. Soc.*, 1452 (1932).

solution stood overnight and the solid which was now pale yellow was filtered and washed with water and then pentane to yield 0.63 g (100%), mp 143–170°. Three recrystallizations from methanol gave pale yellow crystals, mp 167–170° (lit.[5] 167°).

The nmr spectrum is discussed above. An infrared spectrum showed peaks at λ_{max} 5.95, 6.28, 6.87–6.97 (d), 8.0 and 10.63–11.37 μ (t).

The other isomer (**7**) may be prepared by the methods of Toji,[16] Barnett, Cook, and Matthews,[6] or by treatment of 4,5-dichloro-10-methoxy-9-anthrone (**8**) with hydriodic acid in acetic acid as described previously.

4,5-Dichloro-10-methoxy-9-anthrone (8).—The reaction was carried out under nitrogen and the reagents used were deoxygenated as in the preparation of 4,5-dichloro-9-methoxyanthracene (**17**).

To a boiling solution of 3 g (7.48 mmol) of dimethyl 4,5-dichloro-10-methoxy-9-anthryl phosphate (**5**) in 50 ml of 2-propanol was added 50 ml of 10% sodium hydroxide solution. The mixture immediately turned dark red and gradually became yellow after 20 hr of refluxing. The hot solution was acidified with concentrated hydrochloric acid; 2.02 g (100%) of **8**, mp 127–133°, was removed by filtration, washed with water and then pentane. Treatment with Norit and several recrystallizations from acetone gave white, diamond-shaped crystals melting at 134–136° (lit.[5] 136°): nmr ($CDCl_3$), 8.1–8.01 (q, 2, *peri* protons), 7.8–7.2 (m, 4), 6.4 (s, 1, H-10), and 2.96 ppm (s, 3, OCH_3); ir, 6.0 6.3 (sh), 6.35 (sh), 7.5–7.94 (t), 9.38–9.5 (d), and 13.37–13.78 (d). After standing overnight in a closed container, the crystals turned pink but there was no change in the nmr or infrared spectra or in the melting point.

(10-Keto-9,10-dihydro-9-anthryl)succinic acid (14).—A solution of 2.9 g (6.7 mmol) of 9-methoxy-10-dimethylphosphato-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid anhydride (**13**) in 15 ml of hydriodic acid and 30 ml of glacial acetic acid was refluxed for 15 hr. When the product was isolated following the procedure for compound **6**, 1.68 g (81%) of **14**, mp 190–195° dec was obtained. Recrystallization from acetone–petroleum ether gave colorless crystals melting at 196–198° dec (lit.[12] 194.3–195.3°). The acid was identified by comparison with an authentic sample prepared from 9-methoxy-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid anhydride.[12]

(4,5-Dichloro-10-keto-9,10-dihydro-9-anthryl)succinic Acid (16).—Hydriodic acid in acetic acid converted 1.34 g (2.69 mmol) of 1,8-dichloro-9-methoxy-10-dimethylphosphato-9,10-ethanoanthracene-11,12-dicarboxylic acid anhydride (**15**) into 0.84 g (72%) of acid **16**, mp 220–260° dec. After two recrystallizations, white crystals were obtained which turned yellow at 240° and melted at 260° dec.

Anal. Calcd for $C_{18}H_{12}Cl_2O_5$: C, 57.01; H, 3.19. Found: C, 56.97; H, 3.15.

An infrared spectrum showed peaks at λ_{max} 3.4 (broad s), 5.83–5.94 (d), 6.03 (sh), 6.87–7.07 (t), 7.77 and 8.05 μ.

(1,8-Dichloro-10-keto-9,10-dihydro-9-anthryl)succinic Acid (19).—The procedure was previously described. Cleavage of 2.16 g (5.76 mmol) of 1,8-dichloro-10-methoxy-9,10-dihydro-9,10-ethanoanthracene-11-12-dicarboxylic anhydride (**18**) gave 1.37 g (65%) of pale yellow crystals, mp 230–245° dec. The analytical sample melted at 245–255° dec.

Anal. Calcd for $C_{18}H_{12}Cl_2O_5$: C, 57.01; H, 3.19. Found: C, 57.30; H, 3.39.

An infrared spectrum showed peaks at λ_{max} 3.2 (broad s), 5.55 (sh), 5.85–5.95 (d), 6.25, 6.3 (sh), 6.9, 7.65, 8.8 and 13.5 μ.

3-(4,5-Dichloro-10-keto-9,10-dihydro-9-anthryl)propionic Acid (21).—From a hydriodic acid cleavage as before, a quantitative yield of acid **21**, mp 200–205° dec, was obtained from 0.37 g (0.748 mmol) of 1,8-dichloro-9-methoxy-10-dimethylphosphato-9,10-dihydro-9,10-ethanoanthracene-12-carboxylic acid (**20**). The analytical sample melted at 204–206° dec.

Anal. Calcd for $C_{17}H_{12}Cl_2O_3$: C, 60.91; H, 3.61. Found: C, 60.83; H, 3.53.

An infrared spectrum showed peaks at λ_{max} 3.43 (broad m), 5.88–5.93 (d), 6.27–6.35 (d), 6.88–7.12 (t), 8.04–8.15 (d), 10.58–10.97 (t), and 12.45–12.72 μ (t).

3-(1,8-Dichloro-9-keto-9,10-dihydro-10-anthryl)propionic Acid (23).—A solution of 0.65 g (1.97 mmol) of 1,8-dichloro-10-methoxy-9,10-dihydro-9,10-ethanoanthracene-12-carboxylic acid (**22a**) or the cyano derivative (**22b**) in 5 ml of hydriodic acid and 10 ml of glacial acetic acid was refluxed for 2.5 hr. The same open acid (**23**) was obtained from both starting materials in quantitative yield and the analytical sample melted at 175–178°.

Anal. Calcd for $C_{17}H_{12}Cl_2O_3$: C, 60.91; H, 3.61. Found: C, 61.06; H, 3.64.

An infrared spectrum showed peaks at λ_{max} 3.4 (broad m), 5.75 (sh), 5.83–5.97 (d), 6.26, 6.85–9.4 (t), 7.6–8.0 (m), 8.8, 10.48 and 12.72–13.70 μ (t).

Registry No.—**5**, 16622-38-1; **8**, 16622-39-2; **12**, 16622-40-5; **13**, 16622-41-6; **15**, 16622-42-7; **16**, 16622-43-8; **18**, 16622-44-9; **19**, 16622-45-0; **20**, 16622-46-1; **21**, 16622-47-2; **22a**, 16622-48-3; **22b**, 16622-49-4; **23**, 16622-50-7.

Isoprene Chlorination

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Received August 18, 1967

The chlorination of isoprene does not appear to be a free-radical chain reaction either in the liquid or the gas phase at low temperatures. A mixture of substitution and addition products is obtained regardless of phase; somewhat more 1-chloro-2-methylbutadiene and less 1,4-dichloride were obtained in the gas phase. Dichlorides were obtained in greater yield when the chlorination was carried out in the presence of chloride ion.

Isoprene has been chlorinated in both liquid[1–4] and gas phase[4–7] to give products of substitution and addition. Because isoprene resembles both butadiene and isobutylene one might expect a common mechanism; however, in a recent study[8] Poutsma favors a radical mechanism for the chlorination of undiluted butadiene in the liquid phase. Isobutylene has been shown to undergo polar chlorination in the liquid phase.[9] Using *t*-butyl hypochlorite rather than chlorine, Oroshnik and Mallory[10] found that with undiluted isoprene in the liquid phase the orientation of 1,4 addition is that typical of a radical mechanism.

In Table I are shown true product yields obtained by chlorination below room temperature in neat liquid isoprene and in the gas phase at 100°. The liquid-phase results are corrected in that the addition products of hydrogen chloride are considered as recoverable isoprene. The conversion was complete with respect to

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(2) D. V. Tischenko, A. Abramova, and E. Yorzhemskaya, *Zh. Obshch. Khim.*, **27**, 227 (1957).
(3) F. G. E. Hawkins and M. D. Philpot, *J. Chem. Soc.*, 3204 (1962).
(4) L. F. Hatch and J. L. A. Rodriguez, University of Texas.
(5) G. H. Morey and R. F. Taylor, U. S. Patent 2,453,089; Commercial Solvents, 1948.
(6) M. B. Berenbaum, U. S. Patent 2,937,125 (Thiokol) (1960).
(7) K. M. Taylor, U. S. Patent 3,202,721 (Monsanto) (1965).
(8) M. L. Poutsma, *J. Org. Chem.*, **31**, 4167 (1966).
(9) R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **70**, 3364 (1948).
(10) W. Oroshnik and R. A. Mallory, *ibid.*, **72**, 4608 (1950).

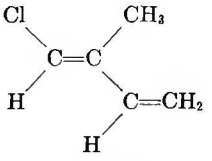
TABLE I[a]

BATCH LIQUID PHASE *vs.* CONTINUOUS VAPOR PHASE CHLORINATIONS

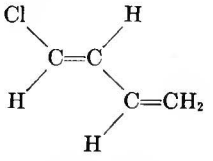
Phase	Temp, °C	2-Chloro-methyl	1-Chloro-2-methyl	Dichlorides 1,2	Dichlorides 3,4	Dichlorides *cis*-1,4	Dichlorides *trans*-1,4	Hydrochlorides[b]
Liquid	−20	42.5	8.0	5.7	0.2	4.6	33.3	15.2
Liquid	8	41.2	9.0	6.7	1.3	4.0	34.4	5.1
Liquid[c]	8	45.1	9.7	6.1	0.4	4.0	31.6	3.7
Liquid	20	44.1	7.3	5.5	2.7	4.1	33.6	4.8
Vapor	100	36.4	30.1	6.5	0.8	3.8	17.4	0.7
Vapor[d]	100	38.2	32.3	7.0	0.5	3.4	15.5	0.3
Vapor[e]	100	33.2	25.0	6.8	0.7	5.4	24.3	Trace

[a] Nitrogen sweep used in all vapor experiments; ratio isoprene to chlorine = 2.5; ratio nitrogen to chlorine = 30. Ratio isoprene to chlorine = 6 in liquid phase chlorinations. [b] Considered as recoverable isoprene. [c] With oxygen, ratio O_2/Cl_2 = 0.25. [d] With oxygen, ratio O_2/Cl_2 = 3. [e] With nitric oxide, ratio Cl_2/NO = 6.

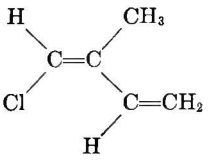
chlorine and the mole ratio of isoprene to chlorine was 2.5 or higher. The substitution products consist of 2-chloromethylbutadiene and 1-chloro-2-methylbutadiene. The *cis* and *trans* isomers of 1-chloro-2-methylbutadiene were obtained in a ratio slightly richer (52%) in that isomer (II) in which methyl and chlorine have *trans* relationship. This was the case in the liquid chlorination at −20° and vapor phase chlorination at 100°. Isomer I is structurally related to *trans*-1-chlorobutadiene and, like it,[11] could be removed selectively from a mixture of isomers by reaction with maleic anhydride.



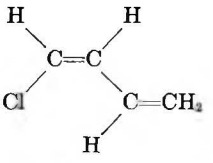
1-chloro-*cis*-2-methylbutadiene (I)



trans-1-chloro-butadiene



1-chloro-*trans*-2-methylbutadiene (II)



cis-1-chloro-butadiene

In liquid phase chlorinations in a nonpolar medium the ratio of yields of 2-chloromethylbutadiene and 1-chloro-2-methylbutadiene was of the magnitude of 5; however, as shown in Table II the ratio dropped when the solvent was aqueous *t*-butyl alcohol or 2,6-lutidine or when a quaternary ammonium chloride was dissolved in the isoprene. Under these conditions the yields of dichlorides, and especially that of the 1,2-dichloride, were increased. It is assumed that the effect of the polar solvents was to provide chloride ion from dissolved or combined hydrochloric acid. That the chloride ion participated in addition implies an ionic mechanism, at least in the polar solvents. The greater reduction in yield of 2-chloromethylbutadiene than of 1-chloro-2-methylbutadiene can be rationalized in terms of a common intermediate by assuming that chloride ion, as a stronger base than hydrogen chloride, tended to remove the more acidic proton from the chlorine-bearing carbon. Dehydrohalogenation of the 1,2-dichloride does not occur under the conditions of chlorination; however, dehydrohalogenation with sodium hydroxide at 60° gives 4.2 times as much 1-chloro-2-methylbutadiene as 2-chloromethylbutadiene.

(11) A. S. Onishchenko and N. I. Aronova, *Dokl. Akad. Nauk SSSR*, **132**, 138 (1960).

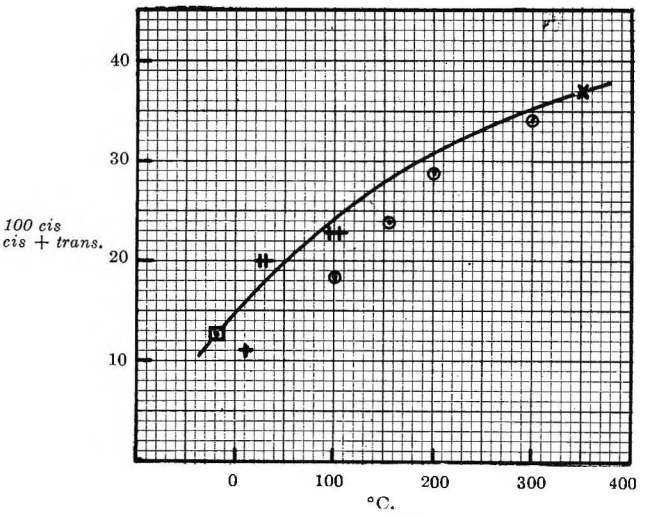


Figure 1.—Ratio of isoprene 1,4-dichlorides derived as follows: ×, rearrangement of 1,2-dichloride; ⊙, gas phase chlorination of isoprene; +, liquid phase chlorination of neat isoprene; ⊡ 2-years' storage of mixture rich in *cis*-1,4-dichloride; ++, treatment of mixture rich in *trans*-1,4-dichloride (considerable by-product formation).

In the absence of chloride ion the greater electron-supplying effect of the methyl group tends to favor the formation of 2-chloromethylbutadiene as it does the formation of methallyl chloride in the chlorination of isobutylene.[9]

The addition of drying agents or ground glass to a liquid-phase chlorination had little effect. There was a minor product change when the Saran vapor phase reactor was packed with glass. Under these conditions some 7% conversion occurred to additional dichlorides, normally obtained in smaller amount.

To establish which products, if any, were not primary ones, several attempts were made to isomerize one to another. Under the conditions of chlorination there was no isomerization; however, the dichlorides could be interconverted by long standing or treatment with zinc chloride. As shown in Figure 1 the mole percentage of *cis* isomer of the 1,4-dichloride increased with increasing temperature, whether the mixture was one obtained directly by chlorination or by isomerization.

Under the conditions of short contact time and excess isoprene neither the monochloro substitution products nor the dichlorides underwent to an appreciable extent further reaction with chlorine or hydrogen chloride. The hydrochlorides did compete with isoprene in addition of hydrogen chloride. There was an indication that the addition of hydrogen chloride to isoprene in the liquid phase was slower than chlorination. Thus the use of a nitrogen sweep to remove hydrogen chloride (or alternatively a partial covolatilization of the isoprene and hydrogen chloride) minimized the formation of addition products of hydrogen chloride to isoprene. As the temperature was increased, relatively more of that hydrogen chloride adduct which did form had the 1,4 structure. Hydrochlorides were not formed in the gas phase reaction.

An attempt was made to obtain product ratios at incomplete consumption of chlorine. In these experi-

TABLE II

LIQUID PHASE BATCH CHLORINATION WITH VARIOUS ADDITIVES

Additive[a]	Temp, °C	2-Chloromethyl-butadiene	1-Chloro-2-methyl-butadiene	Dichlorides 1,2	3,4	*cis*-1,4	*trans*-1,4
Neopentane	−20	39.4	8.4	6.0	0.4	4.6	38.3
(Heptyl)$_4$NCl[b]	−20	9.8	4.0	43.2	3.4	3.9	28.5
t-Butyl alcohol[c]	−20	14.1	10.1	18.2	2.0	2.0	20.2
2,6-Lutidine	−20	10.3	5.1	27.5	2.3	3.6	50.8
Chloroform	−20	38.4	~15.2	6.8	2.1	2.1	27.9
Ground glass	−20	38.1	10.5	5.9	0.7	5.3	31.2
Calcium hydroxide	−20	38.6	8.5	5.8	0.7	5.6	35.7
Sodium sulfate	−20	39.9	9.2	5.5	0.9	<4.8	33.5
Carbon disulfide	−78	37.5	11.9	7.2	~0.7	3.2	38.2
Benzene	5	37.0	14.7	8.4	3.0	3.1	29.0
Cyclohexane	5	37.0	10.2	7.6	~0.7	3.1	33.6

[a] Solvents were used in equal volume with isoprene; solids were added at 2% of isoprene weight and chlorination conducted with agitation. Yields corrected for hydrochloride formation. [b] 10% by weight of isoprene. [c] Containing 10% water.

ments in the gas phase an on-stream mass spectrometer was used. Because of the problems associated with electrode corrosion by chlorine, it was not possible to distinguish isomers or establish K values, but the addition and substitution products were clearly resolved and could be qualitatively compared. These experiments were conducted under vacuum and at several temperatures. It was concluded that the ratio of substitution to addition did not change much with change in temperature between room temperature and 100° in gas phase chlorination.

The reaction went quite well in the dark in both phases and did not seem to depend upon adventitious peroxidic impurities. Purification of the isoprene had no effect nor did addition of peroxide. No inhibitor was found. Oxygen and nitric oxide were ineffective in either phase and bromotrichloromethane and triphenylmethane were ineffective in the liquid phase.

Confirming evidence for the absence of a radical-chain mechanism was found in a competitive chlorination of a mixture of isoprene and ethylene. Except when ultraviolet irradiation was used the ethylene was not attacked either in the liquid or gas phase. As pointed out by Poutsma, chlorine atoms show essentially no discrimination between dienes and olefins.[9]

We conclude therefore that the mechanism operating in the chlorination of isoprene in the dark at 100°, or below, is not a free-radical chain reaction even in the vapor phase. Such an interpretation is not entirely new. Rust and Vaughan[12] found that in the low temperature (below 300°) chlorination of ethylene in the gas phase the ratio of substitution to addition could be increased by increasing reactant pressure and that the former but not the latter could be completely inhibited by oxygen. Propylene showed a similar but less pronounced effect. They concluded that in the case of olefins chlorine addition at low temperatures in the vapor phase can occur by a nonchain reaction in addition to the chain reaction which is produced by free-radical sources.

Inasmuch as the products are not rearranged, any thermodynamic control in the formation of *cis* and *trans* 1,4-addition products must be established in the transition state, and it is tempting to suggest that this state has the form of a π complex. Some evidence exists for the formation of complexes between iodine and aromatic hydrocarbons in the gas phase.[13] The effect of temperature on the proportion of *cis* isomer is consistent with—and may be related to—the expected effect of temperature on the proportion of cisoid isomer in isoprene.

The rate of chlorination of isoprene is inconveniently fast in concentrated solution for kinetic study even at −78°. Kinetic measurements can be made at room temperature at a chlorine concentration of 10^{-3} M which is inconveniently dilute for quantitative vapor phase chromatography.

The rate was followed by disappearance of chlorine absorption at 332 mμ and the half-life was approximately 3 hr. The rate was not changed by raising the ratio of isoprene to chlorine from 2 to 4 but was highly dependent on chlorine concentration. At 10^{-2} M chlorine the half-life was less than 5 min. As shown in Figure 3 the rate was essentially first order in chlorine and subject to pronounced acceleration by intermittent illumination after the addition of *t*-butyl hypochlorite.[13a]

The liquid phase butoxylation of isoprene with *t*-butyl hypochlorite appears to have some free-radical character. Tiglaldehyde and tiglic acid were detected as products, presumably derived from the abnormal substitution product 1-butoxy-2-methylbutadiene which was not itself isolated. 2-Chloromethylbutadiene and 1-chloro-2-methylbutadiene were produced also presumably by concurrent polar mechanism.

Experimental Section

The products of chlorination were analyzed by glpc using matched 9-ft columns (0.375 in. o.d.; 10% FFAP (fatty acid ester of a polyglycol, from Wilkins Instruments on 60–80 mesh acid-washed DMCS treated Chromosorb P) with the temperature programmed at 10°/min from 70 to 170°. The lined injection port temperature was 130°. The carrier gas was helium at a flow rate of 50 cc/min with detection by thermal conductivity. The instrument employed was a Model 1520 manufactured by the Aerograph Co. A typical curve of a liquid phase chlorination product with ethylene dichloride added is shown in Figure 2.

By this schedule the hydrochlorides were evolved below the temperature at which they broke down. The hydrochlorides could be readily converted to 3-hydroxy-3-methyl-1-butene[14] by shaking with dilute sodium hydroxide solution; however, this compound appeared from the column at the same time as isomer

(12) F. F. Rust and W. E. Vaughan, *J. Org. Chem.*, **5**, 472 (1940).

(13) F. T. Lang and R. L. Strong, *J. Amer. Chem. Soc.*, **87**, 2345 (1965).

(13a) NOTE ADDED IN PROOF.—It was discovered later that this catalytic effect could be duplicated by injection of a trace of hydrogen chloride; neither illumination nor *t*-butyl hypochlorite was needed.

(14) A. J. Ultee, *Rec. Trav. Chim. Pays Bas*, **68**, 483 (1949).

II. Several chromatographs of hydrochlorides were made isothermally using a column made with 15% polyethylene glycol on acid-washed Chromosorb. It was not satisfactory. At 100° the amounts of eluted hydrochlorides were much lower than at 80°. The other products were stable on either column. The high-temperature program was especially necessary to elute all of the 1,4-dichlorides.

Peak identification was done by mass, infrared, and nmr spectroscopy after separation of relatively pure components by fractional distillation and collection of fractions from the gas chromatograph.

The tabulations of yields of various products were calculated from area percentages from the gas chromatographs without the use of response factors. It was felt that although such corrections would be desirable they would have little effect on the mechanistic interpretations. Relative response factors were determined, however, for several components and are shown in Table III.

TABLE III

RELATIVE RESPONSE FACTORS THERMAL CONDUCTIVITY DETECTOR (HELIUM CARRIER GAS)

Compound	Relative weight response	Relative molar response
Isoprene	1.23	0.82
trans-1-Chloroisoprene	0.99	0.99
cis-1-Chloroisoprene	0.95	0.95
4-Chloro-2-methyl-2-butene	1.09	1.09
2-Chloromethylbutadiene	1.00	1.00
1,2-Dichloro-2-methyl-3-butene	0.82	1.09
1,4-Dichloro-2-methyl-2-butene	0.77	1.04
Carbon tetrachloride	0.7	1.05
Nitromethane	1.1	0.65
Benzene	1.15	0.87

The identification of the geometric isomers of 1-chloromethylbutadiene was based on nmr spectroscopy and reaction with maleic anhydride. The first isomer to appear in glpc was the isomer removed. A comparison with 1-chlorobutadiene was made. For both the isoprene and butadiene derivatives that isomer which reacted with maleic anhydride had a chemical shift of the single 3-hydrogen of 6.25 ppm, as with isoprene itself, whereas the other isomer had a chemical shift of 6.95 *vs.* TMS. As is the case in butadiene itself[15] the nmr line of the hydrogen in position 1 (*trans* to vinyl) of isomer II was located upfield (0.13 ppm) from and broader than that of isomer I.

After the reported procedure[16] *cis*- and *trans*-1-chlorobutadiene were prepared in approximately equal amounts by the pyrolysis of 1,4-dichloro-2-butene, and the *cis* isomer, by reaction with caustic. They were not separable on the glpc column used in the isoprene work but at 50° on a column containing di-2-ethylhexyl sebacate the *cis* isomer appeared first. The ratio of peak heights of *cis* to *trans* was 0.9. As reported,[11] the *trans* isomer was found to be removable by reaction at 80° for 0.5 hr with maleic anhydride.

A minor by-product of high-temperature chlorination was found to be 3-chloro-2-methylbutadiene.[17] The nmr spectrum showed the CH_3 singlet at 1.95 ppm, and $=CH_2$ multiple peaks at 5.0–5.6 ppm. There was no absorption in the 6.09–6.25-ppm range to indicate Cl—CH=. The mass spectrum was that of a monochlorinated isoprene. The elution time in glpc was after the 1,2-hydrochloride, and before the 1-chloro-2-methylbutadiene. Another isomer having a slightly higher retention time was a small component of liquid phase chlorinations and was assumed to be 4-chloro-2-methylbutadiene.

Rearrangement of the Dichlorides of Isoprene.—Samples (1.0 μl) of the 1,2-dichloride (93.1% purity) were injected into a heated length of 0.0625-in. tubing attached to the glpc column and operated at various temperatures. The contact time was very short but at 250° there was essentially no change. At 350° there was 22% rearrangement. Half of the rearrangement was to the *trans*-1,4-dichloride; 6.5% of the *cis*-1,4-dichloride and 2% of the 3,4-dichloride were formed.

(15) R. T. Hobgood, Jr., and J. H. Goldstein, *J. Mol. Spectrosc.*, **12**, 76 (1964).

(16) L. J. Hughes, French Patent 1,326,120 (Monsanto) (1963).

(17) G. F. Hennion, J. J. Sheehan, and D. E. Maloney, *J. Amer. Chem. Soc.*, **72**, 3542 (1950).

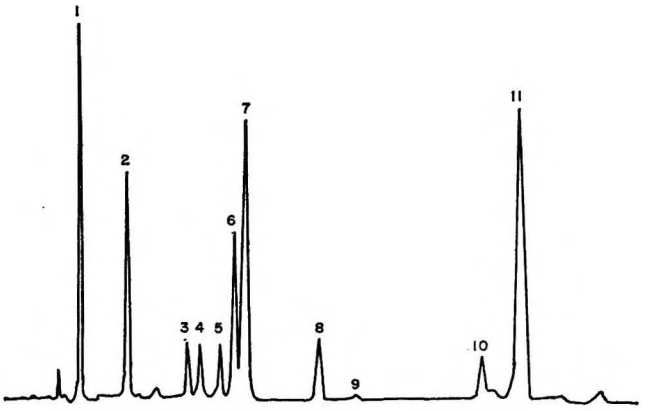


Figure 2.—The order of appearance of FFAP-packed glpc column of isoprene chlorination products plus added ethylene dichloride is as follows (attenuation values are in parentheses): 1, isoprene (128); 2, 1,2-hydrochloride (4); 3, *cis*-1-chloro-2-methylbutadiene (4); 4, *trans*-1-chloro-2-methylbutadiene (4); 5, 1,4-hydrochloride (4); 6, ethylene dichloride; 7, 2-chloromethylbutadiene (8); 8, 1,2-dichloride (4); 9, 3,4-dichloride; 10, *cis*-1,4-dichloride (4); 11, *trans*-1,4-dichloride (4).

A sample (10 ml) of the 1,2-dichloride (93.4% purity) was injected into the Saran gas phase chlorinator and exposed to chlorine at 100°. The injection was accomplished by preheating the dichloride to 100° and sparging the nitrogen through it. The ratio of chlorine to dichloride was 0.8 and the ratio of nitrogen to chlorine was 90. The product was condensed in a sulfite scrubber and analyzed by glpc. No significant change was observed in it.

A sample of the 1,4-dichloride which was 94.2% *trans*- and 2.4% *cis*-1,4-dichloride was saturated with zinc chloride and left at room temperature for 148 hr. The *cis* percentage increased to 17.1 and then dropped to 14.5 after 172 hr whereas the *trans* percentage decreased steadily to 62.6. Some of the 1,2- and 3,4-dichlorides formed.

Another sample was saturated with zinc chloride and heated at 100°. Within 10 min the concentration of the *cis* isomer had reached 22.6% and went no higher, although the 1,4 isomer continued to disappear on prolonged heating. There was first an increase and then decrease of the 1,2- and 3,4-dichlorides.

Secondary Reactions.—Chlorine was bubbled through 2-chloromethylbutadiene of 94% purity at 0°. There was a 5% conversion in 5 min to a variety of chlorinated products whereas the chlorination of isoprene went to completion in less than 0.5 min. The concentration of 1-chloro-2-methylbutadiene was reduced from 1 to 0.6%.

2-Chloromethylbutadiene was saturated with hydrogen chloride at 0° for 1 hr. There was a 3% conversion to a mixture of isoprene 1,2- and 1,4-dichlorides. In contrast isoprene saturated with hydrogen chloride at −20° underwent 16% addition in 2 min to mixed hydrochlorides (51.5% 1,2-hydrochloride; 38.6% 1,4-hydrochloride). 1-Chloro-2-methylbutadiene in a nickel vessel at room temperature was treated with hydrogen chloride at 100 psi for 21 hr. There was 13.7% conversion to a dichloride different from those obtained from isoprene and chlorine.

A mixture of the hydrochlorides and monochloro substitution products of isoprene was treated with hydrogen chloride for 1 hr at 0°. The hydrochlorides reacted preferentially. None of the dichlorides added hydrogen chloride when treated for 1 hr at 0°.

Chlorination in Polar Solvents.—Into a solution of isoprene (100 ml) in 2,6-lutidine (57 ml) stirred at −25° was bubbled chlorine (35.5 g) mixed with air. The vessel was equipped with a condenser chilled with Dry Ice. A yellow precipitate of lutidine hydrochloride formed. The liquid product was washed with water and the glpc analysis of Table II made on it.

In another experiment 2,6-lutidine (57 ml) was dissolved in isoprene (200 ml) and chlorine (35.5 g) introduced at 30°. The amount of chloride ion which formed was 0.088 equiv; of this only a small part (0.005 equiv) was present as a quaternary ammonium chloride resulting from alkylation of the lutidine.

In a Teflon-coated reactor at −20°, isoprene (0.3 mol) was dissolved in an equal volume of aqueous *t*-butyl alcohol solution (10:1 *t*-BuOH/H_2O). Chlorine (0.05 mol) was bubbled into

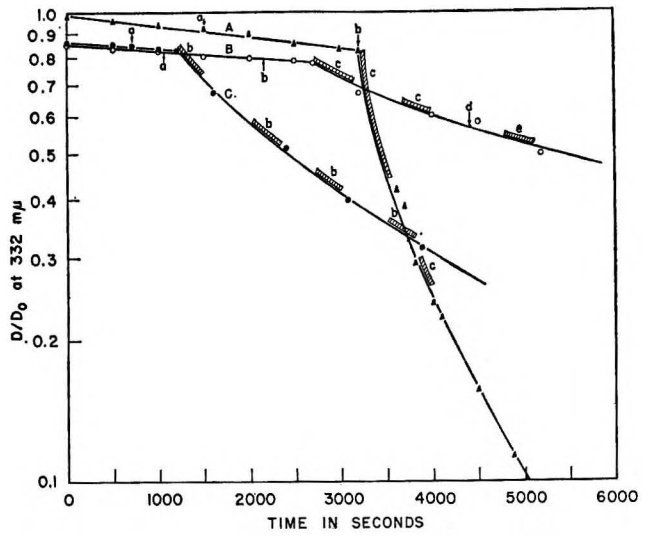


Figure 3.—Reaction of chlorine (0.026 mmol) (0.029 in curve A) and isoprene (0.050 mmol) in carbon tetrachloride (30 ml) under nitrogen; cross-hatched areas represent illumination (3660 Å): (A) at point a additional isoprene added (0.05 mmol), at point b *t*-butyl hypochlorite added (1% of isoprene); (B) at point a air injected (4.8 ml); at point b *t*-butyl hypochlorite added (1% isoprene); at point d additional isoprene added (0.05 mmol); (C) at point a *t*-butyl hypochlorite (1% of isoprene).

this over a period of 33 sec. The product was purged with nitrogen for 15 min.

Tetraheptylammonium chloride (2.04 g) was dissolved in isoprene (0.3 mol, 20.43 g). Chlorine (0.05 mol) was bubbled into this at −20° for a period of 33 sec. The product was purged with nitrogen to remove hydrogen chloride.

Liquid Phase Chlorination.—For batch chlorinations in the liquid phase a Teflon-coated glass reactor of 75-ml capacity was equipped with a condenser containing Dry Ice. The gas inlet tube was also Teflon coated as was the cold finger. The outlet was connected to a cold trap, and in most of the work no precautions were taken to exclude moisture. The liquid volume in the chlorinator was 30 ml, and agitation was only that caused by the gas sparger. The external cooling bath was incapable of preventing a rise in temperature of several degrees during chlorination, especially because the chlorine was added rapidly. The difficulty was minimized by keeping the mole ratios of chlorine to isoprene low.

Isoprene (20.43 g, 0.3 mol) was chilled to −20° and chlorine (0.05 mol) introduced during the period of 33 sec. There was no chlorine in the exit gas. After chlorination the product was purged with nitrogen to remove hydrogen chloride; yield 20.98 g. By glpc the product contained (on an area per cent basis) 79.0% isoprene, 2.2% 1,2-hydrochloride, 0.7% *cis*-1-chloro-2-methylbutadiene, 0.7% *trans*-1-chloro-2-methylbutadiene, 1.0% 1,4-hydrochloride, 7.4% 2-chloromethylbutadiene, 1.0% 1,2-dichloride, 0.03% 3,4-dichloride, 0.8% *cis*-1,4-dichloride, 5.8% *trans*-1,4-dichloride, and six unidentified peaks amounting to a total of 0.9%. The yield of 2-chloromethylbutadiene corrected for hydrochlorides and isoprene was 42.5%.

An experiment was made using isoprene presaturated with about 3% triphenylmethane. The amount of recovered isoprene was 72.2%, and the yield of 2-chloromethylbutadiene was 44.2%. The product composition was essentially the same as without the triphenylmethane.

Reaction of Isoprene with *t*-Butyl Hypochlorite.—Reaction of the premixed ingredients at low temperatures was not controllable. Isoprene (0.68 g, 0.01 mol) and *t*-butyl hypochlorite (1.09 g, 0.01 mol) were mixed at 10°. After 10 min most of the contents were suddenly expelled. The residue contained chlorination products. The ratio of 2-chloromethylbutadiene to 1-chloro-2-methylbutadiene was 4. Although delayed, a similar uncontrolled reaction occurred even when the vessel was kept in the dark.

Isoprene (0.02 mol) was refluxed and *t*-butyl hypochlorite (0.02 mol) added through the condenser over the period of 15 min. Carbonyl- and hydroxyl-containing compounds were formed, one of which was identified by mass spectrometry as tigylaldehyde. In addition, 2-chloromethylbutadiene and 1-chloro-2-methylbutadiene were formed, but none of the abnormal 1,2 adduct.

Chlorination of Isoprene at High Dilution in Carbon Tetrachloride.—Carbon tetrachloride (30 ml) in a 10-cm uv cell was purged with nitrogen to remove oxygen. Chlorine (0.026 mmol) dissolved in carbon tetrachloride, isoprene (0.05 mmol), and *t*-butyl hypochlorite (1% of isoprene, by weight) were added. The disappearance of the chlorine band at 332 mμ was followed at room temperature on a Cary spectrophotometer, Model 15. The reaction was catalyzed by intermittent light exposure (3600-mμ band) with a Bausch & Lomb high intensity monochromator at 10^{16} photons/sec (curve C, Figure 3). Absorption was incomplete. Variations of the above basic procedure (curves A and B, Figure 3) were used with the addition of more isoprene (0.05 mmole) and air (4.8 cc) and catalysis by monochromatic light at the 3660-mμ line.

Vapor Phase Chlorination of Isoprene.—Small-scale vapor phase chlorination of isoprene was carried out in a downflow cocurrent fashion in a 4-ft glass column (20 mm i.d.) containing a full length thermocouple well (6 mm o.d.).

In later experiments a 4 ft × 0.625 in. i.d. Saran pipe was substituted for the glass column and the thermocouple well was omitted. The product distribution was not changed by packing this reactor with glass, except that the minor dichlorides amounted to 7%.

A steam jacket surrounded the column. The gas mixture used in a particular reaction was monitored through flow meters and preheated in a coil by means of steam. Isoprene vapor was sparged into the column with nitrogen from a reservoir kept at room temperature. The chlorine also was diluted with nitrogen and the ratio of nitrogen to isoprene was kept at 30 to prevent condensation. The product gas was passed through a solution of sodium sulfite (12%) and sodium hydroxide (4%) containing antifoaming agent (Dow Corning Antifoam A).

To show that this procedure was adequate to prevent any liquid phase chlorination some isoprene was placed in the scrubber and chlorine passed through the column. Less than 1% chlorination occurred. 2-Chloromethylbutadiene was shown to be stable under the conditions of the scrubber and only slowly chlorinated in the column.

A mixture of isoprene and ethylene was chlorinated using the Saran column heated with steam at atmospheric pressure. The ethylene was passed through the chilled isoprene and into the reactor where it was mixed with chlorine which was diluted with nitrogen. In the first experiment the isoprene was chilled to zero, and the flow was 0.006 *vs.* 0.016 m min^{-1} ethylene. In the second it was chilled to −10° and the flow rate was 0.005 *vs.* 0.023 m min^{-1} ethylene. The chlorine flow rate was half the isoprene flow rate, and the nitrogen flow was 3 l. min^{-1}. In the first experiment the isoprene was 44% converted and in the second 53%, but no ethylene dichloride was detected. The product ratios were similar to those of Table II for gas phase chlorination. The yields were 32% 1-chloro-2-methylbutadiene (44% *cis*), 37% 2-chloromethylbutadiene, and 27% dichlorides (25% *1,2*; 1.8% *3,4*; 12% *cis*-1,4).

Vacuum Chlorination of Ethylene–Isoprene Mixture.—A mixture of 2 vol of ethylene and 1 vol of isoprene was introduced through one orifice and chlorine through another into an evacuated glass vessel 24 cm long consisting of the annular space between a water-cooled core (5 cm o.d.) and a jacket (8 cm i.d.). The pressure was maintained at 3 mm. Chlorine was introduced at half the rate of the hydrocarbon mixture. Immediately downstream from the reactor was an orifice leading to a modified Consolidated Electrodynamics cycloidal mass spectrometer. Some unreacted chlorine entered the mass spectrometer. The substitution and addition products of isoprene fell into two separate groups but were not resolved within these groups. No ethylene dichloride was observed when the chlorination was conducted without ultraviolet illumination. When the vessel was irradiated with a 450-W medium pressure Hanovia lamp, ethylene dichloride was formed. Owing to the heat of the lamp the temperature rose from 17 to 23° and the amount of isoprene chlorination increased. The free chlorine disappeared. When the lamp was turned off the chlorine reappeared and the ethylene dichloride disappeared (the disappearance was delayed owing to some retention in the mass spectrometer). When the reactor was heated

to 50° without illumination, no ethylene dichloride was formed and free chlorine was still observed.

For the purpose of collecting a glpc sample a different reactor was used. Into 75 ft of Saran tubing (0.375-in. i.d.) was introduced at 2 mm pressure the 2:1 ethylene–isoprene mixture, and chlorine at the ratio of 5 mol % of the isoprene. The gas flow was 3×10^{-4} mol/min. The product was condensed with liquid nitrogen, and no chlorine was visible. Ethylene dichloride is resolvable from 2-chloromethylbutadiene, although it appears close to it, and none was observed. The actual conversions were 1,2-hydrocloride, 1.4%; 1-chloro-*cis*-2-methylbutadiene, 0.3%; 1-chloro-*trans*-2-methylbutadiene, 0.4%; 2-chloromethylbutadiene, 0.8%; 1,2-dichloride, 0.5%; *cis*-1,4-dichloride, 0.09%; *trans*-1,4-dichloride, 0.9%.

Registry No.—Isoprene, 78-79-5.

Acknowledgment.—We acknowledge with appreciation the assistance of C. Bredeweg, The Dow Chemical Co., and of Professor Lewis Hatch who sent us the M.S. thesis of J. L. A. Rodrigues, University of Texas (1965), on the vapor phase reaction between chlorine and dienes.

Thermal Decomposition of o-Azidoazobenzenes. I. o,o'-Diazidoazobenzene[1]

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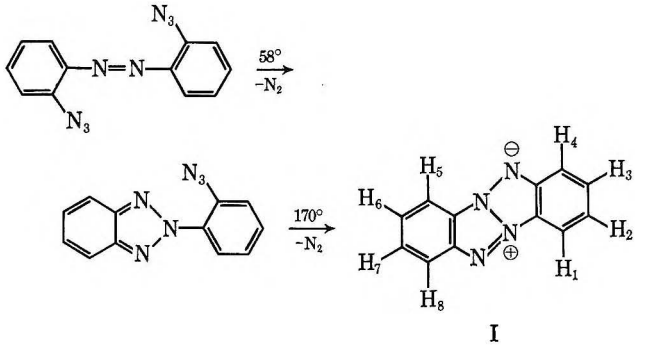
Received August 24, 1967

Thermal decomposition of 2-(2-azidophenyl)-5-methylbenzotriazole has been found to give a mixture of 2-methyl- and 3-methyl-5,6H-dibenzo[*b*,*f*]-1,3a,4,6a-tetraazopentalenes. Each of these products was prepared separately by decomposition of 2-(2-azido-5-methylphenyl)benzotriazole and 2-(2-azido-4-methylphenyl)benzotriazole, respectively. The results of an nmr study on the parent 5,6H-dibenzo[*b*,*f*]-1,3a,4,6a-tetraazopentalene as well as the 2-methyl and 3-methyl derivatives is presented. The chemical shifts were found to be consistant with electron distribution calculations of Chia and Simmons[5d] and with the observations of Carboni, *et al.*,[5d] on orientation effects in electrophilic substitution reactions.

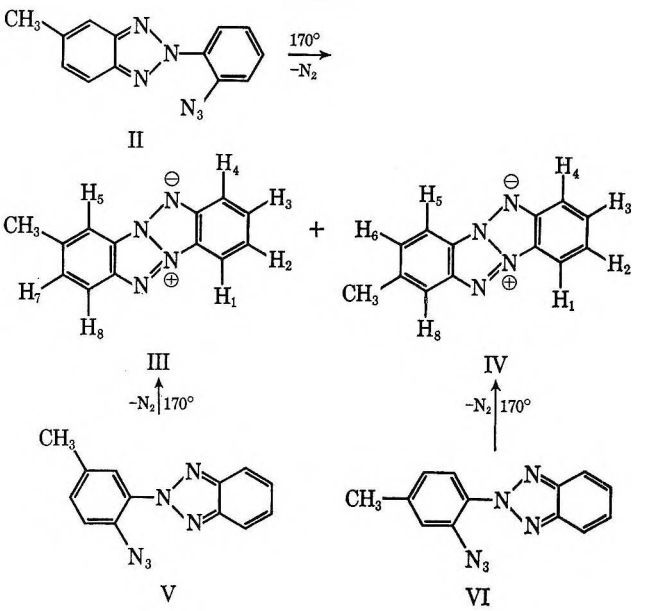
The thermal decomposition of *o,o'*-diazidoazobenzene has been shown to proceed by stepwise loss of nitrogen to give 5,6H-dibenzo[*b*,*f*]-1,3a,4,6a-tetrazopentalene (I).[2,3] A preliminary report of an X-ray study of I described it as having two different N–N bond distances and as probably being planar.[4] In recent work, chemical evidence for structure I was presented and alternate methods of synthesis were described.[5]



I

In a further investigation of this interesting aromatic system, we prepared 2-(2-azidophenyl)-5-methylbenzotriazole (II) and studied the decomposition in decalin at 170° (Scheme I). A yellow solid was obtained, mp 184–185°. Because of the sharpness of the melting point, this solid was initially felt to be a single compound. However, in order to be certain, the two possible products, III and IV, were independently synthesized. Compound III was prepared by thermal decomposition of 2-(2-azido-5-methylphenyl)benzotriazole (V) and compound IV was prepared by thermal decomposition of 2-(2-azido-4-methylphenyl)benzotriazole (VI). The syntheses of V and VI were accomplished by condensation of 2-azidoaniline with the corresponding nitroso compound in acetic acid to give the substituted 2-azido-2'-nitroazobenzene. The azo compound was not isolated but was decomposed during the work-up of the reaction mixture to give the substituted 2-(2-nitrophenyl)benzotriazole. The nitro group was reduced with iron and acetic acid to the amine. Diazotization of the amine followed by treatment of the diazonium salt solution with sodium azide gave the sub-

SCHEME I



(1) (a) Acknowledgment is made to the donors to the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. (b) This work was taken in part from the M.A. Thesis of John G. Stephanie.

(2) (a) R. A. Carboni and J. E. Castle, *J. Amer. Chem. Soc.*, **84**, 2453 (1962); (b) R. A. Carboni, U. S. Patent 2,904,544 (Sept 1959); (c) R. A. Carboni, U. S. Patent Reissue 25,238 (Sept 1962).

(3) Other names that have been used include 5,11-dehydrobenzotriazole-[2,1-*a*]benzotriazole, dibenzo[*c*,*g*]-1,2,5,6-tetraazocine, 5H,11H-benzotriazolo[2,1-*a*]benzotriazol-6-ium salt, and dibenzo[2,3;4,5]-1,3a,4,6a-tetraazopentalene.

(4) M. E. Burke, R. A. Sparks, and K. N. Trueblood, *Acta Cryst.*, **16**, A64 (1963).

(5) (a) R. A. Carboni, J. C. Kauer, J. E. Castle, and H. E. Simmons, *J. Amer. Chem. Soc.*, **89**, 2618 (1967); (b) R. A. Carboni, J. C. Kauer, W. R. Hatchard, and R. J. Harder, *ibid.*, 2626 (1967); (c) J. C. Kauer and R. A. Carboni, *ibid.*, 2633 (1967); (d) Y. T. Chia and H. E. Simmons, *ibid.*, 2638 (1967); R. J. Harder, R. A. Carboni, and J. E. Castle, *ibid.*, 2643 (1967).

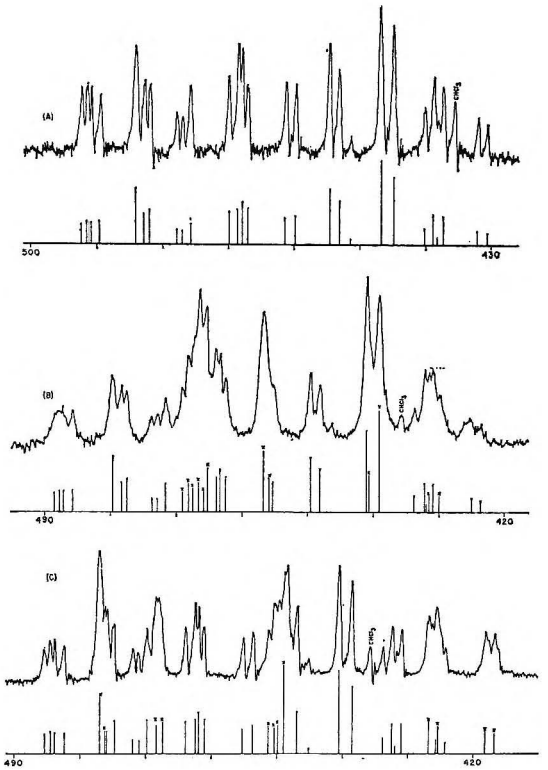
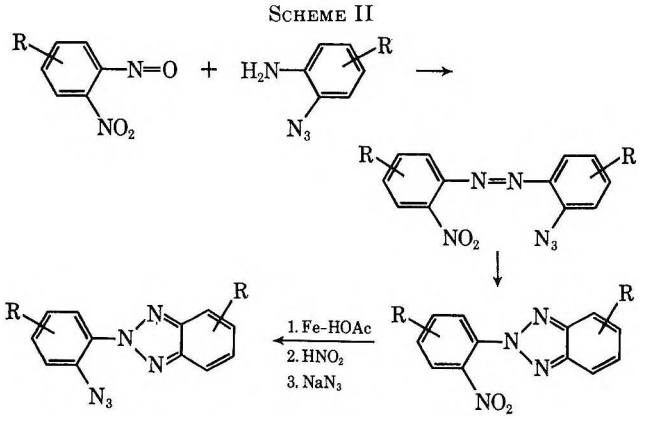


Figure 1.—Nmr spectra of A, 5,6H-dibenzo[*b*,*f*]-1,3a,4,6a-tetraazopentalene (I); B, the 2-methyl derivative (III); and C, the 3-methyl derivative (IV). The bands in the calculated spectra B and C that are marked with × are the bands of the methyl-substituted ring.

stituted 2-(2-azidophenyl)benzotriazole. The synthesis of II was accomplished by a similar method in which 2-nitronitrosobenzene was condensed with 2-azido-4-methylaniline. This method seems to be a general method for the production of the heterocyclic ring system I. The general procedure is outlined in Scheme II.

SCHEME II



Thermal decomposition of V gave a yellow solid, mp 194°. Decomposition of VI gave a yellow solid, mp 198°. The infrared spectra of these two compounds were almost identical. However, a mixture melting point gave a depression. Also, the nmr spectra of each of these compounds was found to be different as shown in Figure 1. Furthermore, the nmr spectrum of the material obtained by decomposition of II contained all of the peaks present in the spectra of III and IV. Thus, decomposition of IV does give a mixture of isomeric products. Careful analysis of the nmr spectrum indicates that the ratio of IV/III produced by decomposition of II is 1.9. The preference for cyclization to the position *para* to the methyl group to give IV is consistant with the known electrophilic character of the intermediate produced in azide decompositions.

The nmr spectrum of I would be expected to be an ABCD-type spectrum. In order to verify that the observed pattern was an ABCD type, a detailed study of the nmr specturm of I, III, and IV was undertaken. One of the first observations on these spectra was the unusual width of the absorption band. In each case, these bands were spread out over a range of about 70 cps. In general, such broad bands are normally observed in *ortho* substituted benzenes when the groups attached are greatly different in electronic character; that is, one is electron donating and the other is electron withdrawing. Often such spectra are first order. The 60-Mc nmr spectrum of I has 26 observable peaks compared to the expected 32 for first-order behavior, indicating that the spectrum is not first order. However, examination of this spectrum (Figure 1) reveals that it has considerable symmetry. The right half of the spectrum has a center of symmetry and also the left half has a center symmetry. Careful analysis of this spectrum shows that it is almost first order. The nmr spectra of I, III, and IV (Figure 1) were compared. All of the peaks found in the spectrum of I were also found in the spectra of III and IV. In fact it was found possible to subtract the spectrum of I from the spectra of III and IV and obtain the ABC spectra of the methyl substituted rings of III and IV. Examination of the ABC systems allowed assignment of the peaks to particular protons in III and IV and also in the parent compound I. Estimation of the chemical shifts and approximate coupling constants were made for each of these compounds. This information was fed into an IBM 7040 computer. Using the LAOCN-3 program,[6] the theoretical spectra, the accurate chemical shifts, and accurate coupling constants were calculated. This information is tabulated in Table I. The H_1 and H_4 of I, *ortho* to the nitrogens, are located further downfield than H_2 and H_3. However, H_4 is further upfield than H_1, a reflection of its location *ortho* to the nitrogen carrying the formal negative charge. Similarly, the H_2 proton is located further upfield than the H_3 proton due to its location *para* to the negative charge. Examination of the chemical shifts of the methyl-substituted derivatives, III and IV, reveal a similar situation, *i.e.*, the protons located *ortho* and *para* to the nitrogen with the formal negative charge are further upfield than the protons located *ortho* and *para* to the nitrogen with the formal positive charge. These results are in excellent agreement with the shifts expected based on the electron distribution calculations of Chia and Simmons.[5d] Also, it is in agreement with the observed orientation effects in electrophilic substitution reactions.[5b]

The upfield shift of the protons *ortho* and *para* to one nitrogen and the downfield shift of the protons *ortho* and *para* to the second nitrogen accounts for the unusually broad nmr spectra of I and its derivatives and provides further evidence that the mesionic structure I as proposed by Carboni and Castle[2] is correct. The fact that the nmr spectrum of I can be completely accounted for

(6) A. A. Bothner-By and S. Castellano, "LAOCN-3," Mellon Institute, Pittsburgh, Pa.

TABLE I
COUPLING CONSTANTS AND 60-MC CHEMICAL SHIFTS

	Compound		
Chemical shifts	I	III	IV
H_1	486.7	482.7	479.7
H_2	440.0	433.8	433.7
H_3	453.1	448.2	447.0
H_4	471.5	467.0	465.5
H_5	486.7	467.9	471.9
H_6	440.0		422.1
H_7	453.1	436.2	
H_8	471.5	460.1	450.1
CH_3		150	149
Coupling constants			
$J_{1,2}$	8.47	9.17	8.56
$J_{1,3}$	1.05	1.06	1.16
$J_{1,4}$	0.79	0.75	0.87
$J_{2,3}$	7.00	7.59	7.05
$J_{2,4}$	0.93	0.70	0.79
$J_{3,4}$	8.73	9.30	8.82
$J_{5,6}$	8.47		8.72
$J_{5,7}$	1.05	1.52	
$J_{5,8}$	0.79	0.87	0.89
$J_{6,7}$	7.00		
$J_{6,8}$	0.93		1.40
$J_{7,8}$	8.73	9.21	

by treatment as an ABCD system indicates that both of the benzenoid rings are identical. The fact that the aromatic rings are benzenoid is indicated by the coupling constants in Table I. All of the values are normal for benzene derivatives. Finally, on examination of the data in Table I, it can be seen that the introduction of a methyl group in one of the rings affects the chemical shifts of protons in the other ring. For example, in compound IV, the presence of the methyl group on one ring has shifted the H_{1-4} protons upfield by 6–7 cps. The fact that the electronic effect of the methyl group is felt over such large distances is consistent with the aromatic character of I.[6d]

Experimental Section

All of the microanalyses were preformed by Alfred Bernhardt Microanalytical Laboratories, Mulheim, West Germany. All melting points were taken on a calibrated Kofler hot bench. The nmr spectra were run on a Varian A56/60 spectrometer. The theoretical spectra, coupling constants, and chemical shifts were calculated using the LAOCN-3 program on a 7040 IBM computer.

2-(2-Nitrophenyl)-5-methylbenzotriazole.—Finely powdered *o*-nitrosonitrobenzene (8.8 g, 0.058 mol) was placed in 250 ml of glacial acetic acid. To this stirred slurry was added 8.6 g (0.058 mol) of 2-azido-4-methylaniline in 50 ml of acetic acid. After stirring for 4 days at room temperature, the mixture was poured into water and the product was extracted with ether. The ether was washed with dilute acid, sodium carbonate solution, and water. Evaporation of the ether gave a red semisolid. Recrystallization from boiling ethanol completed the cyclization of the intermediate 2-azido-4-methyl-2'-nitrobenzene and gave 11.9 g (81%) of the benzotriazole, mp 85–87°. Further recrystallizations from ethanol raised the melting point to 91.5–92°.

Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.42; H, 3.94; N, 22.05. Found: C, 61.32; H, 4.07; N, 22.25.

2-(2-Nitro-5-methylphenyl)benzotriazole.—In 250 ml of hot glacial acetic acid was dissolved 4.14 g (0.025 mol) of 2-nitro-5-methylnitrosobenzene. The solution was cooled rapidly in ice with shaking to crystallize the nitroso compound in finely divided form. The mixture was warmed up to room temperature and 3.41 g (0.025 mol) of *o*-azidoaniline was added. After stirring for 3 hr, the solution was poured into 1 l. of water and the product was extracted into ether. The ether was washed with sodium hydroxide solution to remove the remaining acetic acid. Evaporation of the ether under an air stream gave a gummy red solid. The 2-nitro-5-methyl-2'-azidoazobenzene obtained could not be purified due to its low decomposition temperature. The crude product was dissolved in 100 ml of dioxane and the solution was refluxed until the nitrogen evolution had ceased. The dioxane was evaporated. The residue was dissolved in a minimum of benzene and the solution placed on a 1.5 × 25 cm alumina column. Elution of the column with benzene (45 ml) gave the product in the first band, yield 3.50 g. After two recrystallizations from carbon tetrachloride, an analytical sample, mp 100–102°, was obtained.

Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.03. Found: C, 61.23; H, 4.37; N, 22.17.

2-(2-Nitro-4-methylphenyl)benzotriazole.—In a mixture of 80 ml of methylene chloride and 10 ml of glacial acetic acid was placed 1.66 g (0.01 mol) of 4-nitroso-3-nitrotoluene and 1.34 g (0.01 mol) of 2-azidoaniline. The mixture was stirred at room temperature for 4 days. It was then extracted with sodium carbonate solution to remove the acetic acid. The methylene chloride was evaporated and the residue dissolved in a minimum of benzene. Chromatography on a 2 × 25 cm alumina column (Fisher A-540) gave 2.44 g of crude product in the first 180 ml of benzene eluent. Recrystallization from ethanol gave 1.87 g (74%) of pure material, mp 94°. The infrared spectrum of this compound indicated by the absence of an azido peak that cyclization of the intermediate 2-nitro-4-methyl-2'-azidoazobenzene had occurred.

2-(2-Amino-4-methylphenyl)benzotriazole.—In 45 ml of acetone was dissolved 1.68 g (0.00661 mol) of the nitro compound. To this refluxing solution was added 5 ml of glacial acetic acid and 5 ml of water. Over a period of 30 min, 5 g of powdered iron was added in small portions. After stirring vigorously for 3 hr, the solution was cooled and filtered to remove the insoluble salts. The acetone filtrate was washed with concentrated sodium carbonate solution to remove any remaining acetic acid. Dilution of the acetone with water gave 1.14 g (77%) of the amine, mp 105°.

Anal. Calcd for $C_{13}H_{12}N_4$: C, 69.54; H, 5.36; N, 25.00. Found: C, 69.44; H, 5.40; N, 24.90.

2-(2-Amino-5-methylphenyl)benzotriazole.—The corresponding nitro compound (3.50 g, 0.0138 mol) was dissolved in a mixture of 100 ml of acetone, 12 ml of water, and 12 ml of glacial acetic acid. To this stirred refluxing solution was added 7 g of powdered iron in small portions over a period of 30 min. Refluxing and stirring was continued for 20 hr. The solution was then cooled and filtered to remove the iron salts. The filtrate was washed with a concentrated sodium carbonate solution to remove acetic acid. The acetone layer was concentrated until a precipitate started to form. It was then poured into 450 ml of water. The solid was filtered, washed with water, and dried: yield 2.9 g (93%); mp 133–134°.

Anal. Calcd for $C_{13}H_{12}N_4$: C, 69.54; H, 5.36; N, 25.00. Found: C, 69.63; H, 5.63; N, 24.54.

2-(2-Aminophenyl)-5-methylbenzotriazole.—To 100 ml of acetone was added 0.50 g (1.97 mol) of 2-(2-nitrophenyl)-5-methylbenzotriazole. To the solution was added 10 ml of glacial acetic acid, 10 ml of water, and 0.67 g (12 mmol) of powdered iron. The mixture was refluxed and stirred for 12 hr. It was then cooled and filtered to remove the iron salts. The filtrate was shaken with a nearly saturated solution of sodium carbonate to remove the acetic acid. Separation of the acetone layer followed by its dilution with 400 ml of water gave 0.29 g (66%) of the amine. Recrystallization from ethanol gave an analytical sample which melted 78–79° if the melting point was taken in the usual manner. However, if the melting point was taken rapidly, the solid melted at 68–70°. The compound appears to exist in two different crystal structures.

Anal. Calcd for $C_{13}H_{12}N_4$: C, 69.64; H, 5.36; N, 25.00. Found: C, 69.60; H, 5.35; N, 24.90.

2-(2-Azidophenyl)-5-methylbenzotriazole.—In 10 ml of 6 *N* hydrochloric acid was dissolved 0.28 g (1.25 mol) of 2-(2-aminophenyl)-5-methylbenzotriazole. The solution was cooled to 0° and diazotized by the addition of 0.10 g (1.45 mmol) of sodium nitrite in water. After 15 min, 0.18 g (2.5 mmol) of sodium azide in water was added. After standing 3 hr, the solid was filtered and washed thoroughly with water, yield 0.26 g (84%). Recrystallization from ethanol gave colorless needles, mp 83.7–84°.

Anal. Calcd for $C_{13}H_{10}N_6$: C, 62.40; H, 4.00; N, 33.60. Found: C, 62.17; H, 3.95; N, 33.43.

2-(2-Azido-4-methylphenyl)benzotriazole.—In 30 ml of water was slurred 1.03 g (0.046 mol) of finely powdered 2-(2-amino-4-methylphenyl)benzotriazole and 10 ml of concentrated hydrochloric acid was added all at once. The slurry was cooled 0° by the addition of ice and then diazotized by the dropwise addition of 0.37 g of sodium nitrite. After stirring for 1 hr, all of the hydrochloride salt had dissolved. The solution was filtered to remove trace impurities. To the cold solution was added 0.30 g of sodium azide in a minimim of water. After 30 min, the precipitated solid was filtered and washed with water: yield 1.02 g (89%); mp 88°.

Anal. Calcd for $C_{13}H_{10}N_6$: C, 62.40; H,4.00; N, 33.60. Found: C, 62.28; H, 4.02; N, 33.52.

2-(2-Azido-5-methylphenyl)benzotriazole.—In 25 ml of water was placed 2.9 g (0.013 mol) of finely powdered 2-(2-amino-5-methylphenyl)benzotriazole. To this slurry was added all at once 10 ml of concentrated hydrochloric acid. Ice was added to cool the mixture to 0° and it was then diazotized by dropwise addition of 1.0 g of sodium nitrite in 10 ml of water. After 40 min, the hydrochloride salt had all dissolved. The solution was filtered and to the filtrate was added 1.0 g of sodium azide in water. After 30 min, the solid azide was filtered and washed with water: yield 2.85 g (88%); mp 90°. Recrystallization from petroleum ether (bp 60–90°) gave an analytical sample, mp 91°.

Anal. Calcd for $C_{13}H_{10}N_6$: C, 62.40; H, 4.00; N, 33.60. Found: C, 62.56; H, 4.11; N, 33.79.

2-Methyl-5,6H-dibenzo[*b*,*f*]-1,3a,4,6a-tetraazapentalene (III).—2-(Azido-5-methylphenyl)benzotriazole (2.85 g, 0.0114 mol) was dissolved in 8 ml of decalin and the solution was refluxed for 80 min. At the end of this time it was cooled in ice. The solid which separated was filtered and washed with petroleum ether: yield 1.83 g (72%): mp 185–188°. Recrystallization from ethanol gave an analytical sample, mp 194°.

Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.27; H, 4.50; N, 25.23. Found: C, 70.42; H, 4.60; N, 24.90.

3-Methyl-5,6H-dibenzo[*b*,*f*]-1,3a,4,6a-tetraazapentalene (IV).—2-(2-Azido-4-methylphenyl)benzotriazole (0.91 g 0.00364 mol) was placed in 10 ml of decalin and the solution was heated to 165–175° for 15 min, followed by 15 min of refluxing at 195°. On cooling, needles separated, which were filtered and washed with petroleum ether: yield 0.68 g (94%) of IV; mp 198°. Recrystallization from methanol and acetone gave an analytical sample.

Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.27; H, 4.50; N, 25.23. Found: C, 70.48; H, 4.56; N, 24.89.

Thermal Decomposition of 2-(2-Azidophenyl)-5-methylbenzotriazole.—In 50 ml of decalin was placed 4.74 g (0.0189 mol) of the azide and the solution was heated to 165–175° for 40 min. After standing overnight at room temperature, the mixture of III and IV was filtered and washed with petroleum ether: yield 3.36 g (80%); mp 184–185°. Recrystallization did not raise the melting point. Attempts to separate the mixture by chromatography on alumina were unsuccessful.

Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.27; H, 4.50; N, 25.23. Found: C, 70.22; H, 4.64; N, 25.19.

Registry No.—I, 7120-73-2; II, 16710-40-0; III, 16710-41-1; IV, 16710-42-2; 2-(2-nitrophenyl)-5-methylbenzotriazole, 16710-43-3; 2-(2-nitro-5-methylphenyl)benzotriazole, 16710-44-4; 2-(2-nitro-4-methylphenyl)benzotriazole, 16710-45-4; 2-(2-amino-4-methylphenyl)benzotriazole, 16710-46-6; 2-(2-amino-5-methylphenyl)benzotriazole, 16710-47-7; 2-(2-aminophenyl)-5-methylbenzotriazole, 16710-48-8; *o*,*o*′-diazidoazobenzene, 3364-08-7; V, 16710-49-9; VI, 16710-50-2.

Notes

Thermal Decomposition of *o*-Azidoazobenzenes. II. Synthesis of 2-Substituted Benzotriazoles[1]

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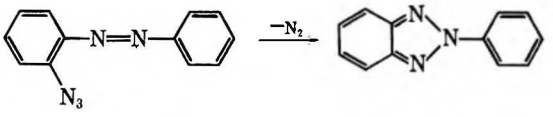
Received August 24, 1967

The fact that thermal decomposition of *o*-azidoazobenzenes results in cyclization to give 2-benzotriazoles was reported by Zincke and coworkers[2] many years ago. Since this early work, the reaction has escaped attention until more recent times when Carboni and coworkers[3] reported a number of examples. The lack of study of the reaction has undoubtedly been due in part to the difficulty in synthesizing *o*-aminoazobenzenes, from which the *o*-azidoazobenzenes could be prepared.



The report of the synthesis of *o*-azidoaniline,[4] however, has provided the needed starting material for two routes to *o*-azidoazobenzenes. The first of these involves the condensation of *o*-azidoaniline with arylnitroso compounds, examples of which are reported in paper I.[5] The second involves the diazotization of *o*-azidoaniline, followed by coupling of the diazonium salt with various phenols and amines. It is this latter method that is described in this paper.

o-Azidoaniline was found to diazotize smoothly at 0° using sodium nitrite in dilute hydrochloric acid. The cold diazonium salt solution was quite stable. No explosions were encountered. When the diazonium salt solution was added to cold basic solutions of phenol, *p*-cresol, and 2-naphthol, coupling occurred to give the

(1) Presented at 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

(2) (a) T. Zincke and J. Jaenke, *Ber.*, **21**, 540 (1888); (b) T. Zincke and A. T. Lawson, *ibid.*, **20**, 1176 (1887).

(3) (a) R. A. Carboni and J. E. Castle, *J. Amer. Chem. Soc.*, **84**, 2453 (1962); (b) R. A. Carboni, U. S. Patent 2,904,544 (Sept 1959); (c) R. A. Carboni, U. S. Patent Reissue 25,238 (Sept 1962); (d) R. A. Carboni, J. E. Castle, and H. E. Simmons, *J. Amer. Chem. Soc.*, **89**, 2618 (1967); (e) R. A. Carboni, J. C. Kauer, W. R. Hatchard, and R. J. Harder, *ibid.*, 2626 (1967); (f) J. C. Kauer and R. A. Carboni, *ibid.*, 2633 (1967).

(4) (a) P. A. S. Smith, J. H. Hall, and R. O. Kan, *ibid.*, **84**, 485 (1962); (b) L. Krbechek and H. Takimoto, *J. Org. Chem.*, **29**, 3630 (1964).

(5) J. H. Hall, J. G. Stephanie, and D. K. Nordstrom, *ibid.*, **33**, 2951 (1968).

TABLE I

PHYSICAL PROPERTIES AND ANALYTICAL DATA

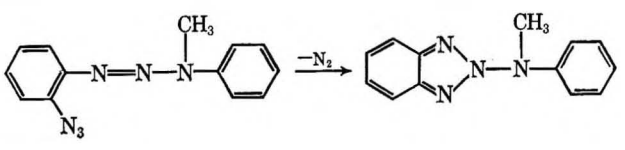
Compound[a]	Yield, %	Mp, °C	Crystallization solvent	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Azides										
4-(2-Azidophenylazo)phenol	18	53–61 dec	[b]							
2-(2-Azidophenylazo)-4-methylphenol	78	73–76 dec	EtOH–H_2O	$C_{13}H_{11}N_5O$	61.6	4.37		67.6[c]	4.92[c]	
1-(2-Azidophenylazo)-2-naphthol		[d]	C_6H_6	$C_{16}H_{11}N_5O$	66.42	3.84		65.82	3.75	
N-Methyl-N-(2-azidophenylazo)aniline	90	64–66 dec	Petroleum ether	$C_{13}H_{12}N_6$	61.89	4.79		62.05	4.85	
4-(2-Azidophenylazo)-N,N-dimethylaniline	86	102 dec[e]	MeOH	$C_{14}H_{14}N_6$	63.14	5.30		63.38	5.20	
2-Azidodiazoaminobenzene		81–86	EtOH							
2,2′-Diazidodiazoaminobenzene	81	123	EtOH	$C_{12}H_9N_9$	51.61	3.25	45.14	51.37	3.25	45.39
Benzotriazoles										
2-(2-Hydroxy-5-methylphenyl)-	99	131.5–133[f,g]	EtOH	$C_{13}H_{11}N_3O$	69.32	4.93		69.82	5.02	
2-(4-Hydroxyphenyl)-		220.5–221.5[h]								
2-(4-Dimethylaminophenyl)-	100	185.5–186.0	EtOH	$C_{14}H_{14}N_4$	70.56	5.92	23.64	70.95	6.04	23.15
2-(N-Methylanilino)-	63	99–101	EtOH	$C_{13}H_{12}N_4$	69.62	5.39		69.65	5.29	
2-(2-Hydroxy-1-naphthyl)-	45	144	EtOH–H_2O	$C_{16}H_{11}N_3O$	73.55	4.24		73.43	4.40	
2-(4-Hydroxy-1-naphthyl)-	20	202–203	EtOH–H_2O	$C_{16}H_{11}N_3O$	73.55	4.24		73.46	4.30	

[a] Registry no. are given in descending order: 16675-37-9, 16675-38-0, 16675-39-1, 16675-40-4, 16675-41-5, 16675-42-6, 16703-92-7, 2440-22-4, 3682-83-5, 16675-45-9, 16675-46-0, 16675-47-1, 16675-48-2. [b] Purified by dissolving in base and treating with charcoal. Acidification, followed by crystallization from aqueous ethanol, gave the product as needles. The C, H, and N analyses indicated that the compound had decomposed by the time it was analyzed. [c] The compound decomposed before it could be analyzed. Calculated C/H ratio, 1.41. Found, 1.38. This ratio should not change since the decomposition involves loss of only nitrogen. [d] Decolorizes without melting to give the benzotriazole. [e] Rapid heating. The crystals were square hollow needles. [f] This compound exists in two crystal forms. When crystallized from hot ethanol, rhombohedrons are obtained, mp 131.5–133°. When crystallized from ethanol at room temperature, needles are obtained which melt at 100°. The melt then solidifies and remelts at 131.5–133°. [g] No melting point depression with a sample prepared by electrolytic reduction of 2-(2-nitrophenylazo)-4-methylphenol; an adoption of a method reported by H. Itomi [*Mem. Coll. Sci. Kyoto, Ser. A, 12*, 343 (1929)] for 2-(4-hydroxyphenyl)benzotriazole. [h] No melting point depression of a sample prepared by electrolytic reduction of 4-(2-nitrophenylazo)phenol (see footnote *g*).

expected *o*-azidoazo compounds. In the case of 1-naphthol it was not found possible to purify the *o*-azidoazo compound. Attempts at purification gave the cyclized product, 2-(4-hydroxy-1-naphthyl)benzotriazole. Coupling of the diazonium salt with aniline, *o*-azidoaniline, and N-methylaniline in sodium acetate–acetic acid buffer likewise proceeded normally giving the corresponding *o*-azidodiazoamino compound. Coupling with N,N-dimethylaniline in sodium acetate–acetic acid buffer gave the brilliant red *o*-azido-*p*′ dimethylaminoazobenzene. The yields are given in Table I.

The *o*-azidoazo compounds differed considerably in stability. The *o*-azidoazophenols and naphthols were found to undergo slow decomposition even at room temperature. In each case, by the time elemental analyses were obtained, appreciable loss of nitrogen had occurred. In contrast, *o*-azido-*p*′-dimethylaminoazobenzene, N-methyl-N-(*o*-azidophenylazo)aniline, and *o*,*o*′-diazidodiazoaminobenzene were all quite stable at room temperature. *o*-Azidodiazoaminobenzene, although formed readily and moderately stable, was never obtained in pure form. Numerous attempts at recrystallization failed to remove an impurity in the compound.

Thermal decomposition of 2-azido-4′-hydroxy-, 2-azido-4′-dimethylamino-, and 2-azido-2′-hydroxy-5′-methylazobenzenes in refluxing dioxane gave the corresponding 2-substituted benzotriazoles in high yields (Table I). A considerably lower yield was obtained in the decomposition of 1-(2-azidophenylazo)-2-hydroxynaphthalene. *o*-Azidodiazoaminobenzene decomposed in refluxing dioxane to an intractable tar. N-methyl-N-(*o*-azidophenylazo)aniline was found to be much more stable and had to be refluxed in a higher boiling solvent, xylene, before decomposition was complete. The benzotriazole was obtained in 63% yield. Suspecting that the failure of *o*-azidodiazoaminobenzene to cyclize to the benzotriazole might be due to the fact that the proton was on the nitrogen next to the azido group, *o*,*o*-diazidodiazoaminobenzene was also synthesized and decomposed. However only a polymer was obtained. Apparently the diazoamino linkage is less stable than the azido group.



Experimental Section

All of the melting points were determined on a Kofler hot stage. The elemental analyses were performed by Weiler and Strauss Microanalytical Laboratory, Oxford, England. The physical properties and analytical data are given in Table I. The following procedure is typical of that used for coupling of *o*-azidobenzenediazonium chloride with phenol, *p*-cresol, and 2-naphthol.

4-(2-Azidophenylazo)phenol.—In 3 ml of concentrated hydrochloric acid and 30 ml of water was dissolved 1.34 g (0.01 mol) of *o*-azidoaniline.[4] The solution was cooled to 0° and diazotized by the dropwise addition of 0.71 g of sodium nitrite in 10 ml of water. After standing 15 min, the solution was filtered into a stirred solution of 0.94 g (0.01 mol) of phenol in 100 ml of water containing 1.20 g (0.03 mol) of sodium hydroxide. A bright red precipitate formed immediately. After standing 1 hr, the solution was acidified and the yellow solid filtered and washed with water. The crude material was dissolved in 150 ml of ethanol and filtered to remove 0.33 g of an insoluble solid (not investigated). Dilution of the filtrate with water gave 1.90 g (81%) of 4-(2-azidophenylazo)phenol. The compound melted with decomposition at 53–61°. Attempts to recrystallize the solid resulted in decomposition. It was purified by dissolving it in sodium hydroxide, treating with charcoal, and filtering. Acidification of the filtrate gave the solid back. It was then dissolved in a minimum amount of aqueous ethanol and cooled in ice to give needles.

The coupling of *o*-azidobenzenediazonium chloride with aniline, N-methylaniline, and N,N-dimethylaniline was accomplished by means of the following general procedure.

N-Methyl-N-(*o*-azidophenylazo)aniline.—*o*-Azidoaniline (1.34 g, 0.01 mol) was dissolved in 30 ml of water containing 3 ml of concentrated hydrochloric acid. The solution was cooled to 0° and diazotized with 0.71 g of sodium nitrite. The diazonium

salt solution was filtered into an ice-cold solution of N-methylaniline (1.07 g, 0.01 mol) in 50 ml of water containing 3 ml of concentrated hydrochloric acid. Sodium acetate (5 g) was added to the solution. After 1 hr stirring, the precipitated solid was filtered and washed with water: yield 2.26 g (90%); mp 55–60°. Recrystallization from petroleum ether (bp 30–60°) gave sulfur-colored granuals, mp 64–66° with partial decomposition.

o,o'-Diazidodiazoaminobenzene.—*o*-Azidoaniline (1.34 g, 0.01 mol) was dissolved in 30 ml of water and 3 ml of concentrated hydrochloric acid. The solution was half-diazotized by the addition of 0.35 g (0.05 mol) of sodium nitrite at 0°. A solution of 5 g of sodium acetate in 50 ml of water was added all at once. The solution was kept cold by the addition of ice. After stirring for 40 min, the solution was allowed to stand overnight at room temperature. The precipitate was filtered and washed with water. Recrystallization from absolute ethanol (charcoal) gave 1.13 g (81%), mp 123°. Thermal decomposition of this solid in refluxing dioxane gave only polymeric products.

The following procedure is typical of that used for the decomposition of the *o*-azidoazobenzenes. Procedure A was used to prepare 2-(2-hydroxy-5-methylphenyl)-, 2-(4-hydroxyphenyl)-, 2-(4-dimethylaminophenyl)-, and 2-(2-hydroxy-1-naphthyl)-benzotriazoles.

2-(2-Hydroxy-5-methylphenyl)benzotriazole. A.—In 5 ml of dioxane was placed 0.05 g (0.002 mol) of 2-(*o*-azidophenylazo)-4-methylphenol and the solution was heated. Evolution of nitrogen was noticeable at 65°. After refluxing for a few minutes, the colorless solution was cooled and poured into 50 ml of water, and the precipitated solid was filtered: yield 0.44 g (99%); mp 130–132°. This compound exists in two crystalline forms. When it crystallizes from hot 95% ethanol, rhombohedrons are obtained which melt at 131.5–133°. When crystallization from 95% ethanol occurs at room temperature, long needles are formed which melt at *ca.* 100° when heated rapidly. The melt then solidifies and remelts at 131.5–133°.

B.—2-(2-Nitrophenylazo)-4-methylphenol (0.05 g, 0.019 mol) was dissolved in 80 ml of water containing 1.6 g of sodium hydroxide. The solution was electrolyzed for 1.5 hr using a copper cathode and carbon anode.[6] The current through the cell varied from 2 to 0.5 A. The temperature during the electrolysis rose to 65°. At the end of this time, the solution was treated with charcoal and filtered, and the filtrate was acidified. The small amount of solid which precipitated was filtered and recrystallized from ethanol, yield 0.04 g (9%). This product had the same melting point characteristics and the same ir spectrum as the compound prepared by thermal decomposition of 2-(2-azidophenylazo)-4-methylphenol.

2-(N-Methylanilino)benzotriazole.—N-Methyl-N-(*o*-azidophenylazoaniline (0.05 g, 0.002 mol) was decomposed by refluxing it in *m*-xylene (5 ml) for 1 hr. The xylene was distilled off on the steam bath under vacuum. The residual oil solidified on cooling. Recrystallization of the solid from 95% ethanol gave 0.28 g (63%) of the benzotriazole, mp 99–101°.

2-(4-Hydroxy-1-naphthyl)benzotriazole.—*o*-Azidoaniline (2.69 g, 0.02 mol) was dissolved in 60 ml of water containing 6 ml of concentrated hydrochloric acid, cooled to 0°, and diazotized with 1.44 g of sodium nitrite. This solution was added with stirring to a cold solution of 2.88 g (0.02 mol) of 1-naphthol in 100 ml of water containing 2.40 g of sodium hydroxide. The resulting dark red precipitate (3.7 g) was filtered and washed thoroughly with water. This solid was stirred with 52 ml of 3 *N* sodium hydroxide for 1 hr. The dark red base-insoluble solid (A) was then filtered, washed with water, and air dried. The sodium hydroxide solution was treated with charcoal and then filtered. Acidification of the solution with hydrochloric acid gave 1.16 g (20%) of a flesh-colored precipitate (B).

Several recrystallizations of B from aqueous alcohol gave an analytical sample, mp 202–203°. The infrared spectrum of this material showed the azide group to be absent, indicating that the decomposition to the benzotriazole had already occurred. The analysis was correct for 2-(4-hydroxy-1-naphthyl)benzotriazole.

Compound A was very insoluble in all solvents and could not be purified. When 0.11 g of A was refluxed several hours in dioxane, the dark red color was discharged. Cooling of the dioxane solution gave 0.008 g of colorless needles, mp 289–299°. The analysis of the compound is consistant with an empirical formula of $C_{22}H_{14}N_8O$. This product is base insoluble, does not give an acetyl derivative with acetyl chloride, and does not show an OH absorption in its infrared spectrum.

Anal. Calcd for $C_{22}H_{14}N_8O$: C, 69.83; H, 3.73; N, 22.21. Found: C, 69.81; H, 3.94; N, 21.98.

(6) See Table I, footnote *g*.

Nuclear Magnetic Resonance Studies of Triazoles. I. Tautomerism of 1,2,4-Triazole[1a]

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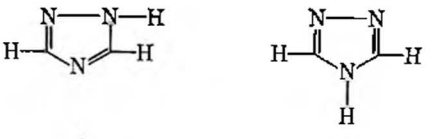
Received January 25, 1968

If tautomerism involving only N–H hydrogen is considered, all triazoles, tetrazoles, and unsymmetrically substituted imidazoles and pyrazoles can exist in at least two tautomeric forms similar in form to 1 and 2.



1 2

Under appropriate conditions proton magnetic resonance has been shown to provide valuable information as to the nature of tautomerism in heterocycles.[2] Previous publications concerning the nmr spectrum of 1,2,4-triazole have either not treated the problem of tautomerism[3] or worked in solvents contaminated with water.[4]

Experimental Section

Proton magnetic resonance data was taken with a Varian A-60 spectrometer equipped with a Varian Model V-6057 variable temperature accessory. Temperature given was accurate to ±2°. Each spectrum was taken a minimum of five times with the indicated chemical shift determined by weighted average. Concentrations given as percentages are weight per unit weight and are accurate to 0.0001 g. Concentrations given in terms of moles are accurate to ±0.01 *M*. Each sample contained tetramethylsilane (TMS) as an internal reference.

The solvents used were spectroscopy grade hexadeuteriodimethyl sulfoxide (DMSO-d_6) and reagent grade hexamethylphosphoramide (HMPT). The DMSO-d_6 was dried by distillation at reduced pressure from sodium sulfate and kept in an anhydrous nitrogen atmosphere. The HMPT was purified by distillation at reduced pressure and stored in an anhydrous nitrogen atmosphere. The nmr tubes used were filled in an anhydrous nitrogen atmosphere and stored with pressure caps in a calcium chloride desiccator. No changes in the spectra due to water were observed over an interval of 6 months.

(1) (a) This work was supported by Research Grant No. CY3908, from the National Institutes of Health and a North Texas State University Faculty Grant. (b) Address inquiries to this author at Texas Instruments Incorporated, Richardson, Tex.

(2) (a) S. Gronowitz and R. A. Hoffman, *Ark. Kemi*, **16**, 459 (1960); (b) D. O'Brien and J. Gates, Jr., *J. Org. Chem.*, **31**, 1538 (1966); (c) J. Pople, W. Schneider, and H. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 223; (d) D. W. Moore and A. G. Whittaker, *J. Amer. Chem. Soc.*, **82**, 5007 (1960); (e) C. L. Habraken and J. A. Moore, *J. Org. Chem.*, **30**, 1892 (1965); (f) L. Tensmeyer and C. Ainsworth, *ibid.*, **31**, 1878 (1966).

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1,2,4-Triazole was purchased from Aldrich Chemical Co., Milwaukee, Wis. Purification was accomplished by sublimation followed by storage in an anhydrous nitrogen atmosphere.

Discussion

The nmr spectrum of liquid 1,2,4-triazole, examined just above the melting point (125°) of the compound, consists of two singlets at 13.9 and 7.85 ppm with relative intensities of 1:2 (see Table I). The upfield signal corresponds to the C-3 and C-5 hydrogens. This assignment is in agreement with corresponding assignments for 1,2,4-triazoles.[3b,d]

TABLE I
CHEMICAL SHIFTS FOR 1,2,4-TRIAZOLE

Solvent	Temp, °C	Signal assignments[a] C–H	N–H
Neat	125	7.85	13.9
DMSO-d_6 (3.8%)	37	8.25	13.9
HMPT (4.3%)	37	8.17	15.1

[a] In parts per million from tetramethylsilane (TMS). Although all the signals are downfield from TMS, the negative sign has been omitted from the resonance assignments for convenience.

The downfield N–H signal in 1,2,4-triazole is very sharp due to rapid exchange of this proton.[5] This is supported by the coalescence of the N–H signal on addition of water.[6]

The spectrum of 1,2,4-triazole in anhydrous DMSO-d_6 (10.3%, 37°) is essentially similar to that observed for liquid 1,2,4-triazole. The C-3 and C-5 hydrogen peak is shifted downfield to 8.25 ppm and the N–H resonance occurs at 13.9 ppm as a very broad signal. A comparison of the chemical shifts for 1,2,4-triazole in solvent and as a pure liquid is given in Table I.

In carefully distilled hexamethylphosphoramide (HMPT), two distinct C–H peaks are observed at temperatures below 0° (see Table II). In a 4.3% solution, a maximum separation of 56 Hz is observed at −34°.

TABLE II
TEMPERATURE DEPENDENCE OF 1,2,4-TRIAZOLE NMR SPECTRA[a]

Temp, °C	Signal assignments N–H	C–H
37	15.0	8.17
10	15.09	8.03 (broad)
0	15.10	8.95, 8.59
−10	15.15	8.72, 7.87
−34	15.25	8.85, 7.92

[a] 4.3% in HMPT. Chemical shifts are in parts per milion relative to TMS.

In the absence of rapid inter- or intramolecular exchange, the spectra of **1** and **2** would be expected to be different due to symmetry considerations. In the unsymmetrical isomer, **1**, the C-3 hydrogen is in a region of greater electron density than the C-5 hydrogen which is adjacent to the ring hydrogen and, as a result, the downfield peak of the high-field doublet is assigned to the C-3 hydrogen. This assignment parallels designations made for hydrogens found in similar chemical environments.[7]

The intensity of the low-field N–H signal in 1,2,4-triazole in HMPT solutions remains constant relative to the intensity of the C–H signals with changes in temperature indicating that the N–H hydrogen is not exchanging with the solvent or with traces of water. The N–H resonance shifts downfield with decreasing temperature due to increasing intermolecular hydrogen bonding at lower temperatures.[8]

The nmr spectrum shows that at −34° there is only (1H)-1,2,4-triazole (**1**). From potentiometrically determined ionization constants of 1- and 4-alkyltriazoles, Froger and Freiberg[9] estimated the tautomeric ratio of (1H)- to (4H)-1,2,4-triazole to be 5–10:1 (20°, 0.01 *M* in water). Quantitative calculations of the π-electron densities in the neutral 1,2,4-triazole nucleus yield various values of the electron density on N-1 and N-4 due to differences in the choice of parameters.[10] Atkinson and Polya found values of 1.136 for N-1 and 1.093 for N-4[11] which agree with the result of the qualitative assignment of electron density based on the nmr results.

In order to corroborate the assignments made for the nmr spectra of 1,2,4-triazole, the N-methyl derivatives were prepared by the procedure of Pellizzari and Solidi.[12] The nmr spectrum of 1-methyl-1,2,4-triazole(**3**) consists, in HMPT at 37°, of a singlet at 3.64 (three hydrogens) and two singlets at 8.01 and 8.70 ppm each equivalent to one hydrogen. The upfield peak in this group is ascribed to the C-5 hydrogen in **3** because the local diamagnetic shielding from the electron-donating methyl group would be expected to cause an upfield shift of an adjacent proton.[13] The nmr spectrum of 4-methyl-1,2,4-triazole (**4**) in HMPT at 37° is composed of singlets at 3.64 (three hydrogens) and 8.20 ppm (one hydrogen). At −40° the spectra were shifted downfield so that the low field singlets occur at 8.02 and 8.93 (**3**) and 8.34 ppm (**4**) with the same relative intensities as above. The low field signal of **4** is found to occur in the region of the averaged signals for the carbon-bound hydrogens in 1,2,4-triazole.

That the local diamagnetic screening and electron density for N-1 and N-4 in 1,2,4-triazole are very similar[14] is shown by the fact that the methyl resonance of **3** and **4** are the same.

The mean half-life of the N–H hydrogen on N-1 at about 10° is estimated[15,2c] to be 4×10^{-3} sec by using the separation of the C–H peak at −34° as the maximum separation.

The N-1 hydrogen multiplicity in 1,2,4-triazole cannot be distinguished at −34° due to the broadness of the N–H hydrogen resonance resulting from quadrapole effects associated with the N^{14} nucleus.

Registry No.—**1**, 288-89-1; **3**, 6086-21-1; **4**, 10570-40-8.

(5) M. Takeda and E. Stejskal, *J. Amer. Chem. Soc.*, **82**, 25 (1960).
(6) F. Duderck, R. Degrote, J. Delannoy, R. Nasielski-Hinken, and J. Nasielski, *Bull. Soc. Chim. Belg.*, **74**, 119 (1965).
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Synthesis of Isoquinolines. VIII. 3,4,11,11a-Tetrahydro-1H-benzo[*b*]quinolizin-2(6H)-ones[1]

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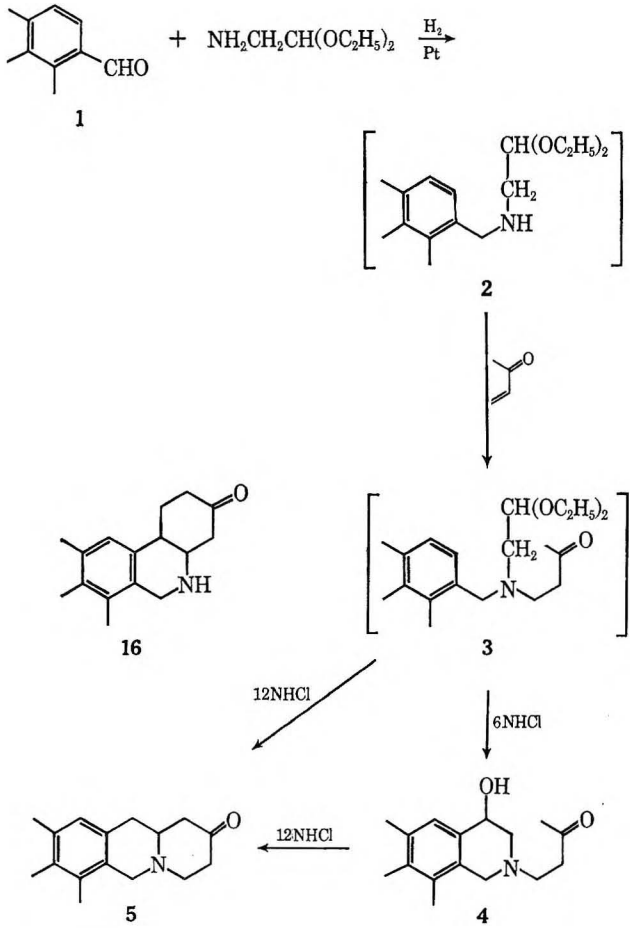
Received January 2, 1968

In the past few years we have been able to develop a new and facile synthesis of a number of oxygenated isoquinolines.[3] In at least one of these reaction schemes (leading to 4-benzylisoquinolines[4]) the reactions appear to take place through an intermediate 1,2-dihydroisoquinoline. The 1,2-dihydroisoquinolines are susceptible to nucleophilic attack at position 3 and to electrophilic attack at position 4.[4,5] We have now incorporated the reactivity of position 3 into our general methods and have developed the synthesis shown in the reaction scheme for the preparation of 3,4,11,-11a-tetrahydro-1H-benzo[*b*]quinolizin-2(6H)-ones.

The syntheses and stereochemistry of a series of derivatives of 3,4,11,11a-tetrahydro-2H-benzo[*b*]quinolizin-1-(6H)-one has been recently studied by Kupchan and DeGrazia.[6]



The benzylaminoacetaldehyde acetals **2** were prepared by our previous methods[7] and allowed to react with methyl vinyl ketone to yield the addition products **3**. These addition products, on treatment with 6 *N* hydrochloric acid, cyclized to yield the N-substituted 4-hydroxy-1,2,3,4-tetrahydroisoquinolines (**4**).[1] The specific compounds obtained and their yields are recorded in Table I. The yields are over-all yields (**1** → **3** → **4**). When either **3** or **4** was treated with 12 *N* hydrochloric acid, the tricyclic ketones (**5**) resulted. The specific compounds obtained and the yields are recorded in Table II. The yields are over-all yields (**1** → **3** → **5**) and were slightly erratic. In none of the reactions was there any evidence for alternate ring closure (*ortho* rather than *para*, for example in the synthesis of **6**, **7**, or **10**).

The structure proof of compounds **6**–**15** is based upon their mode of formation, their elemental analyses, their ir spectra, and their nmr spectra. The methyl singlet in the nmr spectra of **4** appeared in the range of τ 7.7–7.8 and was absent in **5**. The spectra of **4** were similar to those of the 4-hydroxy-1,2,3,4-tetrahydroisoquinolines previously reported.[1] The aromatic protons appeared as predicted. The various other protons appeared as unresolvable patterns in the region τ 7.1–7.5. The members of the series had nearly identical spectra in this region.

The isomeric structure (**16**) could also result from the ring-closure reaction if the methyl vinyl ketone had come off during the reaction and condensed at the 3,4 positions. However, the ir spectrum of **15** (having no phenolic hydrogens), in solution, showed the complete absence of any N–H adsorption. This conclusion can be extrapolated to the other members of the series through the similar nmr spectra.

Experimental Section[8]

N-(3-Oxobutyl)-4-hydroxy-1,2,3,4-tetrahydroisoquinolines (4). General Procedure.—Substituted N-benzylaminoacetaldehyde diethyl acetals **2** were prepared from the appropriate benzaldehydes **1** in 0.02-mol quantities by a general procedure already described.[7] The oily bases were dissolved in 5 ml of ether and covered with a nitrogen atmosphere. Methyl vinyl ketone (0.02 mol, 1.4 g) was added and the solutions were allowed to stand at room temperature from 10 to 26 hr. The time required for each compound was determined by tlc (ether–methanol, 6:1, on silica gel G). The ether was evaporated on a rotary vacuum evaporator and the residual oil was treated with 60 ml of cold 6 *N* hydrochloric acid. The acid solution was then washed three times with 30-ml portions of a 3:2 mixture of ether–benzene and allowed to stand at room temperature for 10–18 hr. The acid solution was cooled in an ice bath and made basic with aqueous ammonia. The free amine was extracted from the aqueous solution with several portions of chloroform and the chloroform extracts were combined and concentrated on a rotary vacuum evaporator. At this point the addition of ethanol to **6**, **7**, and **8** gave crystals. Methanol was added to crystallize compound **9**. The products were collected by filtration. The general procedure is valid with the following exceptions: the acid solution of **7** was heated at 45–50° for 0.5 hr after extracting it with ether–benzene; and compound **10** was obtained as a hydrochloride after concentration of the acid solution under vacuum and precipitation with ethanol. Compounds **6** and **7**

(1) Paper VII: J. M. Bobbitt and J. C. Sih, *J. Org. Chem.*, **33**, 856 (1968).

(2) (a) National Aeronautics and Space Agency Fellowship recipient. (b) Abstracted in part from the Ph.D. Thesis of T. E. M., The University of Connecticut, 1968.

(3) See ref 1 and the preceding papers of this series.

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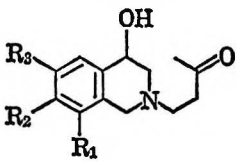
(8) All melting points were taken on a Thomas–Hoover apparatus and are corrected. The nmr spectra were measured on a Varian A-60 instrument and the shifts are measured from tetramethylsilane as an external standard. The microanalyses were performed by H. Fröhofer of the Organic Chemistry Institute of the University of Zürich, Switzerland.

TABLE I

N-(3-OXOBUTYL)-4-HYDROXY-1,2,3,4-TETRAHYDROISOQUINOLINES

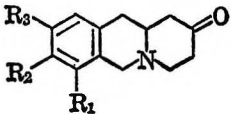


Compd	R_1	R_2	R_3	Yields,[a] %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
6	H	OH	OCH_3	51	135–137	63.40	7.17	5.28	63.16	7.26	5.50
7	H	OCH_3	OH	53	138–141	63.40	7.17	5.28	63.12	7.14	5.32
8	H	OCH_3	OCH_3	72	128–128.5	64.50	7.58	5.01	64.41	7.67	5.00
9	OH	OCH_3	H	76	136.5–138.5	63.38	7.22	5.28	63.31	7.22	5.13
10[b]	H	OCH_2O		33	184.5–185.5	56.09	6.06	4.67	56.54	6.22	4.41

[a] Yields are based upon starting aldehydes. [b] Isolated and characterized as hydrochloride salt and as picrate. *Anal.* Calcd: Cl, 11.83. Found: Cl, 11.93.

TABLE II

3,4,11,11a-TETRAHYDRO-1H-BENZO[*b*]QUINOLIZIN-2-(6H)-ONES



Compd	R_1	R_2	R_3	Yield,[a] %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
11	H	OH	OCH_3	68 (55)	192.5–193.5	68.00	6.93	5.66	68.31	6.86	5.67
12	H	OCH_3	OH	40 (74)	212–213	68.00	6.93	5.66	67.99	6.86	5.65
13	H	OCH_3	OCH_3	66 (22)	140.5–141.5	68.94	7.33	5.36	68.61	7.58	5.29
14	OH	OCH_3	H	60 (59)	163–164	68.00	6.93	5.66	68.10	7.11	5.51
15	H	OCH_2O		41 (79)	168–169	68.56	6.16	5.71	68.69	6.29	5.65

[a] The yields given refer to the sequence 1 → 2 → 3 → 5. The yields in parentheses refer to the conversions of 4 → 5.

were recrystallized from absolute ethanol; **8** was recrystallized from 95% ethanol; **9** was recrystallized from 1-propanol and **10** was recrystallized from methanol. The picrate of **10** was prepared in ethanol from the hydrochloride and recrystallized from methanol to yield an analytical sample, mp 160° dec.

Anal. Calcd for $C_{20}H_{20}N_4O_{11}$: C, 48.81; H, 4.10; N, 11.39. Found: C, 48.73; H, 4.41; N, 11.20.

3,4,11,11a-Tetrahydro-1H-benzo[*b*]quinolizin-2(6H)-ones (5). General Procedure.—The oily tertiary amines (**3**), prepared as described above, were dissolved in 50 ml of concentrated hydrochloric acid. The solutions became hot and were cooled and washed with three portions of a 3:2 mixture of ether–benzene. The acid solutions were then heated at 45–50° for 30 min. The cooled solutions were diluted with water and made basic with aqueous ammonia to pH 9–10. In the cases where the amine did not precipitate at this point (**13** and **14**), the basic, aqueous solution was extracted with chloroform. The chloroform extracts were concentrated to an oil which, when cooled and diluted with a little ethanol, crystallized. The products were collected by filtration. The general procedure is valid with the following exceptions: in the preparation of **13**, the acid solution was heated to 88–95° for 15 min before extracting it with ether–benzene; in the preparation of **14**, the best yields were obtained when the acid solution was allowed to stand at room temperature for about 11 hr instead of heating it. Compounds **12**, **13**, and **15** were recrystallized for analysis from 95% ethanol; **11** was recrystallized from absolute ethanol; and **14** was recrystallized from methanol.

The conditions for the conversion of the 4-hydroxyisoquinolines (**4**) into the tricyclic ketones (**5**) are identical with those given for the conversions of **3** into **5**. The yields are given in parentheses in Table II.

Registry No.—**6**, 16675-64-2; **7**, 16675-65-3; **8**, 16675-66-4; **9**, 16675-67-5; **10** HCl, 16675-68-6; **10** picrate, 16675-69-7; **11**, 16675-70-0; **12**, 16675-72-2; **13**, 16675-71-1; **14**, 16675-73-3; **15**, 16675-74-4.

The Reaction of Piperidoneenamines with Methyl β-Vinylacrylate. A Route to Quinolines and Isoquinolines[1]

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Received December 21, 1967

Berchtold and Ciabattoni[2] were the first to report on the cycloaddition reaction of enamines with β-vinylacrylic esters. The synthetic importance of this reaction arises from the subsequent retro Michael elimination of the amine function to produce 1,3-cyclohexadienes not otherwise readily preparable.[3] These systems can in turn be aromatized to produce benzene rings.[4] For example, the reaction of the pyrrolidineenamine of cyclopentanone (**1**) and methyl β-vinylacrylate (**2**) affords the fused bicyclic system **3**, which undergoes an elimination reaction to give **4**, which may subsequently be aromatized to **6**. In a concurrent study in this laboratory,[5] the cycloaddition–retro

(1) This research was supported by a grant from the Petroleum Research Fund of the American Chemical Society.

(2) G. A. Berchtold, J. Ciabattoni, and A. A. Tunick, Abstracts, the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 35.

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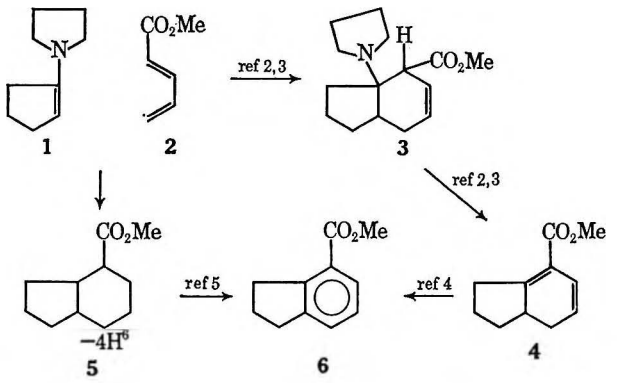
(4) H. O. House and T. H. Cronin, *ibid.*, **30**, 1061 (1965).

(5) S. Danishefsky and R. Cunningham, *ibid.*, **30**, 3676 (1965).

Michael sequence was also noted, although the product obtained was an isomeric mixture of cyclohexadienes, **5**,[6] which could be aromatized either oxidatively or thermally. These results are summarized in Scheme I.

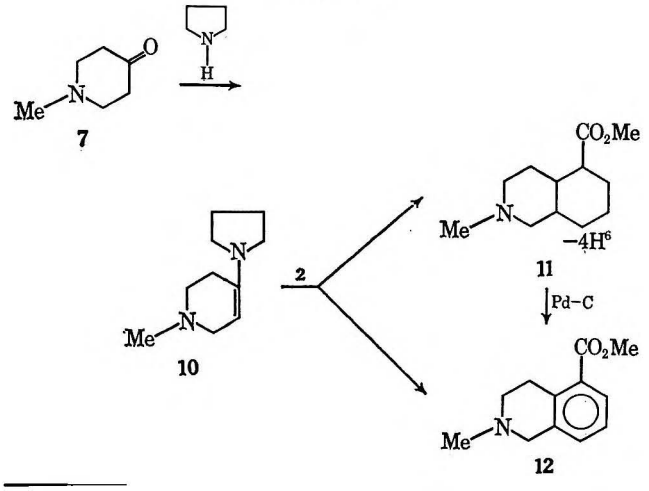
SCHEME I



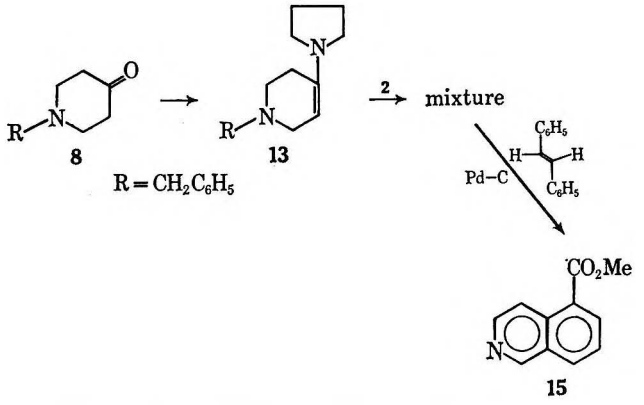
In this paper we report the extension of these reactions to the synthesis of heterocyclic ring systems.[7] Selected for study were the N-substituted piperidones **7**, **8**, and **9**.

Treatment[8] of compound **7** with pyrrolidine afforded the enamine **10** in 91% yield. When this compound was allowed to react with the ester **2**,[9] there was obtained, in 94% yield, a mixture (**11**) of three compounds. Treatment of the mixture with 5% Pd–C in methanol solution under reflux afforded a 93% yield of the 2-methyl-5-carbomethoxy-1,2,3,4-tetrahydroisoquinoline (**12**). This compound was one of the three components present in the original mixture, the other two presumably being isomeric hexahydro derivatives which underwent monodehydrogenation to yield **12**. The structure of **12** was established by its combustion analysis, by infrared (ir) and nuclear magnetic resonance (nmr) spectra, and *via* preparation of a picrate (see Experimental Section). The conversion of compound **7** into the isoquinoline **12** is 80% from the starting piperidone. These results are summarized in Scheme II.

SCHEME II



The possibility of using an N-benzyl system with the potentialities inherent in debenzylation was also examined. Thus, compound **8**, upon treatment with pyrrolidine, gave the enamine **13** in 95% yield. Reaction of this enamine with the ester **2** gave an 81% yield of a mixture of 1-benzyl-5-carbomethoxyhydroisoquinolines signified as mixture **14**. Treatment of this mixture with 5% Pd–C in the presence of excess *trans*-stilbene afforded a 72% yield of the previously known[10] 5-carbomethoxyisoquinoline **15**. The exact sequence of steps leading to the noteworthy result of threefold dehydrogenation[11] and onefold hydrogenolysis has not been established.



The reaction of pyrrolidine with 1-benzyl-3-piperidone (**9**) might, in principle, have given either the enamine **16** or its isomer **17** or a mixture of these compounds. In practice, this reaction gave an exceedingly unstable enamine (84% yield) whose structure was clearly **16** since its nmr spectrum contained a singlet encompassing one proton at τ 5.15. While we have not established whether **16** arose from kinetic or thermodynamic control, one might assume that it is the more stable of the two enamines since it contains conjugation of the "lone pair" of the N-benzyl nitrogen atom with the double bond.

The enediamine system **16** offers, in principle, the interesting possibility of ambident nucleophilic activity at C_1 or C_2. Attack of an electrophile at C_1 would be favored on steric grounds. On the other hand, attack at C_1 requires coplanarity of the pyrrolidine and tetrahydropyridine ring systems for maximum overlap of the "lone pair" of the N-pyrrolidino nitrogen with the double bond. Attack at C_2 requires a conformation already present in the ground state, *i.e.*, with the benzyl group quasi-equatorial and the unshared electron pair of the N-benzyl nitrogen quasi-axial and well disposed for overlap.

In practice, reaction of the enamine **16** with compound **2** gave a mixture (**18**) of hydroquinolines. Analysis of the mixture through combined gas chromatography–mass spectrometry[12] showed it to consist of a 4:1 ratio of hexahydro/octahydro isomers.[13] Dehy-

(6) The number under the formula represents the number of hydrogen atoms required for saturation, *e.g.*, −4H is a mixture of bisdehydro compounds.

(7) For some recent applications of this reaction to heterocyclic synthesis, see F. Bohlman, D. Habeek, F. Poetsch, and D. Schumann, *Chem. Ber.*, **100**, 2742 (1967).

(8) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(9) E. Adlerova, L. Blaha, M. Borovicka, I. Ernest, J. O. Jilek, B. Kabac, L. Novak, M. Rajaner, and M. Protiva, *Collect. Czech. Chem. Commun.*, **25**, 221 (1960).

(10) F. T. Tyson, *J. Amer. Chem. Soc.*, **61**, 183 (1959).

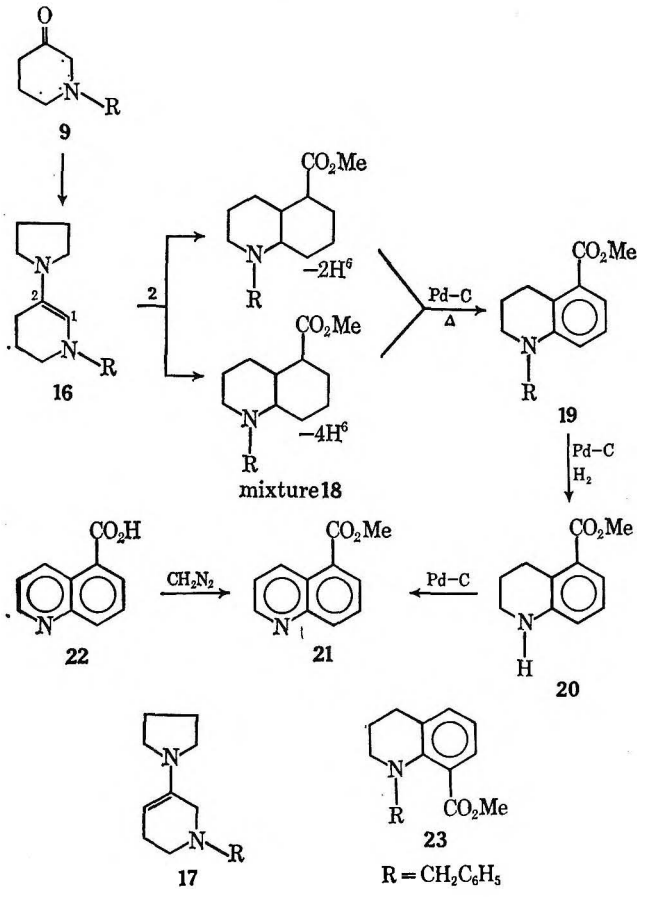
(11) This assumes the major portion of the reaction mixture to be hexahydroquinoline isomers.

(12) The mass spectra were obtained from an LKB 9000 by Mr. J. Nawarol.

(13) The octahydro isomers undoubtedly arose from disproportionation of the hexahydro systems. We were unable to detect any of the corresponding tetrahydro system (**19**) in the reaction mixture at this stage.

drogenation with Pd–C in toluene afforded a 41% yield (based on **16**) of compound **19**. The structure of **19** follows from its debenzylation[14] and dehydrogenation to afford compound **21**. The compound thus obtained was identical with that obtained by treating the known quinoline-5-carboxylic acid (**22**) with diazomethane. These results are summarized in Scheme III.

SCHEME III



Since all cycloaddition reactions of enamines with compound **2** thus far studied are directionally specific in the Michael–Mannich sense, it is clear that the sequence of reactions leading to **19** rather than **23** must have begun with electrophilic attack at C_1 of the ambident enamine **16**. However, since the yield of compound **19** is only 41%, the possibility of the formation of products arising from initial electrophilic attack at C_2 can hardly be excluded.

Experimental Section[15]

Preparation of Enamines.—The following enamines were prepared according to the general procedure of Stork.[8]

N-Methyl-4-piperidonepyrrolidineenamine (**10**) was a yellow oil (91%): bp 78–80° (0.1 mm); ir ($CHCl_3$), 6.10 μ (enamine); nmr (neat), τ 5.93 (t, 1, J = 4 Hz), 6.9–8.4 (m, 17, with a singlet at 7.93).

Anal. Calcd for $C_{10}H_{18}N_2$: C, 72.24; H, 10.91; N, 16.85. Found: C, 72.13; H, 11.07; N, 16.96.

N-Benzyl-4-piperidonepyrrolidineenamine (**13**) was a yellow oil (92%): bp 138–140° (0.05 mm); ir (CCl_4), 6.07 (enamine), 14.32 μ; nmr (neat), τ 2.6–2.8 (m, 5), 5.8–6.0 (poorly resolved triplet, 1) 6.50 (s, 2), 6.8–8.5 (m, 14).

Anal. Calcd for $C_{16}H_{22}N_2$: C, 79.29; H, 9.15. Found: C, 78.96; H, 9.15.

N-Benzyl-3-piperidonepyrrolidineenamine (**16**) was a yellow oil (84%): bp 133–137° (0.06 mm); ir (CH_2Cl_2), 6.10 μ (enamine); nmr ($CDCl_3$), τ 3.15 (broad singlet, 5), 5.15 (s, 1), 6.50 (s, 2), 7.18–8.5 (m, 14).

Reaction of Enamine 10 with Methyl β-Vinylacrylate (**2**).—A solution of 16.5 g (0.147 mol) of the ester **2**, and 24 g (0.144 mol) of the enamine **10** was heated in 50 ml of dry benzene under reflux in a nitrogen atmosphere for 20 hr. After cooling, the solution as extracted with 150 ml of 10% HCl. The aqueous layer was washed with 100 ml of ether, made basic by the cautious addition of excess solid Na_2CO_3 and extracted with three 100-ml portions of ether. The ethereal solution was dried ($MgSO_4$) and concentrated *in vacuo* to afford a residue which upon distillation gave 28 g (94%) of a yellow oil (**11**): bp 94–97° (0.05 mm); ir ($CHCl_3$), 5.80 μ (unsaturated ester); vpc (8-ft 20% "FFAP" on Chromosorb W, flow rate 82 ml/min, temperature = 200°), retention time in min (approximate area), 33 (1) 34 (3) 42 (3).

2-Methyl-5-carbomethoxy-1,2,3,4-tetrahydroisoquinoline (**12**).—A solution of 1.95 g (9.4 mmol) of the above mixture in 10 ml dry methanol was heated under reflux with 0.3 g of 5% Pd–C for 6 hr. The catalyst was filtered and washed with ether, the filtrates were combined, the solvents were removed at the water pump, and the residue was distilled from an oil-jacketed flask. There was thus obtained 1.8 g (93%) of **12**, bp 110° (0.1 mm). Vpc analysis showed this to be homogeneous and the same as the component with retention time of 42 min in the previous experiment: ir ($CHCl_3$), 5.81, 6.3, 6.4, 6.9 μ; nmr (CCl_4), τ 2.67 (apparent triplet, 1, J = 4 Hz); 3.30 (apparent doublet, 2, J = 4 Hz), 6.42 (s, 3), 6.72 (s, 2), 6.8–7.8 (m, 14), 7.82 (s, 3).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.04; H, 7.53; N, 6.90.

The picrate had mp 166–167° (EtOH).

Anal. Calcd for $C_{18}H_{18}N_4O_9$: C, 49.47; H, 4.18; N, 12.90. Found: C, 49.50; H, 4.13; N, 13.15.

Reaction of Enamine 13 with Methyl β-Vinylacrylate (**2**).—A solution of 13.5 (0.12 mol) of compound **2** and 24.2 g (0.10 mol) of the enamine **13** in 100 ml of benzene was heated under reflux in a nitrogen atmosphere for 18 hr. The solution was cooled and extracted with 150 ml of 10% HCl. The acidic layer was washed with 50 ml of ether, made basic with excess sodium carbonate, and extracted with three 100-ml portions of ether. The ethereal extracts were dried (Na_2SO_4), concentrated under reduced pressure, and distilled to give 24.9 g (81%) of mixture **14**: bp 160–161°; ir (CCl_4), 5.79, 6.7, 14.3 μ.

5-Carbomethoxyisoquinoline (**15**).—A solution of 4.8 g (0.017 mol) of the above mixture with 15 g (0.083 mol) of *trans*-stilbene and 2.0 g of 5% Pd–C in 100 ml of *p*-cymene was stirred and heated under reflux for 42 hr. After cooling, the catalyst was filtered and washed with ether. The washings were combined with the cymene solution and the total solution was extracted with 50 ml of 10% HCl. The acidic layer was washed with 50 ml of ether, made basic with excess sodium carbonate, and extracted with five 20-ml portions of ether. The ether extracts were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The residue when distilled gave 2.3 g (73%) of **15**, bp 90–120°, which solidified in the receiving flask. Recrystallization afforded **15** as a solid: mp 66° (lit.[10] mp 66°); ir ($CHCl_3$), 5.81, 6.15, 6.20, 8.0, 11.9 μ; nmr ($CDCl_3$), τ 0.79–0.94 (m, 1), 1.24–1.44 (m, 2), 1.54–1.80 (m, 1), 1.84–2.04 (m, 1), 2.34–2.59 (m, 1), 6.00 (s, 3).

Reaction of Enamine 16 with Methyl β-Vinylacrylate (**2**).—A solution (under nitrogen) of 8 g (0.033 mol) of **16** and 8 g (0.071 mol) of compound **2** in 40 ml of dry benzene was heated under reflux for 16 hr. The solution was extracted with 75 ml of 10% HCl. The aqueous layer was washed with 50 ml of ether and made basic with excess sodium carbonate. The emulsion was extracted with three 50-ml portions of ether. The ethereal solution was dried (Na_2SO_4) and concentrated under reduced pressure. The concentrate was distilled to afford 7.5 g (80%) of mixture **18** as a yellow oil: bp 160–165° (0.08 mm); ir ($CHCl_3$), 5.82, 6.15, 14.30 μ; vpc (6.3% OV-17 on "Gas-Chrom G" −215°, 100 ml/min), retention time in min (relative area),

(14) Attempts to isolate the intermediate debenzylation product, **20**, gave irreproducible results.

(15) All melting points are corrected. Infrared spectra were determined with either a Beckman IR-8 or a Perkin-Elmer 137 Infracord. Nmr spectra were determined with a Varian A-60 spectrometer and are reported in parts per million downfield from tetramethylsilane. Combustion analyses were conducted by Galbraith Laboratories, Inc., Nashville, Tenn. Gas chromatograms were obtained on a Varian Associated A-90 P-3 instrument. The piperidones were obtained from the Aldrich Chemical Co. and distilled before use. The 5% Pd–C catalyst was obtained from Englehard Corp. The quinoline-5-carboxylic acid was purchased from K & K Laboratories.

molecular weight in *m/e*, 13 (2), *m/e* 285, 15 (1), *m/e* 285, 21 (5), *m/e* 283, 24 (7), *m/e* 283.

1-Benzyl-5-carbomethoxy-1,2,3,4-tetrahydroquinoline (19).—A solution of 2.5 g (0.009 mol) of mixture **18** in 10 ml of toluene was heated under reflux with 1 g of 5% Pd–C for 26 hr. The catalyst was filtered and washed with ether. The washings were combined with the toluene solution and concentrated *in vacuo*. The residue was chromatographed on 100 g of Woelm neutral alumina. With benzene as the eluent, 1.3 g (51%) of compound **19** was obtained. Recrystallization from ethanol afforded an analytical sample of **19**: mp 77–78°; ir ($CHCl_3$), 5.84, 6.29, 14.4 μ; nmr ($CDCl_3$), τ 2.6–3.5 (m, 8), 5.55 (s, 2), 6.17 (s, 3), 6.5–7.1 (m, 4), 7.8–8.2 (m, 2).

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.65; H, 6.72; N, 4.99.

5-Carbomethoxyquinoline (21).—A solution of 102 mg of compound **19** in 5 ml of absolute ethanol was treated with 500 mg of 5% Pd–C for 2 hr at atmospheric pressure and room temperature. *An evolution of gas was noted.* The catalyst was filtered and washed with ethanol. The washings were combined with the filtrate and concentrated *in vacuo* whereupon a solid residue was formed. Recrystallization from ether at −70° gave 55 mg (81%) of compound **21**: mp 39–41°; ir ($CHCl_3$), 5.82, 6.64 μ; nmr ($CDCl_3$), τ 0.50–0.70 (m, 1), 1.51–1.75 (m, 1), 2.10–2.30 (m, 2), 2.65–2.74 (m, 2), 6.00 (s, 3).

5-Carbomethoxyquinoline (21) by Known Synthesis.—A solution of 25 mg of quinoline-5-carboxylic acid in 50 ml of methanol was treated with excess diazoamethane. Evaporation of the solvent left a residue which was purified through preparative scale gas chromatography on a 5-ft, 20% SE-30 column at a flow rate of 90 ml/min and a column temperature of 190°. There was thus obtained 16 mg of ester **21**, mp 39–31° (undepressed on admixture with **21** from above).

Registry No.—**2**, 2409-87-2; **10**, 16675-55-1; **12**, 16675-56-2; picrate of **12**, 16675-57-3; **13**, 16675-58-4; **15**, 16675-59-5; **16**, 16675-60-8; **19**, 16675-61-9; **21**, 16675-62-0.

Mass Spectrometry in Structural and Stereochemical Problems. CLX.[1] On the Supposed *peri* Interaction in 4-Isobutylquinoline[2]

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Received March 14, 1968

In a previous publication from this laboratory,[3] the mass spectrum of 4-isobutylquinoline was reported. At 70 eV the base peak appeared at *m/e* 170, corresponding to the loss of a methyl radical. Even at 12 eV, this peak was second only to the molecular ion (*m/e* 185) in intensity, indicative of a highly facile mode of decomposition. Such behavior has been noted in 8-alkylquinolines, *e.g.*, 8-propylquinoline[3] where it has been attributed to ring closure with the suitably situated nitrogen atom. Since the concept of *peri* interactions in mass spectral fragmentations is being recognized more frequently,[4] the preferred loss of a methyl radical was rationalized in terms of a cyclized structure (a), which would imply that in this instance (contrary to 8-propylquinoline) the presence of the heteroatom played no significant role in promoting this decomposition.

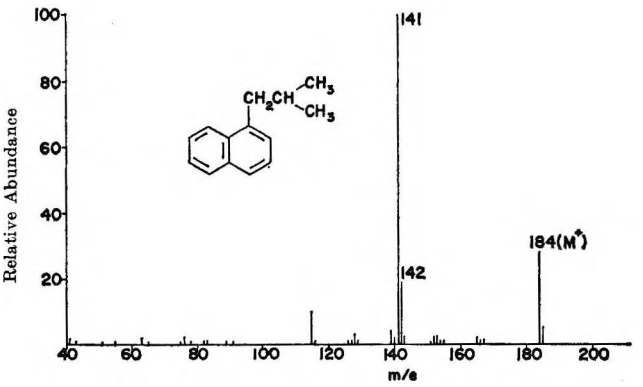


Figure 1.—Mass spectrum of 1-isobutylnaphthalene.

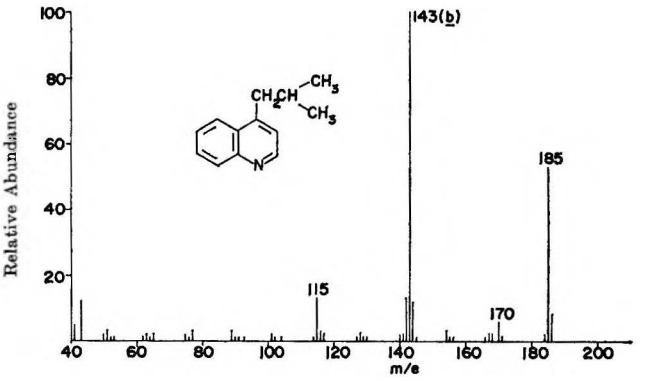


Figure 2.—Mass spectrum of 4-isobutylquinoline.

Accordingly, similar behavior would be expected in the hydrocarbon analog, *i.e.*, 1-isobutylnaphthalene. Consequently, this compound was prepared, as well as 1- and 2-butylnaphthalene. The occurrence of *peri* interaction would be expected to produce distinct qualitative differences between the 1- and 2-alkylnaphthalenes. In fact, the spectra of the three butylnaphthalenes are essentially identical. The reproduced spectrum (Figure 1) of 1-isobutylnaphthalene is representative. No evidence of significant *peri* interaction was obtained.

The dichotomy of these results cast suspicion on the original 4-isobutylquinoline spectrum.[3] The sample previously investigated was of commercial origin, and we were unable to determine the synthetic route used for its preparation. Gas chromatographic analysis revealed it to be a mixture of two major components in approximately 2:1 ratio, the greater one being 8-*t*-butylquinoline (as demonstrated by nmr spectroscopy) and the lesser one being quinoline. The presence of the former provides a simple explanation for the facile loss of a methyl radical.[3]

Consequently, authentic 4-isobutylquinoline was prepared by an unambiguous route as described in the Experimental Section. Its mass spectrum (Figure 2) is in marked contrast to that previously reported[3] and is completely consistent with the spectra[3] of other alkylquinolines. Thus the base peak at *m/e* 143 (70 eV) is due to the ubiquitous McLafferty rearrangement (I →

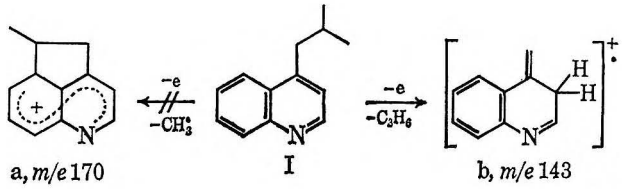
(1) For paper CLIX, see A. V. Robertson, M. Marx, and C. Djerassi, *Chem. Commun.*, 414 (1968).

(2) Support by the National Institutes of Health (Grant No. GM 11309) is gratefully acknowledged.

(3) S. D. Sample, D. A. Lightner, O. Buchardt, and C. Djerassi, *J. Org. Chem.*, **32**, 997 (1967).

(4) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, p 518.

b), while m/e 142 is associated with benzylic fission with loss of a propyl radical and m/e 115 with subsequent expulsion of the elements of hydrogen cyanide (appropriate metastable peak observed). *peri* interactions thus do not exist in 1-alkylnaphthalenes or 4-alkylquinolines.



Experimental Section[5]

Butylnaphthalenes.—The three butylnaphthalenes were prepared by a Wurtz–Fittig coupling reaction[6] and purified by vpc.

4-Isobutylquinoline.—The synthesis was based on a modification[7] of the Blaise–Maire synthesis[8] of 4-alkylquinolines, which involves as a precursor a 2-chloroethylalkylketone obtained by condensation of a dialkycadmium reagent with the appropriate acid chloride.[9]

Isobutylmagnesium bromide was prepared from 7.9 ml of isobutyl bromide (0.073 mol) and 1.77 g of magnesium turnings (0.073 g-atom) in dry ether. This Grignard reagent was treated with 7.36 g of finely powdered dry cadmium chloride (0.040 mol) to produce diisobutylcadmium. The ether was removed by heating and replaced with benzene. After cooling of the vigorously stirred suspension in an ice bath, a solution of 5.7 ml of 3-chloropropionyl chloride (0.059 mol) in benzene was added slowly with continuous stirring. Ice-bath temperature was maintained for 0.5 hr and was followed by a 45-min reflux. The reaction mixture was then cooled and filtered, and the precipitate washed with benzene. After extraction with 10% aqueous sodium bicarbonate and drying with magnesium sulfate, the benzene solvent was evaporated under water aspiration, leaving 1-chloro-5-methyl-3-hexanone (1.1 g) as a sweet-smelling oil which was used directly in the next step.

To an absolute ethanol solution of 35.1 g of stannic chloride pentahydrate (0.10 mol) and 1.45 ml of distilled aniline (0.155 mol) was added 1.1 g of above described chloro ketone. The solution was then heated under reflux for 4 hr. Upon cooling, the ethanol solution was poured into water; the pH was adjusted to neutral by the addition of solid sodium bicarbonate; and the product was extracted with ether. The ether was then partially evaporated and extracted three times with 10% aqueous hydrochloric acid. The aqueous extract was neutralized with aqueous ammonia and extracted three times with ether. The residue after removal of the ether was heated with excess acetic anhydride at steam-bath temperature for 2 hr in order to facilitate separation of unreacted aniline.

The acetic anhydride solution was mixed with ether and extracted three times with 10% aqueous hydrochloric acid; the aqueous extract was then neutralized and extracted with ether as above, giving in poor yield a solution of tertiary amine in ether. This ether solution was dried with magnesium sulfate, filtered, and evaporated. The resultant red, viscous oil was purified by vpc and shown to contain two components, only one of which was of low enough volatility to be the desired product. The structure was confirmed by proton nmr spectroscopy and the compound was characterized as its picrate (yellow needles, mp 168.5–170°, with sintering at 165° after three recrystallizations from 95% ethanol).

Anal. Calcd for $C_{19}H_{18}O_7N_4$: C, 55.03; H, 4.39; N, 13.53. Found: C, 55.24; H, 4.41; N, 13.59.

Registry No.—I, 7661-51-0; picrate of I, 16727-90-5; 1-isobutylnaphthalene, 16727-91-6.

(5) The mass spectral data were obtained by Mr. R. G. Ross on an MS-9 mass spectrometer at 70 eV, utilizing a heated glass inlet system at 180° with steel manifolding.

(6) E. Vogel, "Practical Organic Chemistry," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1966, pp 511–512.

(7) J. Kenner and F. S. Statham, *Ber.*, **69**, 16 (1936).

(8) E. E. Blaise and M. Maire, *Bull. Soc. Chim. Fr.*, **3**, 658 (1908).

(9) J. Cason, *Chem. Rev.*, **40**, 15 (1947).

Quinazolines and 1,4-Benzodiazepines. XLI.[1] 1,3-Dihydro-2H-1,4-benzodiazepin-2-one 4-Oxide Previously Described as 1,3-Dihydro-2H-4,1,5-benzoxadiazocin-2-one

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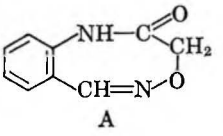
Received February 21, 1968

In a recent publication,[2] we reported the synthesis of a series of 5-substituted 4,1,5-benzoxadiazocin-2-ones by cyclization of 2′-aroyl- (or alkanoyl-) 2-haloacetanilide *syn*[3]-oximes in an alkaline medium. A similar mild alkaline treatment of 2-chloro-2′-formylacetanilide oxime **1** of unspecified configuration was reported by v. Auwers[4] to yield a compound described as 1,3-dihydro-2H-4,1,5-benzoxadiazocin-2-one (A). Since the steric configuration of the oxime is believed to determine the site of attack in intramolecular alkylation,[2] a 4,1,5-benzoxadiazocin-2-one resulting from the *syn*-oximes and a 1,4-benzodiazepin-2-one 4-oxide from the *anti* isomer, a study of the structure of the compound reported by v. Auwers was undertaken.[5]



A

A sample of **3**,[6] prepared as described by v. Auwers, when submitted to mass spectroscopy showed a strong peak at M − 16 indicating the loss of oxygen. This phenomenon is characteristic for nitrones but has not been seen with 4,1,5-benzoxadiazocin-2-ones.[2] The nitrone structure was corroborated by preparation of the nitrone **3**, identical with the material prepared directly from **1**, by rearrangement of 2-chloromethylquinazoline 3-oxide (**2**)[7] on treatment with dilute alkali. Catalytic reduction of the nitrone with Raney nickel catalyst removed the N-oxide oxygen and also reduced the 4,5 double bond resulting in the formation of the 1,3,4,5-tetrahydro-1,4-benzodiazepin-2-one (**5**). This compound was identical with the product prepared by reduction of the corresponding 1,3-dihydro-1,4-benzodiazepin-2-one (**8**) which had been synthesized from **7** according to the classical method shown. When

(1) Paper XL: J. V. Earley, R. I. Fryer, D. Winter, L. H. Sternbach, *J. Med. Chem.*, in press.

(2) A. Stempel, I. Douvan, E. Reeder, and L. H. Sternbach, *J. Org. Chem.*, **32**, 2417 (1967).

(3) The terms *syn* and *anti* are used as defined in ref 2, footnote 7. This is particularly important in a discussion of benzaldehyde oximes since these terms are then in conflict with the traditional definition in which the position of the oxime hydroxyl is considered in reference to the aldehydic hydrogen. To be consistent, in this report the configuration will be named based on the relationship of the oxime hydroxyl to the amino-substituted phenyl ring in both aldehydic and ketonic oximes.

(4) K. v. Auwers and E. Frese, *Ann. Chem.*, **450**, 273 (1926). These authors named the compound 4,5-benzo-7-oxy-oct-1,2,6-oxdiazin.

(5) While our work was in progress, the product of an analogous reaction carried out with 2,4′-dichloro-2′-formylacetanilide oxime, again of unspecified configuration, was reported in a Dutch patent to be 7-chloro-1,3-dihydro-2H-1,4-benzodiazepin-2-one 4-oxide but no proof of structure was offered: Grindstedvarket, A.S., Netherlands Patent 6,608,039 (Dec 12, 1966).

(6) In view of the evidence discussed below we shall present this compound as the N-oxide **3** rather than the earlier incorrect structure A.

(7) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

compound **3** was reduced in acetic acid using palladium on charcoal as catalyst, in addition to **5**, a small amount of the hydroxylamino compound **6** was also obtained. The reactions discussed above show beyond any doubt that the structure of the compound described by v. Auwers is that of the nitrone (**3**) and not a benzoxadiazocin-2-one.

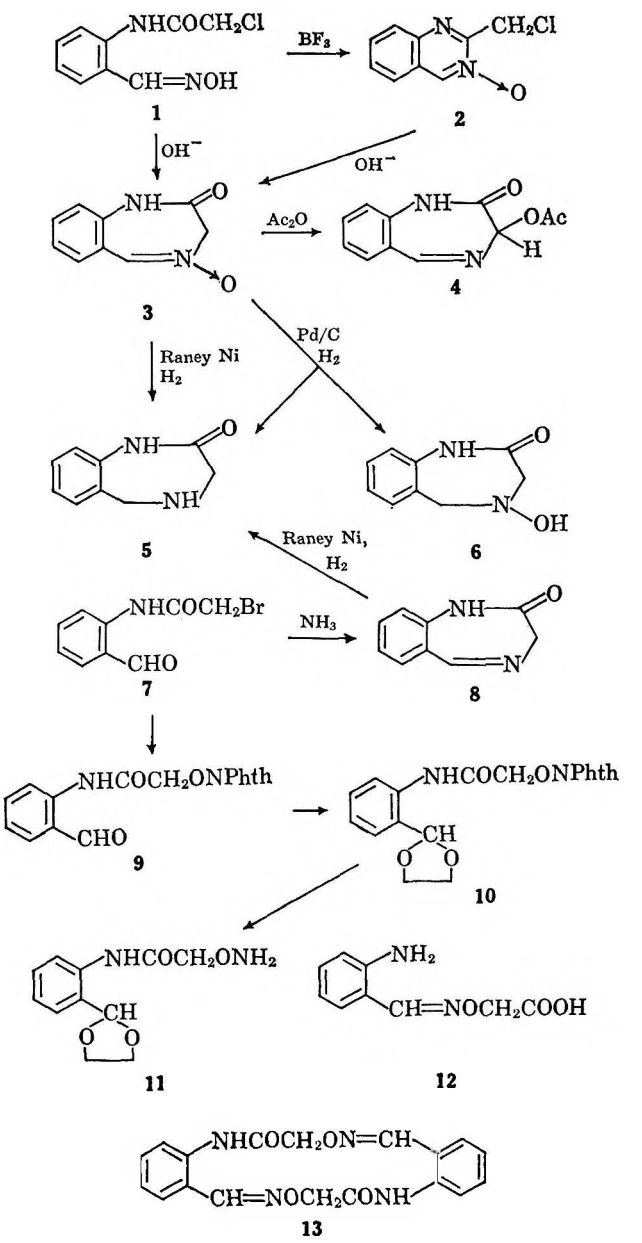
The "monoacetyl derivative" prepared by v. Auwers[4] by reaction of the compound described as A with acetic anhydride is then the product of the Polonovski rearrangement of the nitrone **3** and has the structure **4**. This was confirmed by the infrared spectrum which showed two carbonyl bands, at 1750 (ester) and 1690 cm^{-1} (amide CO) and the nmr spectrum with one proton each at C_3 and C_5. These two protons exhibited an "allylic" coupling (J = 3 cps) similar to that reported recently[8a] in a closely related system.[8b]

If the rules for intramolecular alkylation of oximes stated earlier[2] are valid then the configuration of the oxime **1** should be *anti*. The infrared spectrum of **1** in very dilute solution showed hydrogen bonding in the NH region. This had been observed in corresponding acylated aminobenzophenone *anti*-oximes but not in the *syn* isomers.[9] Nevertheless, it would be difficult to assign a definite configuration based on the infrared spectra since only one isomer of **1** was obtained. For the same reason interpretation of the nmr spectra cannot be used for structural assignment.

Since it is known[10] that the *syn* and *anti* forms of aldoximes are not very stable and are readily convertible into each other, it is reasonable to assume that the oxime would react in a manner as to yield the thermodynamically most favored product. It is, therefore, not astonishing and in good agreement with our former findings that the seven-membered benzodiazepine N-oxide and not the eight-membered benzoxadiazocine is formed.

In order to be able to study the properties and stability of this latter compound, we attempted the synthesis of the 4,1,5-benzoxadiazocin-2-one (A) but were not successful. Compound **9** was prepared as outlined from **7** (Chart I) and attempts were made to convert it into A as described for the benzophenone derivatives.[2] On treatment of **9** with hydrazine hydrate or **11** with dilute acid or pyridine hydrochloride, the product obtained was shown by mass spectroscopy to be predominantly a dimer (*m/e* 352, possibly **13**). Similar results were also obtained in an attempted cyclization of **12** with dicyclohexylcarbodiimide.

CHART I



Phth = phthaloyl

Experimental Section[11]

1,3-Dihydro-2H-1,4-benzodiazepin-2-one 4-Oxide (3). Method A.—To a solution of 5.0 g (23.5 mmol) of 2-chloro-2′-formylacetanilide oxime (**1**) in 150 ml of dioxane, 25 ml of 2 *N* sodium hydroxide was added. After stirring at room temperature for 4 hr, the reaction mixture was diluted with 100 ml of water (pH 11.9) and acidified to pH 1.5 by addition of 3 *N* hydrochloric acid. On concentration under reduced pressure to remove dioxane, a crystalline product formed which was separated by filtration to give 2.1 g of **3** (50%, mp 252–255° dec). Recrystallization from dilute ethanol gave colorless needles melting at 259–260° dec (lit.[4] mp 251–252°): ir (KBr disk) 3205 (NH), 1675 cm^{-1} (amide C=O); (nmr (DMSO-d_6), δ 4.50 (s, 2, CH_2), 8.12 (s, 1, CH=N), 10.2 (s, 1, NH).

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.41; H, 4.36; N, 15.78.

Method B.—A stirred solution of 21.7 g (0.16 mol) of 2-aminobenzaldoxime in a mixture of 500 ml of ether and 300 ml of water was cooled to 5° and 19.5 g (13 ml, 0.17 mol) of chloroacetyl chloride was added slowly while keeping the reaction mixture slightly alkaline by the addition of 10% sodium hydroxide. After stirring for 1 hr in an ice bath, the reaction mixture was allowed to warm to room temperature; the solid that had sepa-

(8) (a) R. I. Fryer, D. Winter, and L. H. Sternbach, *J. Heterocycl. Chem.*, **4**, 355 (1967). (b) One of the referees has suggested that the Polonovski rearrangement could occur at C_5. This would be inconsistent with the nmr data unless isomerization to the $\Delta^{3,4}$ compound had occurred. A comparison of the uv spectra of **4** and **8** showed only minor differences. A similar comparison of the uv spectra (unpublished) of the $\Delta^{3,4}$ and $\Delta^{4,5}$ compounds reported in ref 8a showed major differences in the spectra.

(9) A. Stempel, E. Reeder, and L. H. Sternbach, *J. Org. Chem.*, **30**, 4267 (1965).

(10) J. Meisenheimer in "Stereochemistry," K. Freudenberg, Ed., Franz Deuticke, Leipzig, 1933, pp 987–990.

(11) All melting points were taken in a Thomas–Hoover melting point apparatus and are corrected. Infrared spectra were determined using a Beckmann IR-5 or IR-9 grating spectrophotometer, mass spectra with a CEC 21-110 spectrometer, and nmr spectra with a Varian A-60 spectrometer. Identity of compounds was established by comparison of spectra and mixture melting point. In reporting infrared and nmr data, only the significant peaks are noted.

rated dissolved upon addition of 10% sodium hydroxide. The aqueous layer was separated, cooled, and acidified with concentrated hydrochloric acid. Compound **3** crystallized and was filtered to separate 19.7 g of product (70%, mp 255–257° dec) identical with material prepared by method A.

Method C.—A solution of 1.0 g (5 mmol) of 2-chloromethylquinazoline 3-oxide (**2**) in 25 ml of 1 *N* sodium hydroxide was stirred for 45 min at room temperature then acidified by the addition of 3 *N* hydrochloric acid. The solid that formed was separated by filtration to give 0.5 g of crude **3** (mp 235–240°). Recrystallization from ethanol gave 0.1 g of **3** (mp 258–259 dec) identical with material prepared by method A.

2-Chloromethylquinazoline 3-Oxide (2).—A mixture of 14 g of **1** and 13 ml of boron trifluoride etherate in 500 ml of benzene was stirred and heated to reflux for 8 hr. After cooling, water was added, the mixture was stirred, and the organic phase was separated and washed with dilute sodium bicarbonate. An oily brown residue that remained in the flask was dissolved in methylene chloride, washed with 5% sodium bicarbonate, and combined with the benzene layer. The mixture was dried (Na_2SO_4) and concentrated to dryness under reduced pressure. Crystallization of the residue from a mixture of benzene and hexane gave 4.4 g of **2**, mp 148.5–149°. A second crop (1.7 g, mp 145–146.5°) was obtained from the mother liquors (total yield 48%). Further crystallization from a mixture of benzene and hexane gave yellow needles of **2**: mp 150–151.5°; ir ($CHCl_3$) 1613 (w), 1563 (m), 1488 cm^{-1} (m); nmr (DMSO-d_6), δ 5.07 (s, 2, CH_2) and 9.50 (s, 1, CH=N).

Anal. Calcd for $C_9H_7ClN_2O$: C, 55.54; H, 3.62; N, 14.39. Found: C, 55.34; H, 3.68; N, 14.14.

3-Acetoxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one (4).—A stirred mixture of 5.0 g of **3** in 20 ml of acetic anhydride was warmed on a steam bath for 15 min. After 10 min, the temperature rose to 108° and a clear solution resulted. On cooling, **4** crystallized and was separated by filtration (3.2 g, mp 199–200° dec, 51%), lit.[4] mp 197–198° dec. Crystallization from tetrahydrofuran gave colorless plates of unaltered melting point: uv (*i*-PrOH) max 227 (ϵ 37,500), infl 255 (ϵ 4750), max 312 (ϵ 1800); ir (KBr disk) 1750 (ester CO) and 1690 cm^{-1} (amide CO); nmr (DMSO-d_6), δ 2.22 (s, 3, CH_3COO), 5.72 (d, 1, J = 3 cps, –CHOAc–N=), 8.63 (d, 1, J = 3 cps, –CH=N).

Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.41; H, 4.68; N, 12.89.

1,3,4,5-Tetrahydro-2H-1,4-benzodiazepin-2-one (5). A. From 3.—A solution of 1.8 g (10 mmol) of **3** in 250 ml of dimethylformamide containing a suspension of *ca.* 5 g of Raney nickel was reduced at atmospheric pressure and room temperature. The uptake of hydrogen stopped when slightly more than 20 mmol had been absorbed. Solvent was removed by distillation under reduced pressure and the residue crystallized from acetonitrile to give colorless needles of **5** (1.2 g, 67%, mp 151–154°). Further crystallization from a mixture of methylene chloride and hexane gave a pure product melting at 150–151°: ir ($CHCl_3$) 3350 (NH), 3215 (NH) and 1660 cm^{-1} (amide CO); nmr ($CDCl_3$), δ 2.0 (s, 1, NH), 3.83 (s, 2, CH_2), 4.02 (s, 2, CH_2) and 9.03 (s, 1, NH).

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.48; H, 6.24; N, 17.23.

B. From 8.—A solution of 1.6 g (10 mmol) of **8** in 100 ml of dimethylformamide containing *ca.* 5 g of Raney nickel catalyst was reduced as above. Reduction stopped when about 10 mmol of hydrogen was absorbed. Following removal of solvent by distillation under reduced pressure, the residue was crystallized from a mixture of chloroform and hexane to give **5** (1.0 g, 62%, mp 150–151°) which was identical with material prepared from **3**.

4-Hydroxy-1,3,4,5-2H-1,4-tetrahydrobenzodiazepin-2-one (6) and 5.—A solution of 1.8 g (10 mmol) of **3** in 200 ml of acetic acid containing 0.5 g of 10% palladium on charcoal was reduced at atmospheric pressure and room temperature. The reduction stopped when about 16 mmol of hydrogen had been absorbed. After filtration to remove the catalyst and distillation under reduced pressure to remove solvent, the residue was stirred with methylene chloride. The solid that formed was separated by filtration to give 300 mg of crude **6**, mp 190–192°. Recrystallization from acetonitrile gave a product melting at 207–208°: ir (KBr disk) 3200 (NH) and 1660 cm^{-1} (amide CO); nmr peaks (DMSO-d_6), δ 3.40 (s, 2, CH_2), 3.93 (s, 2, CH_2), 8.40 (s, 1, OH), 9.88 (s, 1, NH). The mass spectrum showed the molecular ion at 178.

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 61.00; H, 5.52; N, 15.72. Found: C, 60.67; H, 5.66; N, 15.72.

Addition of hexane to the methylene chloride filtrate obtained above gave a crystalline material melting sharply at 109–111°. This was **5** containing solvent of crystallization since on prolonged drying at 78° under reduced pressure, the melting point became 149–151° and the product was identical with **5** prepared as described above.

2-Bromo-2′-formylacetanilide (7).[12]—A solution of 36.4 g (0.22 mol) of 2-aminobenzaldehyde dimethyl acetal in 1200 ml of ether was stirred with 700 ml of water at 0–5° and 48.2 g (20.8 ml, 0.24 mol) of bromoacetyl bromide dissolved in 50 ml of ether was added slowly while maintaining the reaction mixture slightly alkaline by addition of 10% sodium hydroxide. The organic layer was washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The residue was extracted with two 250-ml portions of hot hexane. On cooling, 16.3 g of **7** crystallized, mp 68–71°. From the mother liquors an additional 3.3 g (mp 72–74°) separated. A methylene chloride solution of the hexane insoluble material, after filtration through Florisil, gave 3.3 g of **7** for a total of 22.9 g (43%). Recrystallization of a sample from hexane gave colorless prisms: mp 73–75°; ir ($CHCl_3$) 3250 (NH), 2850, 2755 (CHO), 1690 (infl, aldehyde), 1670 (amide CO), 1525 cm^{-1} (amide II); nmr (DMSO-d_6), 4.25 (s, 2, CH_2), 10.03 (s, 1, CHO), 11.27 (s, 1, NH).

Anal. Calcd for $C_9H_8BrNO_2$: C, 44.65; H, 3.33; N, 5.79. Found: C, 44.92; H, 3.15; N, 5.59.

1,3-Dihydro-2H-1,4-benzodiazepin-2-one (8).—A solution of 9.1 g (37.6 mmol) of 2-bromo-2′-formylacetanilide (**7**) in 150 ml of tetrahydrofuran was added slowly to 300 ml of liquid ammonia while stirring and allowed to reflux for 5 hr. The ammonia was then evaporated slowly. The solid that formed was separated by filtration, stirred with water and again filtered to give 4.0 g of **8**, mp 216–218°. An additional 1.0 g was obtained from the filtrate after addition of water and evaporation of tetrahydrofuran under reduced pressure (total yield, 5.0 g, 83%). Recrystallization from acetonitrile gave colorless rods: mp 225–227°; uv (*i*-PrOH) max 228 mμ (ϵ 43,000), 254 (8400), 320 (3100); ir (KBr disk) 3300 (NH) and 1670 cm^{-1} (amide CO); nmr (DMSO-d_6), δ 4.07 (s, 2, CH_2), 8.75 (s, 1, CH=N), 10.75 (s, 1, NH).

Anal. Calcd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.33; H, 5.11; N, 17.61.

2′-Formyl-2-phthalimidoxyacetanilide (9).—A solution of 6.3 g (26 mmol) of **7** and 4.25 g (26 mmol) of N-hydroxyphthalimide in 60 ml of tetrahydrofuran containing 4.4 ml of triethylamine was stirred and heated to reflux for 75 min. The solid, which formed after 5 min, was separated by filtration, after cooling, and stirred for 10 min with 200 ml of water. Filtration gave 6.3 g of crude **9**, mp 193–205°. An additional 1.4 g (mp 195–198°) was obtained from the tetrahydrofuran filtrate after concentration under reduced pressure and addition of water. Recrystallization from benzene gave 5.4 g (65%): mp 200–201° (further recrystallization did not alter the melting point); ir ($CHCl_3$) 3250 (NH), 2850, 2755 (CHO), 1790, 1740 (phthalimide CO), 1715 (infl, CHO), 1690 cm^{-1} (amide CO).

Anal. Calcd for $C_{17}H_{12}N_2O_5$: C, 62.96; H, 3.73; N, 8.64. Found: C, 63.20; H, 3.52; H, 8.82.

2′-(1,3-Dioxolan-2-yl)-2-phthalimidoxyacetanilide (10).—To a solution of 5 g (15 mmol) of **9** in 500 ml of benzene, 1.1 ml of ethylene glycol and several crystals of *p*-toluenesulfonic acid were added, and the mixture was stirred and refluxed for 2 hr while separating water in a Dean–Stark tube. The benzene solution was washed with dilute sodium bicarbonate, dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Warming the residue with ethanol gave 0.7 g of unreacted starting material (**9**), mp 191–192°. The ethanol filtrate was concentrated to dryness and, on trituration of the residue with ether, 3.8 g of **10** (mp 112–115°) was obtained. Recrystallization from ethanol gave colorless rods: mp 118–120°; ir ($CHCl_3$) 3350 (NH), 1800, 1750 (phthalimide CO), 1690 (amide CO), 1540 cm^{-1} (amide II).

Anal. Calcd for $C_{19}H_{16}N_2O_6$: C, 61.95; H, 4.38; N, 7.61. Found: C, 62.16; H, 4.39; N, 7.52.

2-Aminoxy-2′-(1,3-dioxolan-2-yl)acetanilide (11).—A solution of 3.2 g (9 mmol) of **10** in a mixture of 100 ml of chloroform and 100 ml of ethanol containing 0.9 ml of water and 0.9 ml (18 mmol) of hydrazine hydrate was kept at room temperature for 17 hr.

(12) First prepared in these laboratories by Dr. W. Metlesics from 2-aminobenzaldehyde and bromoacetyl bromide (unpublished).

The phthalhydrazide that formed was separated by filtration. The filtrate was concentrated to a small volume under reduced pressure and partitioned between methylene chloride and water. After drying the organic phase (Na_2SO_4), it was concentrated to dryness and the residue crystallized from a mixture of benzene and hexane to give 1.1 g of **11**, mp 47–51°. An additional 0.25 g (mp 51–54°) was obtained from the filtrate. Recrystallization of a sample from a mixture of ether and hexane gave colorless prisms: mp 51–54°; ir ($CHCl_3$) 3360 (NH), 1690 (amide CO), 1520 cm^{-1} (amide II).

Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.47; H, 6.14; N, 11.44.

2-(2-Aminobenzylideneaminoxy)acetic Acid (12).—To a solution of 13.6 g (0.1 mol) of 2-aminobenzaldoxime in 300 ml of ethanol containing 10.8 g (0.2 mol) of sodium methoxide, 9.5 g (0.1 mol) of chloroacetic acid was added. The mixture was stirred and heated to reflux for 2 hr and filtered to remove the solid that formed; the filtrate was concentrated to dryness under reduced pressure. On addition of water, **12** crystallized (2.0 g, mp 136–139°) and an additional 8.6 g (mp 134–138°, total yield 55%) was obtained on acidification of the mother liquor with acetic acid. Recrystallization from a mixture of methylene chloride and hexane gave a product melting at 137–139°: ir (KBr disk) 3460, 3450, 3340, 3360 (NH_2), 3200–2600 (associated COOH), 1710 cm^{-1} (carboxyl CO).

Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.46; H, 5.18; N, 14.49.

Cyclization of 11 to 13. A.—To a solution of 1 g (4 mmol) of **11** in 50 ml of ethanol, 16 ml of 1 *N* hydrochloric acid was added. Within 5 min, a white solid formed. After 16 hr at room temperature, the solid was separated by filtration (0.5 g, mp 263–266 dec). Recrystallization from a mixture of methanol and chloroform gave a product melting at 281–282°: ir (KBr) 3280 (NH), 1695 (amide CO), 1613, 1585, 1540 cm^{-1}; mass spectrum *m/e* 352, 176, 147, 118. The peak at *m/e* 176 could indicate the presence of the monomer.

Anal. Calcd for $(C_9H_8N_2O_2)_n$ C, 61.36; H, 4.58; N, 15.90. Found: C, 61.08; H, 4.77; N, 15.78.

B.—A solution of 2.35 g of **11** in 50 ml of pyridine was added during 1 hr to a refluxing solution of 2.35 g of pyridine hydrochloride in 200 ml of pyridine and the mixture refluxed for 4 more hr. Solvent was removed by distillation at reduced pressure and the residue was partitioned between methylene chloride and water. The organic phase was washed with water, dried (Na_2SO_4), and concentrated to dryness. Trituration of the residue with methylene chloride gave 200 mg of solid (mp 270–275°). Recrystallization from a mixture of methanol and chloroform gave a product melting at 269–270°: ir (KBr) 3270 (NH), 1690 (amide CO), 1660, 1620, 1580, 1540, 1500 cm^{-1}, mass spectrum *m/e* 352, 321, 305, 294, 176, 147, 131, 118.

Anal. Found: C, 61.13; H, 4.47; N, 15.83.

Registry No.—**2**, 16780-56-6; **3**, 16780-57-7; **4**, 16780-58-8; **5**, 1824-72-2; **6**, 16780-60-2; **7**, 16780-61-3; **8**, 16780-62-4; **9**, 16780-63-5; **10**, 16780-64-6; **11**, 16780-65-7; **12**, 16780-66-8; **13**, 16780-55-5.

Acknowledgment.—The authors are indebted to Dr. F. Vane, Dr. T. Williams, and Mr. S. Traiman for the spectral data and many helpful discussions and to Dr. F. Scheidl and his staff for the microanalyses.

5-Aroyl- (or -Acyl-) 4-hydroxycoumarins

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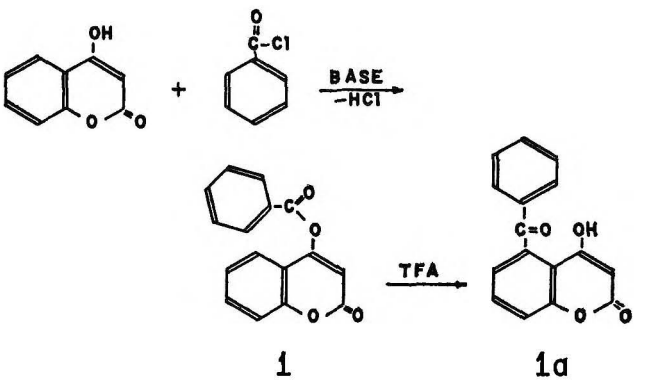
Received August 28, 1967

In this Note we present a novel rearrangement of 4-acyloxy- or 4-aroyloxycoumarins (see Table I) given as the **1–5** series, to give 5-aroyl- (or -acyl-) 4-hydroxy coumarin in good yield. This is the only rearrangement, to our knowledge, involving oxygen heterocycles in which a group has migrated from one ring to another and in this respect is quite different from the recorded instances of the Fries reaction[2] involving coumarins.

The rearranged compounds described in Table II as **1a–5a**, are considered by us to be produced by the reaction for **1a** given in Chart I and may be visualized as the general course of the reaction for the production of all the other members of the series.

CHART I



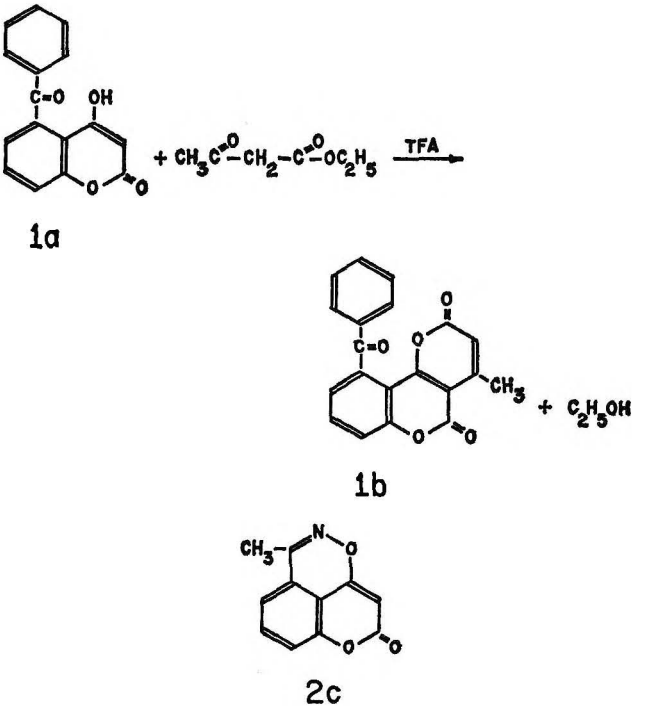
1 **1a**

Compound **2a** is the only member of the series which formed a 2,4-dinitrophenylhydrazone.

The failure of the compounds to form dinitrophenyl hydrazones showed that the ketones were hindered and the infrared spectra showed that they were hydrogen bonded. Therefore, the migrating aroyl or acyl group must have taken up positions 3 or 5 on the ring system.

A comparison of the properties of **2a** with 3-acetyl-4-hydroxycoumarin, which had been very carefully

CHART II



1a

1b

2c

(1) Address all inquiries to this author.

(2) R. C. Elderfield, "Heterocyclic Compounds," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1951, p 195.

TABLE I

AROYLOXY OR ACYLOXY DERIVATIVES OF 4-HYDROXYCOUMARIN

Compd[a]	Aroyl halide or anhydride used	Mp, °C	Yield, %	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % Other	Found, % C	Found, % H	Found, % Other
1	Benzoyl chloride	126.5–127.5	88	$C_{16}H_{10}O_4$	72.17	3.78		72.13	3.94	
2	Acetic anhydride	112–113[b]	92	$C_{11}H_8O_4$	64.70	3.94		64.94	4.17	
3	*p*-Chlorobenzoyl chloride	174–174.5	100	$C_{16}H_9ClO_4$	63.90	3.01	11.79 (Cl)	63.62	3.18	11.94 (Cl)
4	*o*-Chlorobenzoyl chloride	130–132	85	$C_{16}H_9ClO_4$	63.90	3.01	11.79 (Cl)	63.68	3.11	11.87 (Cl)
5	*p*-Nitrobenzoyl chloride	195.5–197	100	$C_{16}H_9NO_6$	61.74	2.91	4.50 (N)	61.49	3.04	4.57 (N)

[a] Registry no. for these compounds are given in descending order: 16709-58-3, 15059-36-6, 16709-66-3, 16709-68-5, and 16709-70-9. [b] Lit. mp 103°, according to I. Heilbron, "Dictionary of Organic Compounds," Vol. 3, 4th ed, Oxford Press, New York, N. Y., p 1666.

TABLE II

5-AROYL- (OR -ACYL-) 4-HYDROXYCOUMARINS

Compound	Yield, %	Mp, °C	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % Other	Found, % C	Found, % H	Found, % Other
5-Benzoyl-4-hydroxycoumarin (**1a**)	85	217	$C_{16}H_{10}O_4$	72.17	3.78		72.24	3.84	
5-Acetyl-4-hydroxycoumarin (**2a**)	88	213–213.5	$C_{11}H_8O_4$	64.70	3.94		64.83	4.04	
5-(4-Chlorobenzoyl)-4-hydroxycoumarin (**3a**)	70	232–233	$C_{16}H_9ClO_4$	63.90	3.01	11.79 (Cl)	63.75	3.20	11.98 (Cl)
5-(2-Chlorobenzoyl)-4-hydroxycoumarin (**4a**)	98	218.5–219	$C_{16}H_9ClO_4$	63.90	3.01	11.79 (Cl)	63.74	3.08	11.90 (Cl)
5-(4-Nitrobenzoyl)-4-hydroxycoumarin (**5a**)	55	215–216	$C_{16}H_9NO_6$	61.74	2.91	4.50 (N)	61.45	3.18	4.73 (N)

TABLE III

SPECTRAL CHARACTERISTICS OF MEMBERS OF 1a–5a SERIES

Compd[d]	Infrared absorption[a,b] bands at 4000–1500 cm^{-1}	Ultraviolet absorption maxima,[c] mμ (log ε)
1a	3400, 2950 b, 2710, 2570, 1695, 1603, 1550, 1502	232 (4.27), 282 (4.30), 306 (4.30)
2a	3375, 2900, 2720, 2580, 1695 vb, 1558	230 (4.18), 281 (4.21), 305 (4.21)
3a	3450, 2960, 2825, 2550, 1673, 1587	210 (4.29), 243 (4.41)
4a	3370 b, 2900, 2720, 2550, 1610, 1593, 1547	225 (4.31), 280 (4.31) pl, 303 (4.32)
5a	3120, 2840 vb, 2660, 2547, 1686, 1601, 1535	230 (4.02), 281 (4.04), 305 (4.03)

[a] Abbreviations used are b = broad, vb = very broad, sh = shoulder. [b] Spectra were taken on Beckman IR-8 spectrometer using KBr pellets. [c] Spectra were taken on Bausch and Lomb Spectronic-505 spectrometer in Spectrograde methanol; pl = plateau. [d] Registry no. are given in descending order: 16709-59-4, 16709-63-0, 16709-66-3, 16709-69-6, and 16709-71-0.

studied[3,4] previously, shows that the migration had not involved position 3; therefore, the migration of the aroyl or acyl group must have been to position 5. The presence of a free 3 position in these products was confirmed by conversion of the 5-benzoyl compound **1a** into **1b** on condensation with acetoacetic ester in the usual way.[5] Reaction of **1a** and **2a** with hydroxylamine under forcing conditions gave products considered to be oxazines **2c** (Chart II).

Experimental Section[6]

4-Acyloxycoumarins.—To a mixture consisting of 0.05 mol of 4-hydroxycoumarin, 0.05 mol of the aroyl halide, and 0.05 mol of pyridine was added 200 ml of benzene. The mixture was gradually brought to its boiling point on a hot plate.

The benzene layer was decanted from the bottom layer, and the solvent was evaporated; the resulting solid was combined with any residue which did not dissolve in the benzene, and the solids were thoroughly washed with warm water to give the aroyloxy compound.

In the case of compound **2** theoretical amounts (0.05 mol) each of acetic anhydride and 4-hydroxycoumarin were heated together in the presence of one drop of concentrated sulfuric acid. The resulting liquid was poured into 150 ml of cold water to give the crude yield.

Compounds **1** and **2** were recrystallized twice from heptane. Compound **3** was purified by dissolving the compound in ethyl acetate and precipitating out the substance with heptane. The process was repeated for a second precipitation.

Compounds **4** and **5** were recrystallized twice from ethyl acetate. Other data on these compounds are given in Table I.

5-Acyl-4-hydroxycoumarins.—A 10-g sample of each of the compounds of the **1–5** series was heated for 15 hr in 30 ml of trifluoroacetic acid. The mixtures were poured into water, chilled, and filtered, and the precipitates were dried in air. The compounds were purified by taking them up in ethyl acetate and precipitating them with heptane. The process was repeated for a second or third recrystallization.

The analytical data for the compounds are given in Table II and the optical characteristics are recorded in Table III.

10-Benzoyl-4-methyl-2H,5H-pyrano[3,2-c][1]benzopyran-2,5-dione (1b).—A mixture of 2.2 g of **1a**, 2 g of ethyl acetoacetate, and 5 ml of trifluoroacetic acid was refluxed for 24 hr. The solution was poured into water, filtered, and dried in air. The yield was 2.5 g. The compound was extracted with cold ethyl acetate and the residue was taken up in tetrahydrofuran and precipitated with heptane, mp 255–256°.

Anal. Calcd for $C_{20}H_{12}O_5$: C, 72.28; H, 3.63. Found: C, 72.02; H, 3.47.

The 2,4-dinitrophenylhydrazone of compound 2a was prepared in the usual way and then recrystallized once from absolute ethanol, mp 273°.

Anal. Calcd for $C_{17}H_{12}N_4O_7$: C, 52.13; H, 3.14; N, 14.57. Found: C, 53.29; H, 3.01; N, 14.78.

Preparation of 3-phenyl-8H-pyrano[2,3,4-*ij*][2,3]benzoxazin-8-one (1c) and 3-methyl-8H-pyrano[2,3,4,-*ij*][2,3]benzoxazin-8-one (2c).—A 3-g sample of each of the compounds (**1a** and **2a**) and 3 g of hydroxylamine hydrochloride were ground together, placed in a flask, and heated in a Fisher Hi-Temp oil bath at 180° for 2 hr. The melt was treated with 100 ml of water, thoroughly extracted with ethyl acetate, and then precipitated with heptane. This process was repeated additionally so that no solid was observed upon taking the melting point of compound **1c** (decomposition above 232°).

Anal. Calcd for $C_{16}H_9NO_3 \cdot HCl$: N, 4.67. Found: N, 4.67.

Since compound **1c** consistently gave correct analyses for the hydrochloride, the purification for **2c** was modified by adding sodium bicarbonate to the water solution and then extracting with ethyl acetate as above for **1c**, finally purified the product to give the salt free **2c**, mp 221–223°.

Anal. Calcd for $C_{11}H_7NO_3$: C, 65.57; H, 3.50; N, 6.96. Found: C, 65.39; H, 3.44; N, 6.84.

(3) H. R. Eisenhauer and K. P. Link, *J. Amer. Chem. Soc.*, **75**, 2046 (1953).
(4) F. D. Chattaway, *J. Chem. Soc.*, 2495 (1931).
(5) L. L. Woods and J. Sterling, *Texas J. Sci.*, **15**, 200 (1963).
(6) Analyses were all performed by Dr. C. Tiedcke, Teaneck, N. J., except for compound **1c** which was done by Galbraith Laboratories, Knoxville, Tenn. All melting points were taken on paired Fisher-Johns melting point blocks.

Registry No.—1b, 16709-60-7; 1c, 16709-61-8; 2a 2,4-dinitrophenylhydrazone, 16709-64-1; 2c, 16709-65-2.

Acknowledgment.—The authors acknowledge with thanks the financial support of this project by the Robert A. Welch Foundation. We wish to thank the Chemical Abstract Service for assistance in the naming of compounds 1c and 2c.

Synthesis of 6-Benzyl-3-oxo-6-azabicyclo[3.2.1]octane[1]

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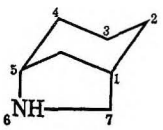
Received January 30, 1968

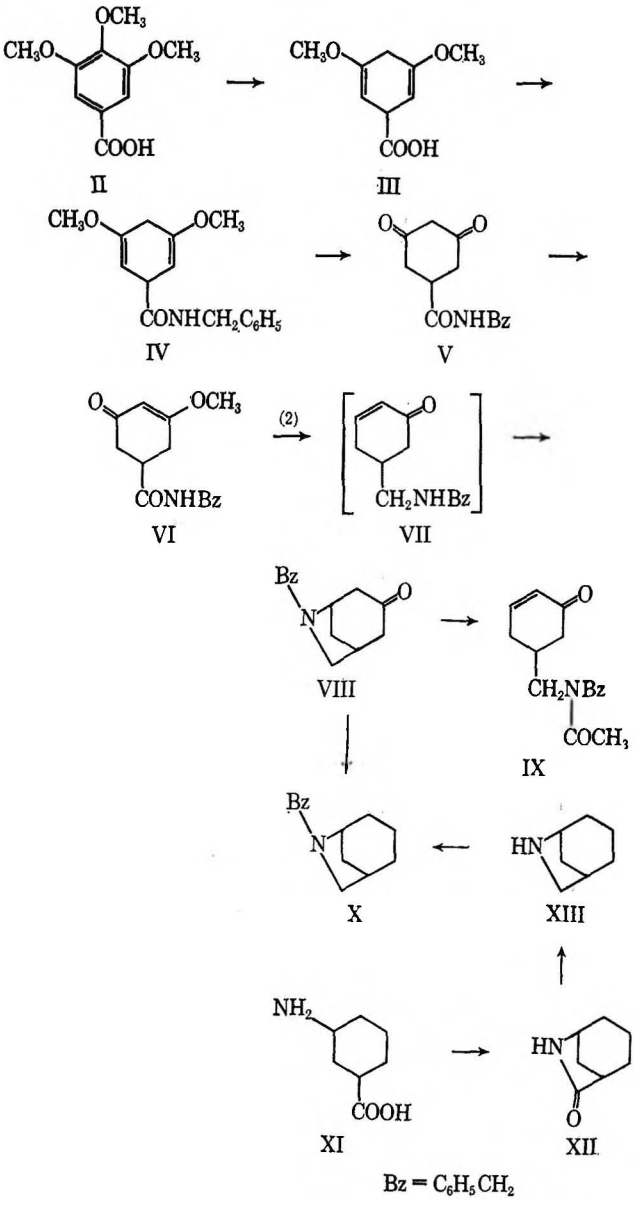
The literature reports only few syntheses of the 6-azabicyclo[3.2.1]octane system (I),[2-4] and only four syntheses of derivatives with a useful function on the three-membered bridge.[5,6] Our interest in this system as well as in other related azabicyclo compounds led us to investigate the sequence described below, which makes the 3-oxo derivative VIII readily available.



I

The starting point (see Scheme I) is trimethylgallic acid (II), which can be converted smoothly by Birch reduction into 3,5-dimethoxy-1,4-dihydrobenzoic acid (III).[7] Treatment of this acid with benzylamine and N,N-dicyclohexylcarbodiimide furnished the N-benzylamide IV. Acid hydrolysis of the enol ether groupings of IV gave diketo compound V which is probably largely enolic. With methanol in the presence of acid, diketo compound V was converted into the β-methoxy-α,β-unsaturated ketone VI. Reduction with lithium aluminum hydride followed by exposure to aqueous sulfuric acid gave rise to the α,β-unsaturated ketone VII,

SCHEME I



which cyclized spontaneously to the desired 6-benzyl-3-oxo-6-azabicyclo[3.2.1]octane (VIII). Interestingly, compound VII with hydroxyl in place of benzylamino appears not to cyclize to the corresponding 6-oxo-6-oxabicyclo[3.2.1]octane.[8] Although the α,β-unsaturated ketone VII could not be obtained, treatment of bicyclo compound VIII with acetic anhydride opened the ring by acyl cleavage to give the N-acetyl derivative IX of VII. The assigned structure for bicyclo ketone VIII was confirmed when its Wolff-Kishner reduction product X proved to be the same as the product obtained by benzylating the known 6-azabicyclo[3.2.1]-octane (XIII). The latter was prepared from 3-aminocyclohexanecarboxylic acid (XI) by cyclization to XII and reduction.[2,3]

Ethylenimine derivatives similar to XVIII have been found to react readily with nucleophiles to give both 6-azabicyclo[3.2.1]octanes (as in XVII) and 2-azabicyclo[2.2.2]octanes (*i.e.*, isoquinuclidines, as in XIX).[5] The possibility of reaching isoquinuclidine XIX was attractive, and the series of reactions V →

(1) This investigation was supported by Public Health Service Research Grant No. CA 08386 from the National Cancer Institute.

(2) F. R. Hewgill and P. R. Jefferies, *J. Chem. Soc.*, 2767 (1955); H. Najer, R. Giudicelli, and J. Sette, *Bull. Soc. Chim. Fr.*, 1593 (1962).

(3) H. K. Ball, Jr., *J. Amer. Chem. Soc.*, **80**, 6412, 6420 (1958); **82**, 1209 (1960).

(4) W. J. Sullivan, *Dissertation Abstr.*, **19**, 682 (1958) (Doctoral Dissertation, University of Michigan, Ann Arbor, Mich., 1957); E. N. Skiest, *ibid.*, **22**, 1021 (1961) (Doctoral Dissertation, University of Michigan, Ann Arbor, Mich., 1961); B. E. Betts and W. Davey, *J. Chem. Soc.*, 1683, 3333 (1961); P. G. Gassman and B. L. Fox, *J. Org. Chem.*, **32**, 3679 (1967). Also *cf.* R. K. Blackwood and C. R. Stephens, *Can. J. Chem.*, **43**, 1382 (1965).

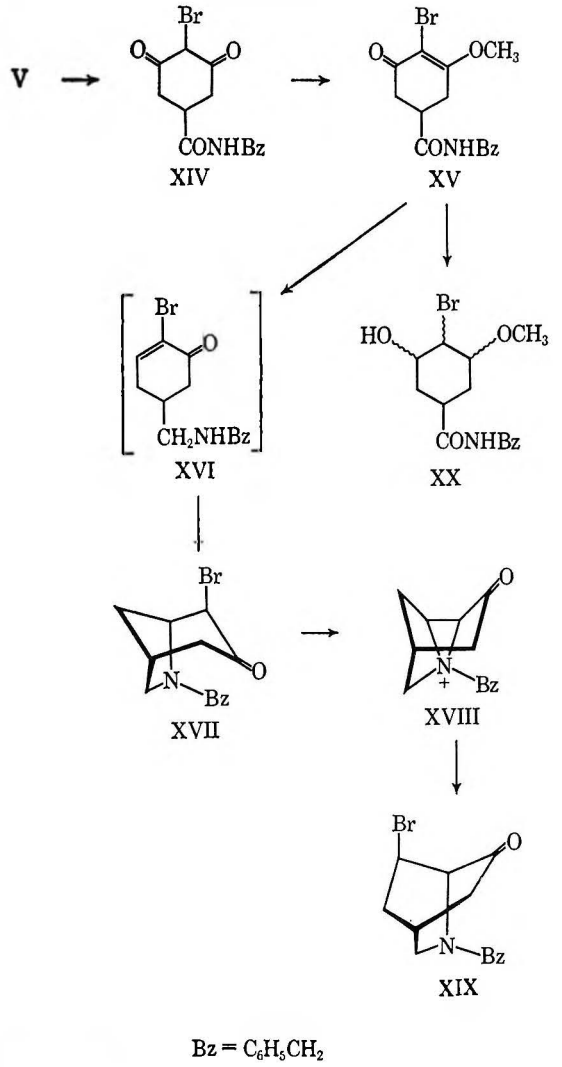
(5) H. R. Snyder, R. B. Hasbrouck, and J. F. Richardson, *J. Amer. Chem. Soc.*, **61**, 3558 (1939); W. A. M. Davies, A. R. Pinder, and I. G. Morris, *Tetrahedron*, **18**, 405 (1962). Actinobolamine, a degradation product from actinobolin, has been described as a 3-oxo-6-azabicyclo[3.2.1]octane derivative by M. E. Munk, C. S. Sodano, R. L. McLean, and T. H. Haskell, *J. Amer. Chem. Soc.*, **89**, 4158 (1967).

(6) W. Nagata, S. Hirai, K. Kawata, and T. Aoki, *ibid.*, **89**, 5045 (1967); W. Nagata, S. Hirai, K. Kawata, and T. Okumura, *ibid.*, 5047; J. W. Huffman and T. Kamiya, *Tetrahedron Lett.*, 1857 (1966).

(7) M. E. Kuehne and B. F. Lambert, *ibid.*, **81**, 4278 (1959); A. J. Birch, P. Hextall, and S. Sternhell, *Aust. J. Chem.*, **7**, 256 (1954); O. L. Chapman and P. Fitton, *J. Amer. Chem. Soc.*, **85**, 41 (1963).

(8) E. E. van Tamelen and G. T. Hildahl, *ibid.*, **75**, 5451 (1953); **78**, 4405 (1956).

SCHEME II



Bz = $C_6H_5CH_2$

XIV →···→ XIX (Scheme II) appeared feasible as well as convenient and well worth exploring. Bromination of dioxo compound V gave the 4-bromo-3,5-dioxo derivative XIV, which could be converted smoothly into the enol ether XV. Here the plan broke down because lithium aluminum hydride reduction of XV gave oils that could not be identified with the key compounds XVI or XVII. Reduction of enol ether XV with sodium borohydride gave a crystalline product to which we have assigned structure XX. This approach was not pursued.

Experimental Section

General.—Melting points were taken in an apparatus calibrated against pure compounds. Infrared absorption curves were taken with the help of a recording spectrophotometer (Perkin-Elmer Model 237). Ultraviolet absorption curves were determined on a Cary Model 14 spectrophotometer. A Varian A-60 spectrometer was used for the nmr work.[9] The adsorbent in the thin layer chromatographic analyses was either silica or alumina. Exposing the developed chromatogram to iodine vapors made the spots visible. Analysis for elements were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Galbraith Laboratories, Inc., Knoxville, Tenn.

N-Benzyl-3,5-dimethoxy-1,4-dihydrobenzamide (IV).—N,N-Dicyclohexylcarbodiimide (7.3 g or 0.035 mol) followed by benzylamine (2.9 g or 0.027 mol) was added to a solution of 3,5-dimethoxy-1,4-dihydrobenzoic acid (III, 5.0 g or 0.027 mol)[7] in 250 ml of methylene chloride. After 2 days of stirring, the mixture was filtered. The slightly yellow filtrate was shaken with 3% hydrochloric acid, then 5% aqueous bicarbonate, and finally with two portions of water. The organic layer was taken to dryness *in vacuo* at room temperature. The residue, rubbed with a small amount of ether, produced a filterable white solid (6.0 g), mp 128–135° (rapid heating). Crystallization from methylene chloride–petroleum ether gave colorless needles (5.0 g or 68%), mp 128–132° (rapid heating). Further crystallization from ethyl acetate–petroleum ether and from benzene–pentane furnished analytically pure N-benzyl 3,5-dimethoxy-1,4-dihydrobenzamide (IV), homogeneous according to thin layer chromatography (chloroform solvent), with mp 127–129°.

Anal. Calcd for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.09; H, 7.39; N, 5.11.

The infrared absorption spectra taken in chloroform solution showed maxima at 3410 (NH), 1690 (enol ether), and 1660 cm^{-1} (amide carbonyl). A 10% solution in deuteriochloroform showed signals at 2.76 (2 H, d, J = 7 cps, with a suspicion of satellite signals at *ca.* 2.55 and 2.95, position 4), 3.50 (6 H, s, 2 OCH_3), 3.6–3.9 (1 H, complex, position 1), 4.36 (2 H, d, J = 6 cps, $ArCH_2$), 4.73 (2 H, d, J = 4 cps, positions 2 and 6), 6.5–6.7 (1 H, broad, NH), and 7.23 ppm (5 H, s, 5 ArH).

N-Benzyl-3,5-dioxocyclohexanecarboxamide (V).—N-Benzyl-3,5-dimethoxy-1,4-dihydrobenzamide (IV, 13.5 g or 0.051 mol) in 150 ml of warm tetrahydrofuran was treated with 100 ml of 5% hydrochloric acid. The homogeneous solution was kept at 50–65° for 2 hr and then concentrated *in vacuo* until much solid was evident. Distilled water (*ca.* 300 ml) was added and the precipitate was collected, rinsed with water, and dried at 120° *in vacuo* over phosphorus pentoxide. The N-benzyl-3,5-dioxocyclohexanecarboxamide (V) obtained in this way weighed 10.5 g and showed mp 183–185°. Two crystallizations from acetone gave white crystals, mp 199–201°, which as a mineral oil mull showed absorption peaks at 3333 (NH), 1642 (amide carbonyl), 1613 and 1550 cm^{-1} (1,3-diketone), and which as a 5.6×10^{-3} M solution in 95% ethanol showed an ultraviolet absorption maximum at 257 mμ (log ϵ 4.01).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.74; H, 6.22; N, 5.55.

N-Benzyl-3-methoxy-5-oxo-3-cyclohexenecarboxamide (VI).—To a warm solution of N-benzyl-3,5-dioxocyclohexanecarboxamide (V, 10.5 g or 0.043 mol) in 200 ml of methanol was added 0.3 g of *p*-toluenesulfonic acid. The solution was allowed to stand for a day at room temperature. Pyridine (four drops) was introduced, and more than half the solvent was removed under reduced pressures at room temperature. The precipitated solids were redissolved by warming and then brought out again by cooling the solution overnight. The collected dried crystals (8.1 g or 73%) melted at 162–164°. A second crystallization did not change the melting point of this N-benzyl-3-methoxy-5-oxocyclohexenecarboxamide (VI), which as a solution in chloroform showed infrared absorption bands at 3440 (NH), 1660 (amide carbonyl), 1650 and 1610 cm^{-1} (COC=$COCH_3$) and as a solution in methanol showed a band at λ_{max} 250 mμ (log ϵ 4.22).

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.39; H, 6.52; N, 5.32, 5.37.

In deuteriochloroform solution, this compound showed nmr signals at 2.2–3.2 (5 H, complex, positions 1,2,6), 3.64 (3H, s, CH_3O), 4.40 (2 H, d, J = 6 cps, $ArCH_2$), 5.27 (1 H, s, C=C—H), 6.71 (1 H, broad s, NH), and 7.23 ppm (5 H, s, aromatic H's).

6-Benzyl-3-oxo-6-azabicyclo[3.2.1]octane (VIII).—A solution of N-benzyl-3-methoxy-5-oxo-3-cyclohexenecarboxamide (VI, 17.0 g or 0.065 mol) in 350 ml of dry tetrahydrofuran was slowly added to a stirred slurry of lithium aluminum hydride (9.88 g or 0.26 mol) in 150 ml of dry tetrahydrofuran. After a 14-hr period of refluxing and stirring, the cooled reaction mixture was treated with 50 ml of 10% sodium hydroxide solution. The organic layer was filtered, and the solids were washed with tetrahydrofuran. The combined filtrate and washings were dried, and all solvent was removed. The residual oil (15.0 g), cooled in an ice bath, was mixed with 20 ml of 25% sulfuric acid. After 1.5 hr of stirring, the mixture was filtered through glass wool, and the filtrate was made strongly basic with 10% aqueous sodium hydroxide (cooling). The alkaline mixture, containing a white precipitate, was extracted with ether, which was then washed twice with water and dried.

(9) We acknowledge the help of the National Science Foundation which, under Research Equipment Grant GP 3618, provided funds for the purchase of this instrument.

Removal of all ether left 14.0 g of an oil, which as a solution in 25 ml of warm benzene, was placed on a 3.3 × 9.8 cm column of neutral 200 mesh alumina. More benzene (200 ml) was passed through the column. Stripping all solvent from the combined eluates left a semisolid mass, which on crystallization from ether–petroleum ether (bp 38–51°) afforded 7.3 g (52% from enol ether VI) of 6-benzyl-3-oxo-6-azabicyclo[3.2.1]octane (VIII) as shiny white flakes, mp 81–82°. A chloroform solution of this material showed an infrared absorption peak at 1715 cm^{-1} (cyclohexanone carbonyl) but nothing attributable to NH or OH. No obvious absorption maxima were noted between 200 and 350 mμ in a 95% alcohol solution.

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.17; H, 7.86; N, 6.41.

Bicyclo compound VIII in deuteriochloroform showed nmr signals at 1.80–2.10 (2 H, complex, CH_2 at position 8), 2.24 (1 H, d, J = 3 cps, position 1), 2.42 (4 H, complex, positions 2 and 4), 2.75 (2 H, s, position 7), 3.30 (1 H, broad, position 5), 3.72 (2 H, s, $ArCH_2$), and 7.22 ppm (5 H, s, ArH's).

Picrate of 6-Benzyl-3-oxo-6-azabicyclo[3.2.1]octane (VIII).—Mixing a hot solution of the azabicyclooctane VIII (0.5 g) in ether (30 ml) with picric acid (0.53 g) in ether (40 ml) produced an immediate separation of yellow crystals. Four crystallizations from methanol gave the shiny yellow, needlelike picrate, mp 157–158°.

Anal. Calcd for $C_{20}H_{20}N_4O_8$: C, 54.06; H, 4.54; N, 12.61. Found: C, 54.28; H, 4.80; N, 12.71.

Ring Opening of Bicyclic Compound VIII with Acetic Anhydride.—The bicyclic amino ketone VIII (5.0 g) was exposed for 10 min to boiling acetic anhydride (6 ml) under nitrogen. Distilled water (50 ml) was added to the cooled mixture, which was then extracted with chloroform. The chloroform solution was washed with water, dried, and warmed *in vacuo* to remove all volatile material. The gummy residue (5.1 g), largely a single product according to thin layer chromatography (two minor spots other than the main spot were evident), could not be induced to crystallize. Attempts at sublimation (175° at 0.05 mm) led only to decomposition.

All of the properties are consistent with acetyl derivative IX. The material did not dissolve in dilute hydrochloric acid. Its infrared absorption spectrum (chloroform solution) showed peaks at 1640 (acetyl carbonyl) and 1680 cm^{-1} (α,β-unsaturated carbonyl). The ultraviolet absorption spectrum, taken with a solution in 95% ethanol, indicated absorption maxima at 217 mμ (log ε 4.33) and 223 mμ (log ε 3.12). A 15% solution in carbon tetrachloride was prepared for the nmr spectrum: 2.02 (3 H, s, CH_3CO), 2.10–3.00 (5 H, complex, saturated ring CH's), 3.25 (2 H, complex, CH_2N), 4.53 (2 H, s, $ArCH_2$), 5.86 (1 H, J = 10 cps =CH–CO), 6.67–7.05 (1 H, complex, —CH=), and 7.21 ppm (5 H, s, ArH's).

The 2,4-dinitrophenylhydrazone of acetyl derivative IX was crystallized from ethyl acetate–ethanol to give shiny orange crystals, mp 178–179°.

Anal. Calcd for $C_{22}H_{23}N_5O_5$: C, 60.40; H, 5.30; N, 16.01. Found: C, 60.62; H, 5.25; N, 16.04.

Hydrochloride of 6-Benzyl-6-azabicyclo[3.2.1]octane (X).—A mixture of keto compound VIII (1.0 g or 4.7 mol) and 99–100% hydrazine hydrate (1.7 g) was boiled for 2 hr. Ethylene glycol (10 ml) plus potassium hydroxide (1.0 g) was added, and the mixture was slowly distilled until the inside temperature was *ca.* 200°. This solution was then boiled for 24 hr.

The cooled reaction mixture was poured into water, and the product was collected by ether extractions. The combined extracts were washed once with water, dried, and then warmed to remove all solvent. The orange residual gum (*ca.* 1.0 g) as a solution in 5 ml of benzene was placed on a 1.5 × 4.4 cm column of neutral alumina (200 mesh), which was then washed with more benzene until the emergent liquid was no longer yellow. The chromatography was repeated. Removal of solvent left a colorless gum (0.47 g), with no infrared absorption attributable to carbonyl or to NH. A 1% solution in deuteriochloroform gave the following nmr signals: 1.28 (10 H, s, cyclohexane H's), 2.47 (2 H, d, J = 4 cps CH_2N), 3.77 (2 H, s, $ArCH_2$), and 7.28 ppm (5 H, s, ArH's).

Treating a cold ethereal solution (1 ml) of the gum with hydrogen chloride produced a white precipitate, which was collected, washed with ether, and recrystallized from ethanol–ether (1:7). The hydrochloride of 6-benzyl-6-azabicyclo[3.2.1]octane (X) was obtained in 43% yield (0.47 g) as shiny, colorless leaflets, mp 217–218°. The mineral oil mull of this material revealed infrared absorption peaks at 2790, 2750, 2595, 2445, 2405, 750, and 695 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}ClN$: C, 70.78; H, 8.43; Cl, 14.94; N, 5.89. Found: C, 71.06; H, 8.71; Cl, 14.85; N, 5.84.

Hydrochloride of 6-Benzyl-6-azabicyclo[3.2.1]octane (X) by Benzylation of 6-Azabicyclo[3.2.1]octane (XIII).—Catalytic hydrogenation of *m*-aminobenzoic acid gave a mixture of *cis*- and *trans*-3-aminocyclohexanecarboxylic acid, mp 270–282°. The melting point reported before was 264°.[10] Pyrolysis[2] at 305–312° produced a mixture, from which after extensive purification, 7-oxo-6-ababicyclo[3.2.1]octane (XII) could be obtained in low yield as waxy prisms, mp 197–199°. A chloroform solution showed infrared absorption maxima at 3460 and 1689 cm^{-1}. The melting point reported before for this lactam is 198–199°.[2] Reduction with lithium aluminum hydride[2] converted the lactam into 6-azabicyclo[3.2.1]octane (XIII) showing the expected NH absorption peak (3378 cm^{-1} in chloroform), but no absorption in the carbonyl region.

A solution of 6-azabicyclo[3.2.1]octane (XIII, 45 mg or 0.41 mmol) in 10 ml of ether to which benzyl chloride (133 mg or 0.41 mmol) in 10 ml of ether had been added was allowed to stand for 24 hr. A 15-min period of boiling produced a solid, which was discarded. Concentrating the pale green filtrate deposited a semisolid, which was dissolved in 4 ml of ethanol and treated with decolorizing charcoal. A white precipitate was obtained when the alcoholic solution was concentrated to *ca.* 1 ml and then flooded with 7 ml of ether. Two crystallizations from ethanol–ether (1:10) afforded the hydrochloride of 6-benzyl-6-azabicyclo[3.2.1]octane (X), which melted alone at 216–219° and, when mixed with the same material described above, at 217–219°. The infrared absorption spectra of the two samples mulled with mineral oil were superposable.

N-Benzyl-3,5-dioxo-4-bromocyclohexanecarboxamide (XIV).—A mixture of N-benzyl 3,5-dioxocyclohexanecarboxamide (V, 2.0 g or 8.0 mmol) and glacial acetic acid was held at 100° until a clear solution resulted. Sodium acetate trihydrate (1.08 g or 8.0 mmol) was added to the cooled solution. Then bromine (0.43 ml or 8.0 mmol) in 10 ml of acetic acid was added to the stirred mixture at 15° over a period of 5 min. A colorless solid precipitated. After stirring for an additional 0.5 hr, 100 ml of water was added, and the solid was collected on the funnel, washed with water, and dried *in vacuo*. This material, the desired product XIV, weighed 2.0 g (75%) and showed mp 175°. Crystallization from acetone–tetrahydrofuran gave mp 180–182°.

Anal. Calcd for $C_{14}H_{14}BrNO_3$: C, 51.88; H, 4.35; Br, 24.66; N, 4.32. Found: C, 52.00; H, 4.43; Br, 24.90; N, 4.11.

The infrared spectrum of compound XIV in mineral oil showed peaks at 3195, 1645, and 1610 cm^{-1}. In a 6.3 × 10^{-5} M ethanolic (95%) solution, the compound had an absorption maximum at 276 mμ (log ε 4.04). A 2% solution in deuterated dimethyl sulfoxide gave signals at 2.5–3.0 (5 H, complex, cyclohexane H's), 4.21 (2 H, d, J = 6 cps, $ArCH_2$), 6.4 (poor integration, broad, NH), 7.19 (5 H, s, ArH's), and 7.9 ppm (1 H, broad, enol OH).

N-Benzyl-3-methoxy-4-bromo-5-oxo-3-cyclohexenecarboxamide (XV).—This enol ether XV was formed from the corresponding dioxo compound XIV essentially according to the directions given for the bromine-free compound VI. The crystalline product, as it deposited from the reaction mixture (8.75 g or 65%), showed mp 199–203°. Recrystallization from methanol gave the analytically pure bromo enol ether XV as needles, mp 205–206°.

Anal. Calcd for $C_{15}H_{16}BrNO_3$: C, 53.25; H, 4.76; Br, 23.62; N, 4.14. Found: C, 53.12; H, 4.82; Br, 23.47; N, 3.95.

As a 6 × 10^{-5} M solution in 95% ethanol, the bromo enol ether XV had an absorption maximum at 277 mμ (log ε 4.08); as a mull with mineral oil, it showed peaks at 3333, 1642, 1565, and 1538 cm^{-1}. A 2–3% solution in deuterated dimethyl sulfoxide showed nmr signals at 2.1–3.2 (5 H, complex, cyclohexane H's), 3.55 (3 H, s, OCH_3), 4.20 (2 H, d, J = 6 cps, $ArCH_2$), 6.4 (poor integration, broad, NH), and 7.18 ppm (5 H, s, ArH's).

Reduction[7] of N-Benzyl-3-methoxy-4-bromo-5-oxo-3-cyclohexenecarboxamide (XV).—Sodium borohydride (2.85 g or 75 mmol) was added over a 10-min period to a stirred suspension of bromo enol ether XV (5.0 g or 15 mmol) in methanol (200 ml) cooled in an ice bath. Solution was complete in an hour. After 1 day of stirring, the reaction mixture was poured into 20 ml of sulfuric acid diluted with 40 ml of water and containing ice.

(10) J. P. Grunstein and J. Wyman, Jr., *J. Amer. Chem. Soc.*, **60**, 2341 (1938).

After 2 hr, solid sodium carbonate was added until all the acid was neutralized, and the mixture was then evaporated to dryness. The residue, treated with 100 ml of water, was extracted with three 50-ml portions of chloroform. The chloroform extracts were washed with water, dried, and warmed to remove all volatile material. The residue was a viscous oil (4.0 g), which could be resolved into two spots (R_f 0.54 and 0.83) on a thin-layer alumina chromatogram with benzene–chloroform (1:1) as the developing solvent. The oil was chromatographed through a 2.2 × 8.6-cm column of neutral alumina prepared from a slurry in benzene–chloroform (1:1). The elution solvents were 50 ml of benzene–chloroform (1:1), 25 ml of benzene–chloroform (1:4), 40 ml of ether–chloroform (1:1), 60 ml of chloroform, and 100 ml of chloroform–methanol. Fractions were monitored by thin-layer chromatography. A clean separation was effected, with the material with R_f 0.53 coming out in the earlier fractions and the material with R_f 0.83 coming out in the later fractions.

The R_f 0.53 material (0.4 g of crystals) was recrystallized three times from chloroform–petroleum ether to give white crystals, mp 124–126°. A mull with mineral oil gave infrared absorption maxima at 3279, 1634, 1538, 1269, and 1242 cm^{-1}. Ultraviolet absorption in the 200–350 mμ region was nil. The sample for analysis, recrystallized further from chloroform–petroleum ether, had mp 125–127°.

Anal. Found: C, 64.44, 64.60; H, 7.00, 7.13; Br, 5.94, 6.19; N, 4.84, 4.65.

The R_f 0.84 material (2.8 g of an oil) was brought out of benzene diluted with ether to give 2.2 g of white crystals XX. Three recrystallizations from acetone–ether furnished material with mp 135–136°.

Anal. Calcd for $C_{15}H_{20}BrNO_3$: C, 52.44; H, 5.97; Br, 23.35. Found: C, 52.38; H, 5.92; Br, 23.42.

A mull in mineral oil gave infrared absorption bands at 3344, 1631, and 1541 cm^{-1}. No ultraviolet absorption was detected between 200–350 mμ. A 3% solution of the borohydride reduction product XX in deuteriochloroform showed nmr signals at 1.7–2.7 (7 H, complex, cyclohexane ring H's), 3.13 (1 H, broad, OH), 3.37 (3 H, s, OCH_3), 4.42 (2 H, d, J = 4 cps, $ArCH_2$), 4.78 (1 H, complex, BrCH), 6.08 (1 H, broad, NH), and 7.27 ppm (5 s, H, ArH's).

Registry No.—IV, 16607-44-6; V, 16607-45-7; VI, 16607-46-8; VIII, 16607-47-9; VIII picrate, 16622-57-4; IX, 16607-48-0; IX 2,4-dinitrophenylhydrazone, 16607-49-1; X, 16607-51-5; X HCl, 16607-50-4; XIV, 16607-52-6; XV, 16607-53-7; XX, 16607-54-8.

Nuclear Magnetic Resonance of 1-Methylimidazole Methiodide. A Correction

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Received February 13, 1968

In the course of our studies in imidazoles, we reinvestigated the nmr spectrum of 1-methylimidazole methiodide (1), which had been reported in 1965.[1] In contrast to the earlier paper, we have now found that the aromatic protons at C-4 and C-5 absorb at a lower field (H-2, τ 1, 22 ppm, s, broad; H-4,5, τ 2.47 ppm, d, J = 1.7 Hz; in water, DSS = 10) than in 1-methylimidazole itself (2.59, 3.14, and 2.95 ppm; in $CDCl_3$, TMS = 10).[2] The chemical shifts of the corresponding protons in pilocarpine methiodide (τ 1.27 and 2.55 ppm in water) are of the same order. These data are in accord with a report of Mannschreck, *et al.*,[3] that the aromatic protons of imidazole are shifted downfield when the nitrogen is protonated in strong acids. Further we succeeded in splitting the N-methyl signal of **1** into a doublet with $J_{NCH_3,H\text{-}2}$ = 0.45 Hz as anticipated by Mannschreck.[3] The coupling between the N-methyl group and H-2 was confirmed by double resonance.

Registry No.—1, 16727-92-7.

(1) C. G. Overberger, J. C. Salomone, and S. Yaroslavsky, *J. Org. Chem.*, **30**, 3580 (1965).

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Ozonations of Olefinic Ferrocenes[1]

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Received February 8, 1968

The relative ease with which ferrocene may be oxidized presents serious difficulties in projected oxidative transformations of ferrocene derivatives. Thus, for example, in our laboratory we have tried a number of well-established procedures for carbon–carbon double-bond cleavage only to find that destruction of the ferrocene nucleus also occurred. In this Note, we report the results of our study on the ozonation of a series of model olefinic ferrocenes.

Our successful ozonation technique lay in the careful treatment of the olefinic ferrocene with the exact molar equivalent of ozone required for reaction with the alkenyl linkage. For this purpose preparation and use of standardized solutions of ozone in anhydrous ether was found to be satisfactory.

With the monosubstituted olefin, vinylferrocene (**1**), ozonization proceeded smoothly, giving hydroxymethylferrocene (**2**) in 74% yield upon reduction with lithium aluminum hydride. Hydrolysis in the presence of zinc dust provided ferrocenecarboxaldehyde (**3**) in 32% yield, while use of the trimethyl phosphite work-up procedure gave the aldehyde in 85% yield. Three examples of disubstituted olefinic ferrocenes were investigated. Lithium aluminum hydride treatment of the ozonization mixture obtained from 1-ferrocenyl-1-phenylethene (**4**) gave ferrocenylphenylcarbinol (**5**) in 51% yield. Benzoylferrocene (**6**) was produced by hydrolysis and by reaction with trimethyl phosphite in yields of 42 and 45%, respectively. Hydride reduction of the mixture obtained from ozonization of cinnamoylferrocene (**7**) gave the new glycol, 1-ferrocenyl-1,2-dihydroxyethane (**8**), in 36% yield, but no ferrocene compound could be detected after the zinc–water treatment

(1) (a) Taken in part from the dissertation submitted by W. D. L. to the Graduate School, University of South Carolina, May 1967, in partial fulfillment of the requirements for the Master of Science degree. (b) For a previous paper related to the present work, see S. I. Goldberg, W. D. Loeble, and T. T. Tidwell, *J. Org. Chem.*, **32**, 4070 (1967).



1, R = —CH=CH$_2$
4, R = —C(C$_6$H$_5$)=CH$_2$
7, R = —C(O)CH=CHC$_6$H$_5$
9, R = —CH=CHCH(CH$_3$)C$_{10}$H$_9$Fe
11, R = —C=CHCH$_2$CH$_2$CH$_2$

2, R′ = —CH$_2$OH
3, R′ = —CH=O
5, R′ = —CH(OH)C$_6$H$_5$
6, R′ = —C(O)C$_6$H$_5$
8, R′ = —CH(OH)CH$_2$OH
10, R′ = —CH(CH$_3$)CH$_2$OH

of the ozonization mixture. Similarly, ozonization of 1,3-diferrocenyl-1-butene (**9**) followed by reduction with lithium aluminum hydride gave hydroxymethylferrocene (**2**) and 2-ferrocenyl-1-propanol (**10**) in 32% yield.[1b] When 1-ferrocenylcyclopentene (**11**), an example of a trisubstituted olefin, was allowed to react with the appropriate stoichiometric amount of ozone under the conditions developed in this work, destruction of the ferrocene nucleus was evident from the outset of the addition, for the reaction mixture immediately became very dark. The system was worked up through hydride reduction, but no ferrocene compound could be found.

Although the emphasis in the present study was placed on the practical aspects of ozonation of olefinic ferrocenes, certain other observations are worth noting. First of all, if one assumes that successful double bond cleavage (avoidance of destruction of the ferrocene nucleus) is due to a difference of reaction rate of ozone with the olefin linkage and the ferrocene nucleus, one is faced with the fact that in ordinary olefins the rate of reaction with ozone increases with increasing degree of substitution on the double bond.[2,3] Therefore, it is possible that ozone is not the oxidizing species in the present procedure, and that the process is more complicated than usual ozonations, particularly since it is known that ozone reacts readily with ethers,[4] probably initiating a radical process.[4] Alternatively, the difference may lie in the way the initially formed ozonides decompose.[5]

These questions not withstanding, the results of the present study appear to set the limit of applicability of ozonation at disubstituted olefinic ferrocenes. Despite this rather limited scope it may be anticipated that the procedure will be of utility because it does represent the only means available for the direct cleavage of a carbon–carbon double bond in the presence of a ferrocene nucleus.

Experimental Section

General.—All temperature readings were uncorrected. Columns for elution chromatography were prepared with Merck acid-washed alumina as a slurry in hexane. Column development and elution for each separation is described under the appropriate experimental account. Thin layer chromatography was carried out on glass plates coated with silica gel (0.25 mm). The solvent mixture used for development was composed of hexane, ethyl acetate, and xylene in volume ratios of 6:1:1. Infrared and electronic spectra were determined with Perkin-Elmer, Model 337, and Perkin-Elmer, Model 202, recording spectrophotometers, respectively. Determinations of nuclear magnetic resonance (nmr) spectra were carried out near room temperature with a Varian, Model A-60, spectrometer at 60 Mc in chloroform-*d* solvent containing tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported under the δ (ppm) convention (TMS at δ 0 ppm). Ferrocene was used as purchased from the Ethyl Corporation. Ozone was generated with a Welsbach, Model T-23, Ozonator. The series of olefinic ferrocenes used in this ozonolysis study were all known compounds prepared according to the following literature procedures. Vinylferrocene (**1**) was obtained *via* the dehydration[1b] of 1-ferrocenylethanol[6] prepared by reduction of acetylferrocene. Preparation of 1-ferrocenyl-1-phenylethene[7] (**4**) paralleled that of vinylferrocene in that ferrocenylmethylphenylcarbinol, obtained from the addition of methylmagnesium iodide to benzoylferrocene, was subjected to a similar dehydration procedure. Cinnamoylferrocene[8] (**7**) was prepared through the Friedel–Crafts reaction of cinnamoyl chloride with ferrocene. Treatment of ferrocene with anhydrous hydrogen fluoride was the procedure[9] used for the preparation of 1-ferrocenylcyclopentene (**11**).

Treatment of Ferrocene with Ozone.—Ozone was bubbled into a solution of ferrocene (1.0 g, 5.3 mmol) in dry ether (50 ml) during 10 min. While the system was maintained at −78° (Dry Ice–acetone bath). The ferrocene solution turned to dark black in color almost immediately upon introduction of the ozone. Removal of the solvent left a dark oil in which no ferrocene could be detected by sensitive chromatograpic methods.[10] Several other attempts using shorter time durations also resulted in complete destruction of the ferrocene.

Treatment of Vinylferrocene with Ozone. A. Addition of Ozone.—In all cases when ozone was bubbled into a cold (−78°) ethereal solution of vinylferrocene complete destruction of the latter resulted. This result was avoided, however, with the use of standardized ethereal solutions of ozone.

B. Standard Ethereal Solutions of Ozone.—In each of the ozonation experiments described below the calculated stoichiometric amount of ozone or ozone equivalent was brought into reaction with each olefinic ferrocene system. This was most readily accomplished through the use of ethereal solutions of ozone which were prepared and standardized according to the following generalized procedure. Ozone was slowly bubbled into an appropriate volume of anhydrous ether, maintained near −78° by means of an external Dry Ice–acetone bath, until the appearance of an iodine coloration in the potassium iodide solution through which the gas exiting the ether was passed. The ozone concentration was then precisely determined by addition of a measured aliquot of the ether solution to an appropriate volume of 2% aqueous potassium iodide solution, followed by titration with standard sodium thiosulfate solution (starch indicator) of the iodine equivalent formed. Anhydrous ether thus treated at −78° was usually found to b near 2.5×10^{-3} *M* in ozone equivalent.

C. Ozonation of Vinylferrocene.—The stoichiometric amount of ozone, contained in a cold (−70°) ethereal solution was added very slowly (~45 min) to an ethereal solution (20 ml) of vinylferrocene (100 mg, 0.472 mmol) cooled by means of a Dry Ice–acetone bath. The color of the reaction mixture changed from orange to dark brown during the addition. After the addition was complete and the temperature of the mixture was allowed to rise to 0°, it was then added slowly to a stirred suspension of lithium aluminum hydride (60 mg, 1.6 mmol) in 30 ml of dry ether. Stirring was continued during 30 min, followed by destruction of the excess hydride by addition of ethyl acetate. After the reaction mixture was hydrolyzed with saturated aqueous ammonium chloride and exhaustively extracted with ether, evaporation of the combined and dried ether extracts gave hydroxymethylferrocene (**2**): 75 mg, 74% yield. Crystallization from hexane gave golden needles, mp 78–79° (lit.[11] mp 77–78°), that gave rise to infrared and nmr spectra found to be superimposable upon those determined from authentic hydroxymethylferrocene.[12]

In another run vinylferrocene (100 mg, 0.472 mmol) was treated with stoichiometric equivalent of ozone as described above. The cold (−78°) reaction mixture was poured into 75 ml

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(6) F. S. Arimoto and A. C. Haven, *ibid.*, **77**, 6295 (1955).
(7) W. Kuan-Li, E. E. Sokolova, L. A. Leites, and A. D. Petrov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 887 (1962).
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(10) S. I. Goldberg, *Anal. Chem.*, **31**, 486 (1959).
(11) G. D. Broadhead, J. M. Osgerby, and P. L. Pauson, *J. Chem. Soc.*, 650 (1958).
(12) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **22**, 906 (1957).

of ice–water containing zinc dust (8 g) and stirred while the temperature was allowed to rise to room temperature. Periodic tests[13] showed the absence of peroxide during the hydrolysis. The ethereal phase was separated, and the aqueous phase was extracted with several portions of ether. Evaporation of the combined and dried ether solutions gave dark red crystals which showed only one major spot corresponding to ferrocenecarboxaldehyde on a thin layer chromatogram. The material was column chromatographed [benzene–ether, 1:1 (v/v)] to give 32 mg (32% yield) of pure ferrocenecarboxaldehyde (3): mp 124–125° (lit.[14] mp 124.5°); infrared and nmr spectra identical with those obtained from authentic material.

In a third run, trimethyl phosphite (91 mg, 0.73 mmol) was added to the cold (−78°) ozonization mixture of vinylferrocene (100 mg, 0.472 mmol), which was obtained as described above. During the addition the temperature of the reaction mixture rose to −20°, and after the addition was complete the mixture was allowed to come to room temperature. The ethereal solution was washed with several small portions of water, dried, and evaporated to a brown oil which was column chromatographed. Elution with benzene provided ferrocenecarboxaldehyde (3), identified by its infrared and nmr spectra (86 mg, 85% yield).

Ozonation of 1-Ferrocenyl-1-phenylethene (4).—1-Ferrocenyl-1-phenylethene (200 mg, 0.694 mmol), dissolved in 20 ml of anhydrous ether and cooled to −78°, was treated with the appropriate amount of standardized ethereal ozone solution in the usual way. During the addition the color changed from deep red to orange, and, after 30 min at −78°, the reaction mixture was allowed to warm to room temperature before it was added to a stirred suspension of lithium aluminum hydride (80 mg, 2.1 mmol) in 100 ml of ether. After the excess hydride was destroyed with ethyl acetate and the mixture hydrolyzed with saturated aqueous ammonium chloride solution, the aqueous phase was separated and extracted with several portions of ether. Evaporation of the combined and dried ether solutions left ferrocenylphenylcarbinol (5) [103 mg, 50.9% yield; mp 81–2° (lit.[7] mp 81–82°)] which gave rise to the infrared and nmr spectra superimposable upon those determined from authentic[7] ferrocenylphenylcarbinol.

The cold (−78°) ozonation mixture, prepared in the usual way from 1-ferrocenyl-1-phenylethene, was poured into 100 ml of ice–water containing zinc dust (8.0 g) and stirred for 1 hr, during which time periodic tests[13] for the presence of peroxide were negative. After the separated ether layer was washed with water and dried, it was evaporated to leave a residue of deep red cyrstals which was column chromatographed. Elution with benzene gave rise to pure 84 mg (42% yield) of benzoylferrocene mp 111–112° (lit.[15] mp 111–112°), whose identity was confirmed by comparison of its infrared and nmr spectra with those obtained from authentic benzoylferrocene.

Trimethyl phosphite (114 mg, 0.919 mmol) was added to the cold ozonization mixture prepared from 1-ferrocenyl-1-phenylethene (200 mg, 0.694 mmol), giving an exothermic reaction. The ethereal solution was washed with several small portions of water, dried, and evaporated to a brown oil which was column chromatographed. Elution of the prominent red band with benzene gave 91 mg (45% yield) of benzoylferrocene, mp 111–112°. Both admixture melting with authentic benzoylferrocene and comparison of infrared spectra were used to establish the identity.

Ozonization of Cinnamoylferrocene (7).—An ethereal solution (20 ml) of cinnamoylferrocene (157 mg, 0.497 mmol) was cooled to −78° and treated with an equivalent amount of ozone contained in cold (−78°) ether. The original orange color persisted while the mixture was kept at −78° during 30 min. At that time the cold solution was added to a stirred suspension of lithium aluminum hydride (80 mg, 2.1 mmol) in 100 ml of ether. After 30 min of stirring the excess hydride was destroyed by addition of ethyl acetate, and the reaction mixture was hydrolyzed with saturated aqueous ammonium chloride solution. The ether extracts of the aqueous phase were combined with the original ethereal phase, and the whole was dried and evaporated to give an orange gum which was carefully placed onto a silica gel column. Elution of the major band (orange) gave a substance whose spectral properties were found to be consistent with 1-ferrocenyl-1,2-dihydroxyethane (8): 44 mg, 36% yield; ir (CCl_4), 3560 (O-H), 3100 (Fc-H), 2950, 2925 (C-H), 1095 and 1000 cm^{-1} (unsubstituted Fc ring); nmr ($CDCl_3$), δ 4.21 (complex, 12), 3.42 (s, 1) and 1.23 (s, 1).

The cinnamoylferrocene ozonization mixture prepared as described above was poured into a stirred mixture of ice–water and zinc dust. As usual periodic spot tests for the presence of peroxide were negative. However, no ferrocene compounds could be found in the ethereal phase or extracts of the hydrolysate, and only some intractable tar was obtained from the aqueous portion.

Treatment of 1-Ferrocenylcyclopentene (11) with Ozone.—1-Ferrocenylcyclopentene (130 mg, 0.516 mmol) was dissolved in 20 ml of anhydrous ether and cooled at −78° while an equivalent of ozone (0.516 mmol) was slowly added *via* the usual standardized ethereal solution. The reaction mixture became brown-black immediately. After it was allowed to warm to room temperature the dark reaction mixture was added slowly to a stirred suspension of lithium aluminum hydride (60 mg, 1.6 mmol) in 100 ml of ether. The stirring was continued for an additional hour before the excess hydride was destroyed (ethyl acetate) and the mixture was hydrolyzed (saturated ammonium chloride). The only material detected and isolated from the ethereal phase and extracts was the starting compound 1-ferrocenylcyclopentene (13 mg, 10% recovery).

Registry No.—8, 12269-77-1.

(13) F. Feigl, "Spot Tests in Organic Analysis," Elsevier Publishing Co., New York, 1960, p 535.

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(15) M. Rausch, M. Vogel, and H. Rosenberg, *J. Org. Chem.*, **22**, 903 (1957).

The Reaction of Phenylacetylene with Nickel Carbonyl and Lithium Dimethylamide

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Received January 18, 1968

It has been known that lithium aroyl, or lithium acyl metal carbonylates $Li[RCOM(CO)_x]$ (R = alkyl or aryl) are formed from the reaction of organolithium compounds with mohonuclear metal carbonyls.[1] Previously, it was reported from our laboratory that lithium aroylnickel carbonylate, one of these unstable complexes, gave ketone or α-diketone by thermal decomposition and acyloin by hydrolysis.[1c] Furthermore, as this complex has a carbon–transition metal σ bond, it undergoes reaction with acetylenic compounds very easily to give 1,4-diketones in high yields.[2]

Analogous to the formation of lithium aroylnickel carbonylate, the formation of lithium carbamoylnickel carbonylate (I), $Li[RR'NCONi(CO)_3]$, from the reaction of lithium amide with nickel carbonyl is predicted. In fact, the formation of I (R = R′ = CH_3) was confirmed by the infrared spectrum of the reaction mixture of lithium dimethylamide and nickel carbonyl. This carbamoyl complex also has a carbon–metal σ bond; so it is expected that the complex undergoes reaction with acetylenic compounds to give succinic acid amide derivatives directly. In the case of lith-

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(2) Y. Sawa, I. Hashimoto, M. Ryang, and S. Tsutsumi, *J. Org. Chem.*, **33**, 2159 (1968).

ium dimethylcarbamoylnickel carbonylate and phenylacetylene, 2-phenyl-N,N,N′,N′-tetramethylsuccinamide (40.7%) and N,N-dimethylcinnamamide (0.6%) were obtained from the reaction in ether at 20°. From acetylenic compounds and nickel carbonyl, acrylic acid derivatives can be obtained by the Reppe reaction,[3] but succinic acid derivatives cannot be obtained. Natta and Albanesi[4] have reported that succinic acid was obtained by the reaction of acetylene with carbon monoxide (250 atm) using $Co_2(CO)_8$ at 110°. On the other hand the succinamide derivative is easily obtained under mild conditions by the present reaction.

Results and Discussion

Treatment of Lithium Dimethylamide with Nickel Carbonyl.—The infrared spectrum of nickel carbonyl shows only one peak at 2057 cm^{-1} in ether or tetrahydrofuran (THF), but when nickel carbonyl is added to the ether (or THF) solution of lithium dimethylamide, the infrared spectrum shows new peaks at 1978 (s), 1958 (m) (terminal metal carbonyls), and 1560 cm^{-1} (broad) in addition to the original peak at 2057 cm^{-1}. As the peak at 1560 cm^{-1} is thought to be due to the carbonyl stretching vibration of the carbamoyl group bonding to nickel atom directly,[5] it is reasonable to consider that nickel carbonyl underwent reaction with lithium dimethylamide to give a carbamoylnickel complex with high electron density on the nickel atom (eq 1). This complex reacts with

$$LiN(CH_3)_2 + Ni(CO)_4 \xrightarrow{\text{ether or THF}} Li[(CH_3)_2NC(=O)Ni(CO)_3] \quad (1)$$

mercuric chloride in THF to give N,N,N′,N′-tetramethyloxamide [30.1 % based on used $LiN(CH_3)_2$], N,N,N′,N′-tetramethylurea (0.2%), and metallic mercury (eq 2).

$$2Li[(CH_3)_2NC(=O)-Ni(CO)_3] + HgCl_2 \xrightarrow{THF} (CH_3)_2NC(=O)-C(=O)N(CH_3)_2 + Hg + 2LiCl + 2(Ni + CO) \quad (2)$$

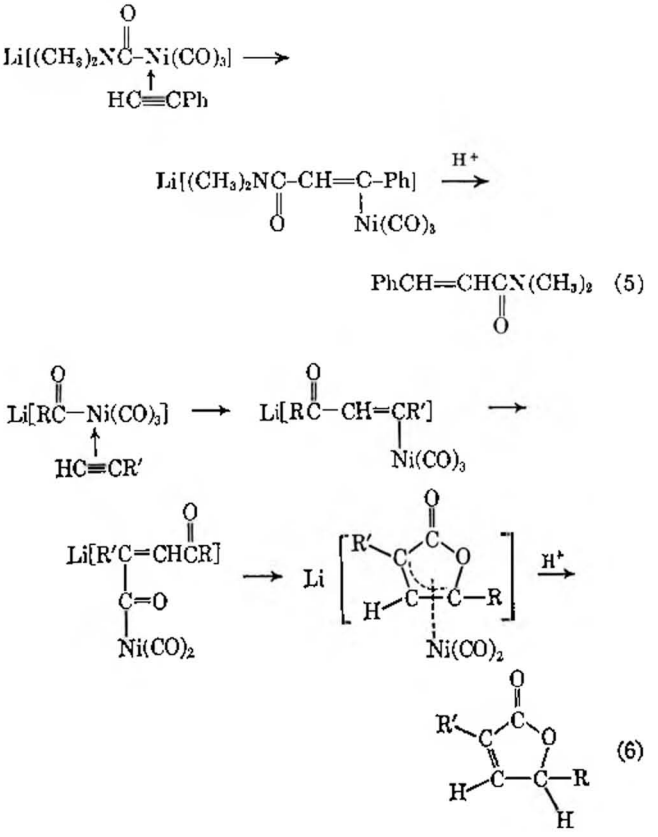
The carbamoylnickel complex is remarkably different from lithium aroylnickel carbonylate in thermal stability and decomposition behavior. That is, lithium aroylnickel carbonylate gives ketone or α-diketone by its decomposition at room temperature, and gives acyloin by hydrolysis at low temperature.[2] On the other hand, the carbamoyl complex is moderately stable at room temperature in solution and does not give a compound corresponding to acyloin or dimethylformamide by hydrolysis with diluted hydrochloric acid but gives only dimethylamine hydrochloride (62%).

Treatment of Phenylacetylene with Lithium Dimethylcarbamoylnickel Carbonylate.—Phenylacetylene undergoes reation with lithium dimethylcarbamoylnickel carbonylate in ether or THF to give 2-phenyl-N,N,N′,N′-tetramethylsuccinamide as a main product and N,N-dimethylcinnamamide as a minor product (eq 3).

$$2Li[(CH_3)_2NC(=O)Ni(CO)_3] + PhC{\equiv}CH \xrightarrow{H^+} (CH_3)_2NC(=O)-CH(Ph)-CH_2C(=O)N(CH_3)_2 \quad (3)$$

This reaction is analogous to the reaction of lithiumacyl nickel carbonylate with acetylenic compounds[2] (eq 4). The mechanism of the formation of 2-phenyl-N,N,N′,N′-tetramethylsuccinamide and 1,4-diketone are not clear. But the mechanism of the formation of N,N-dimethylcinnamamide and unsaturated five-membered-ring lactone, minor products of eq 3 and 4, respectively, are thought to be as shown in eq 5 and 6.

$$2Li[RC(=O)-Ni(CO)_3] + R'C{\equiv}CR'' \xrightarrow{H^+} RC(=O)-CH(R')-CH(R'')-CR(=O) \quad (4)$$



(5)

(6)

Compared with the Reppe reaction the formation of N,N-dimethylcinnamamide in this reaction is interesting. In the Reppe reaction, monosubstituted acetylenes react with nickel carbonyl and hydrochloric acid in the presence of water, or an alcohol, or an amine to give compounds of the type $RC(COY) = CH_2$ (Y = OH, OR, NR′R″). In the above reaction it was thought that a proton of the hydronickel carbonyl adds to the terminal carbon atom of the monosubstituted acetylenes and nickel adds to the inner carbon atom to give an alkylnickel complex and the insertion of carbon monoxide into the carbon–nickel bond occurs, followed by hydrolysis, alcoholysis, or aminolysis,[6] but in an acyl–metal complex with a carbon–metal σ

(3) W. Reppe, *Ann. Chem.*, **582**, 1 (1953).
(4) G. Natta and G. Albanesi, *Chim. Ind.* (Milan), **48**, 1157 (1966).
(5) π-Cyclopentadienyl dialkylcarbamoyliron dicarbonyl prepared by R. B. King shows a $\nu_{C=O}$ peak at 1535 ± 10 cm^{-1}: *J. Amer. Chem. Soc.*, **85**, 1918 (1963).
(6) P. L. Pauson, *Proc. Chem. Soc.*, 297 (1960).

bond, the acyl group generally tends to add to the terminal carbon of the monosubstituted acetylenes. In fact, in the case of the reaction of phenylacetylene with a carbamoyl nickel complex, cinnamamide was obtained, and atropic acid amide (product of the Reppe reaction) was not detected.

Experimental Section

All reactions were carried out under nitrogen. Yields were calculated based on the used lithium dimethylamide.

Reaction of Lithium Dimethylamide with Nickel Carbonyl.—*n*-Butyllithium (0.025 mol) was added dropwise to dimethylamine (0.1 mol) dried with potassium hydroxide, and then excess dimethylamine was removed at 40°. The ether (or THF) (20 ml) solution of nickel carbonyl (0.025 mol) was added dropwise to the ether (or THF) solution of lithium dimethylamide at −70°. Then the solution was stirred 5–10 hr at 20°. The infrared spectrum of the orange-red colored reaction mixture showed peaks at 2057 (s) ($\nu_{C\equiv O}$ of nickel carbonyl), 1978 (s) and 1958 (m) ($\nu_{C\equiv O}$ of terminal carbonyl of the anionic complex), and 1560 cm^{-1} (broad) (ν_{C-O} of carbamoyl group directly bonded to nickel). When the solvent was removed from this solution under reduced pressure, an orange-red powder was obtained. This powder was unstable in air and spontaneous ignition occurred. This complex was not isolated pure, but was treated with mercuric chloride (0.01 mol) in THF at −40° (5 hr) to give N,N,N′,N′-tetramethyloxamide 0.055 g (30.1%) and N,N,N′,N′-tetramethylurea 0.002 g (0.2%) as organic products. Mercury and lithium chloride were also obtained as inorganic products. Organic products were confirmed by gas chromatography (column: SE 30, 2.25 *M*, 120–200°; He 7.5 cc/min). When the carbamoyl solution was hydrolyzed by 25 ml of 3 *N* hydrochloric acid, 1.01 g (62%) of dimethylamine hydrochloride was obtained and no compounds resulting from carbon monoxide insertion were obtained.

Reaction of Phenylacetylene with Lithium Dimethylcarbamoylnickel Carbonylate.—Phenylacetylene (5.1 g, 0.05 mol) was added to the ether solution of lithium dimethylcarbamoylnickel carbonylate (0.05 mol) and the mixture was stirred for 4 hr at 20°. After ether and remaining nickel carbonyl were removed under reduced pressure, benzene (150 ml) was added and then 2 *N* hydrochloric acid (80 ml) was added with cooling. From the water-soluble part, 0.50 g (12.4%) of dimethylamine hydrochloride was obtained. The benzene-soluble part was distilled under reduced pressure after removal of benzene to give fractions (1) bp 100–150° (0.6 mm) and (2) bp 150–200° (0.6 mm) in yields of 2.23 g and 0.55 g, respectively. A part of these fractions was separated by column chromatography [silica gel, petroleum ether (bp 35–65°)] to give triphenylbenzene (mixture of 1,3,5- and 1,2,4-) [mp 108–112°; white crystals; nmr, τ 2.5–3.0 (multiplet)] and all-*trans*-1,4-diphenylbutadiene [mp 147.5–149° (white needles)] which were confirmed by a comparison of the infrared spectrum and a mixture melting point determination with an authentic sample prepared by a Wittig reaction of cinnamyl bromide with benzaldehyde. By the recrystallization of these fractions using petroleum ether–benzene, 2-phenyl-N,N,-N′,N′-tetramethylsuccinamide, and N,N-dimethylcinnamamide were obtained. A gas chromatographic analysis (column: SE 30, 2.25 *M*, 200°; He 7.5 cc/min) of fractions 1 and 2 showed that these fractions consisted of 2-phenyl-N,N,N′,N′-tetramethylsuccinamide (2.52 g, 40.7%), N,N-dimethylcinnamamide (0.05 g, 0.6%), a trace of triphenylbenzene, and a trace of all-*trans*-1,4-diphenylbutadiene. 2-Phenyl-N,N,N′,N′-tetramethylsuccinamide had mp 93.1–93.8° (white crystals); the infrared absorptions (KBr) appeared at 3025 (w), 2980 (w), 2810 (m), 1645 (sh), 1630 (vs), 1620 (sh), 1590 (m), 1495 (m) 1458 (m), 1415 (m), 1390 (s), 1268 (s), 1130 (s), 765 (s), 725 (m), and 703 (s) cm^{-1}. The nmr spectrum showed peaks (in τ) at 7.6 (multiplet, 1 H), 7.1 (singlet, 12 H), 6.6 (multiplet, 1 H), 5.6 (multiplet, 1 H), and 2.8 (singlet, 5 H).

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28; mol wt, 248. Found: C, 67.60; H, 8.20; N, 11.27; mol wt, 258 (osmometer in benzene, 25°).

The structure of N,N-dimethylcinnamamide, mp 100.6–101.5° (white needles), was confirmed by mixture melting point determination and infrared and nmr spectral comparison with an authentic sample.

The same reaction was carried out under different conditions. The results are listed in Table I.

TABLE I
YIELDS OF PRODUCTS

Solvent	Temp. °C	Time, hr	% yield: $PhCHCON(CH_3)_2$ | $CH_3CON(CH_3)_2$	% yield: PhCH ‖ $HCCON(CH_3)_2$	% yield: $(CH_3)_2NNHCl$
Et_2O	20	4	40.7	0.6	12.4
Et_2O	−70	33	7.5	4.5	28.8
THF	20	4	14.1	0.2	10.1
THF	−70	33	6.0	0.8	20.8

Registry No.—Phenylacetylene, 536-74-3; nickel carbonyl, 13463-39-3; lithium dimethylamide, 3585-33-9; 2-phenyl-N,N,N′,N′-tetramethylsuccinamide, 16607-43-5.

Reaction of ω-Chloro Ketones with Methylenetriphenylphosphorane[1]

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Received October 13, 1967

In another investigation we required a series of homologous chloro olefins of structure **1** (R = CH_2). As a series of chloro ketones (**1**, R = O) was available from a previous investigation,[3] we investigated the possibility of direct conversion of the chloro ketones into the chloro olefins utilizing methylenetriphenylphosphorane.

$$C_6H_5C(=R)(CH_2)_nCl$$

1

It appears that relatively few investigations of the action of Wittig reagents on halo ketones have been carried out.[4] Siemiatycki and Strzelecka[5] have reported that the reaction of phenacyl bromide with phenacylidenetriphenylphosphorane produced *trans*-dibenzoylethylene (50%), *trans*-1,2,3-tribenzoylcyclopropane (7%), and a nearly quantitative yield of phenacyltriphenylphosphonium bromide. The authors proposed a mechanism for product formation involving phenacyl carbene. Surprisingly, carrying out the reaction in the presence of *cis*-dibenzoylethylene did not result in an increase in the yield of the cyclopropane derivative.[5] Maercker[4] has suggested that the cyclopropane derivative is formed by a Micheal addition of the ylide to dibenzoylethylene followed by ring closure involving an intramolecular displacement.

Bestmann and Schulz[6] have reported that the reaction of phenacyl bromide with carbomethoxymethylenetriphenylphosphorane produced benzoylcarbome-

(1) Research supported by the National Science Foundation, Grant GP-4497.

(2) (a) Alfred P. Sloan Research Fellow, 1967–1969; (b) NASA Predoctoral Trainee.

(3) D. J. Pasto and M. P. Serve, *J. Amer. Chem. Soc.*, **87**, 1515 (1965).

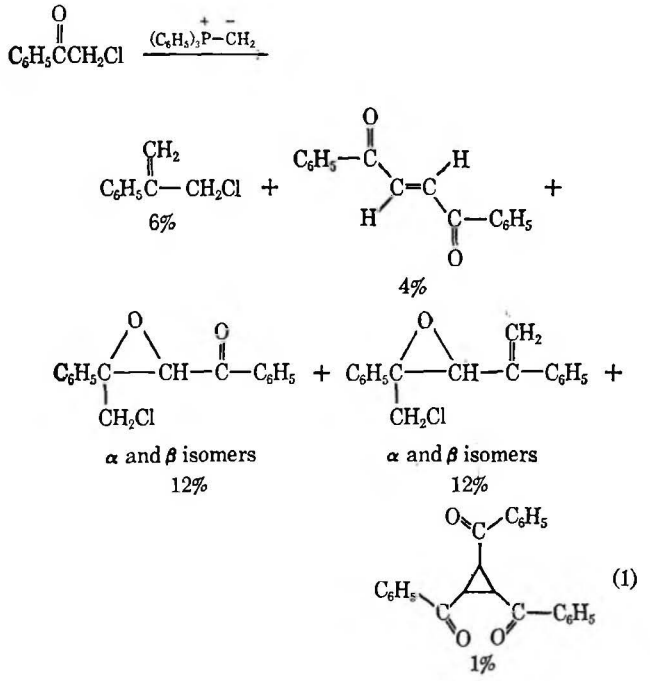
(4) For a recent review, see A. Maercker, *Org. Reactions*, **14**, 270 (1965).

(5) M. Siemiatycki and H. Strzelecka, *Compt. Rend.*, **250**, 3489 (1960).

(6) H. J. Bestmann and H. Schulz, *Angew. Chem.*, **73**, 620 (1961).

thoxyethylene and triphenylphosphine. These authors propose a mechanism involving displacement by the ylide on phenacyl bromide followed by the elimination of proton and triphenylphosphine. Neither of the previous groups of investigators observed the formation of products derived by addition of the Wittig reagent to the carbonyl group. With this limited amount of information available on the reaction of chloro ketones with Wittig reagents we undertook an investigation of the reactions of **1** (R = O) with methylenetriphenylphosphorane.

The reaction of phenacyl chloride produced in low yield the complex mixture of products illustrated in eq 1.



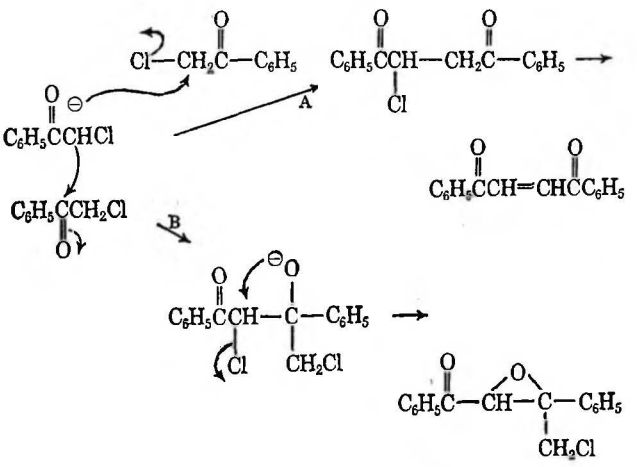
(1)

The mixture of isomeric 4-chloro-2,3-epoxy-3-phenylbutyrophenones was composed of mostly the β isomer.[7] The 5-chloro-3,4-epoxy-2,4-diphenyl-1-pentene fraction consisted of approximately 75% olefin derived from the β isomer and 25% olefin derived from the α isomer.

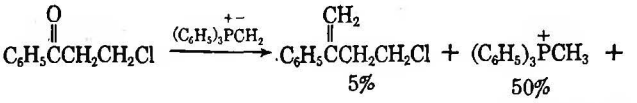
The similarity of the products derived in this reaction with those obtained in various base-catalyzed reactions involving phenacyl chloride[7] suggests that common intermediates are involved in both types of reactions and that the involvement of carbene intermediates does not appear to be necessary.[8] The mechanism for product formation is best represented as involving the formation of phenacyl chloride enolate anion which then affects the nucleophilic displacement of chloride from phenacyl chloride producing 3-chloro-1,4-diphenyl-1,4-butanedione (path A), or undergoes addition to the phenacyl chloride carbonyl group (path B). Michael addition of phenacyl chloride enolate anion to the dibenzoylethylene, formed *via* path A, gives rise to the tribenzoylcyclopropane.

(7) J. A. Berson, *J. Amer. Chem. Soc.*, **74**, 5175 (1952), and references cited therein.

(8) The reaction of phenacyl chloride with methylenetriphenylphosphorane in the presence of a great excess of cyclohexene did not produce any 7-benzoylnorcarane.

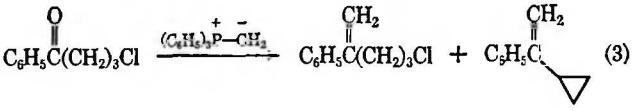


Treatment of 3-chloropropiophenone produced only low yields of the normal Wittig product 4-chloro-2-phenyl-1-butene. Considerable methyl triphenylphosphonium salt was produced in addition to an unidentified phosphorus-containing compound (see Experimental Section for the details).



unidentified material (2)

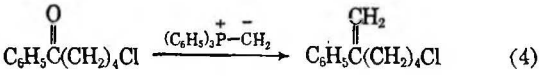
The reaction of 4-chlorobutyrophenone produced respectable yields of a mixture of 1-cyclopropyl-1-phenylethylene (35%), 5-chloro-2-phenyl-1-pentene (30%), trace quantities of cyclopropyl phenyl ketone, and methyltriphenylphosphonium chloride (see eq 3).



(3)

The 1-cyclopropyl-1-phenylethylene is formed *via* the enolate of 4-chlorobutyrophenone which undergoes ring closure to give cyclopropyl phenyl ketone which then reacts further with the Wittig reagent in the normal fashion.

The reaction of 5-chlorovalerophenone with methylenetriphenylphosphorane produces only 6-chloro-2-phenyl-1-hexene in 60% yield (eq 4). Products derived by a proton abstraction mechanism were not detected.



(4)

In all cases, except with 5-chlorovalerophenone, the major reaction path in the reaction of the halo ketones with methylenetriphenylphosphorane involves enolate anion formation with subsequent reactions of the enolate anions giving rise to side-reaction products. With 5-chlorovalerophenone the corresponding enolate may be formed in a reversible reaction but no low energy reaction pathway is immediately available for further reaction thus increasing the probability of ylide attack on the carbonyl group.

Experimental Section

Reaction of Phenacyl Chloride with Methylenetriphenylphosphorane.—To a solution of 9.2 g (0.06 mol) of phenacyl chloride in 50 ml of tetrahydrofuran at −10° was slowly added 0.06 mol of methylenetriphenylphosphorane, prepared from 0.06 mol of methyltriphenylphosphonium bromide in 60 ml of tetrahydrofuran on treatment with 0.06 mol of *n*-butyllithium in hexane (Foote Mineral). The reaction mixture was stirred at room temperature overnight and then refluxed for 30 min. Most of the tetrahydrofuran was removed by distillation. The residue was extracted with several portions of hexane. The hexane extract was washed once with 50 ml of dimethyl sulfoxide–water (1:1) and water and then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The residue (3.15 g) was chromatographed on Florisil giving the following fractions.

Fractions 1 and 2 eluted with hexane gave 0.55 g of a colorless liquid, bp 50–52° at 0.4 mm (for α-chloromethylstyrene lit.[9] 68° at 2 mm). The infrared spectrum (neat liquid) showed no carbonyl absorption, but displayed an intesnse band at 911 cm^{-1} ($C{=}CH_2$). The nmr of the liquid in deuteriochloroform displayed a doublet at −4.45 (2 H, $-CH_2Cl$, J = 0.6 Hz), two broadened singlets at −5.45 and −5.55 (1 H each, $=CH_2$ and a multiplet at −7.3 ppm (5 H, aromatic hydrogens).

Fractions 3 and 4 eluted with hexane–ether (4:1) produced a very viscous liquid with bp 147–149° (0.3 mm). The infrared spectrum displayed no carbonyl absorption but indicated the presence of a terminal methylene producing an absorption peak at 906 cm^{-1}. The nmr spectrum of the sample indicated a mixture of two compounds: complex multiplet centered near −4.0, two equally intense broadened singlets at −5.03 and −5.23, two weak broadened singlets of equal intensity at −5.38 and −5.62, and a complex multiplet at −7.3 ppm. The peaks due to the major component were identical in position and shape with 5-chloro-3,4-epoxy-2,4-diphenyl-1-pentene (see below).

Fraction 5 produced 0.2 g of a pale yellow viscous liquid. The infrared spectrum displayed carbonyl absorption at 1675 cm^{-1} with no absorption in the 900-cm^{-1} region. The material was identical by thin layer chromatography with *trans*-dibenzoylethylene on silica gel employing benzene, chloroform, hexane, and hexane–ether (3:1) solvent systems.

Fraction 6 gave 0.11 g of a crystalline material with mp 103–117°. The infrared spectrum showed carbonyl absorption at 1680 cm^{-1}. The nmr spectrum indicated the fraction was composed of a mixture of probably the α (lit.[10] mp 117–119°) and the β isomers of 4-chloro-2,3-epoxy-3-phenylbutyrophenone.

Fractions 7 through 9 produced 0.75 g of the β isomer of 4-chloro-2,3-epoxy-3-phenylbutyrophenone, mp 145–150° (lit.[10] 147–148°) undepressed on addition of authentic material. The infrared spectrum displayed carbonyl absorption at 1680 cm^{-1}. The nmr spectrum displayed a singlet at −4.35 (1 H, $>CH-CO$), AB doublets centered at −3.89 and −3.99 with J = 12.0 Hz (1 H each, $-CH_2Cl$), and complex multiplets centered at −7.48 and −8.02 ppm (5 H total, aromatic hydrogens).

Fraction 10 produced 0.1 g of a white crystalline material believed to be tribenzoylcyclopropane, mp 215–219 (lit.[5] 221–222°). The infrared spectrum showed carbonyl absorpion at 1680 cm^{-1}.

Preparation of 5-Chloro-3,4-epoxy-2,4-diphenyl-1-pentene.—To a solution of 5.5 g (0.02 mol) of the β isomer of 4-chloro-2,3-epoxy-3-phenylbutyrophenone[10] in 40 ml of tetrahydrofuran at −78° was added 0.2 mol of methylenetriphenylphosphorane. The reaction mixture was stirred at room temperature over night and worked up as described above. Distillation of the product, bp 147–149° at 0.3 mm, gave a viscous colorless liquid.

The nmr spectrum of the olefin displayed AB doublets at −3.84 and −4.00 with J = 12.4 Hz (1 H each, $-CH_2Cl$), a broadened singlet at −3.68 [1 H, $-CH-C(=CH_2)-$], two multiplets at −5.03 and −5.23 (1 H each, $>C{=}CH_2$), and a multiplet at −7.3 ppm.

Anal. Calcd for $C_{17}H_{15}OCl$: C, 75.41; H, 5.58; Cl, 13.10. Found: C, 75.69; H, 5.35; Cl, 13.00.

Reaction of 3-Chloropropiophenone with Methylenetriphenylphosphorane.—To a solution of 10.8 g (0.065 mol) of 3-chloropropiophenone in 75 ml of tetrahydrofuran was added 0.065 mol of methylenetriphenylphosphorane. The reaction mixture was stirred overnight at room temperature and was then refluxed for 2 hr. Water (300 ml) was added and the reaction mixture was extracted wih hexane–ether (50:50). The extract was washed with water and dried over anhydrous magnesium sulfate.

The aqueous layer were combined and concentrated on a rotary flash evaporator giving a pale yellow residue which partially crystallized. The material was removed by filtration giving 6.1 g of pale yellow semicrystalline material. The material could not be purified by recrystallization. Analysis by thin layer chromatography on silica gel using methanol as eluent indicated the presence of methyltriphenylphosphonium ion (by comparison of authentic material) and a second unidentified material. The nmr spectrum of the sample in deuteriochloroform displayed a doublet at −3.14 corresponding to methyltriphenylphosphonium ion in addition to the following peaks: −0.92 ppm broadened triplet of apparent 2 H intensity, −1.6-ppm multiplet with apparent 2 H intensity, −2.88-ppm doublet of apparent 2 H intensity with J_{HP} = 13.2 Hz, and aromatic hydrogen absorption. The infrared spectrum of the mixture showed no absorption in the carbonyl region. The sample was stable at 90° for a period of 3 days.

Evaporation of the organic extract from above gave a small amount of a pale yellowish liquid which was purified by chromatography on Florisil giving 4-chloro-2-phenyl-1-butene, bp 40° (0.2 mm).

The nmr spectrum in deuteriochloroform displayed a multiplet at −2.88 (2 H), a multiplet at −3.48 (2 H), broadened singlets at −5.15 and −5.35 (1 H each), and a multipet at −7.3 ppm (5 H).

Anal. Calcd for $C_{10}H_{11}Cl$: C, 72.07; H, 6.65. Found: C, 72.06; H, 6.70.

Reaction of 4-Chlorobutyrophenone with Methylenetriphenylphosphorane.—To a solution of 19.0 g (0.1 mol) of 4-chlorobutyrophenone in 100 ml of tetrahydrofuran was added 0.1 mol of methylenetriphenylphosphorane. The reaction mixture was stirred overnight at room temperature and was then refluxed for 1.5 hr. Water (300 ml) was added and the mixture was extracted with hexane–ether (50:50). The hexane–ether extract was fractionally distilled giving three fractions: fraction 1, 1.35 g, bp 38–42° (0.3 mm), identified as α-cyclopropylstyrene by infrared and nmr spectral and glpc retention time comparison with authentic material (see below); fraction 2, 1.70 g, 63–64° (0.3 mm), identified as cyclopropyl phenyl ketone[11] by infrared and nmr spectral and glpc retention time comparison with authentic material (Aldrich Chemical Co.); fraction 3, 5.35 g, bp 75–81° (0.3 mm) identified as 5-chloro-2-phenyl-1-pentene. The sample was redistilled giving pure material with bp 59–62° (0.1 mm). The nmr spectrum recorded in deuteriochloroform displayed the following peaks: multiplet at −1.87 (2 H, $-CH_2-CH_2Cl$), broad triplet at −2.71 (2 H, $-C-CH_2(=CH_2)-$), triplet at −3.51 (2 H, $-CH_2Cl$), broadened singlets at −5.03 and −5.23 (1 H each, $>C{=}CH_2$), and a multiplet at −7.27 ppm (5 H, aromatic hydrogens).

Anal. Calcd for $C_{11}H_{13}Cl$: C, 73.12; H, 7.25. Found: C, 73.29; H, 7.09.

Prepartion of α-Cyclopropylstyrene.—Cyclopropyl phenyl ketone (2.97 g, 0.02 mol) was treated with methylenetriphenylphosphorane (0.02 mol) as described above giving 2.0 g of product, bp 63.5° (3 mm).

Reaction of 5-Chlorovalerophenone with Methylenetriphenylphosphorane.—A solution of 6.0 g (0.03 mol) of 5-chlorovalerophenone in 50 ml of tetrahydrofuran was treated with 0.03 mol of methylenetriphenylphosphorane as described above. Distillation of the crude product gve a relatively unstable, colorless liquid, bp 95–97 (0.1 mm).[12] The nmr spectrum displayed the following peaks: broad multiplet at −1.90 (4 H, $CH_2CH_2CH_2Cl$), broadened triplet at −2.70 (2 H, $-C-CH_2(=CH_2)$), triplet at −3.45 (2 H, $-CH_2Cl$), broadened singlets at −5.00 and −5.22 (1 H each, $>C{=}CH_2$), and a multiplet at −7.25 ppm (5 H, aromatic hydrogens).

Registry No.—Methylenetriphenylphosphorane, 3487-44-3; 5-chloro-3,4-epoxy-2,4-diphenyl-1-pentene, 16675-49-3; 4-chloro-2-phenyl-1-butene, 5747-05-7; 5-chloro-2-phenyl-1-pentene, 16675-51-7; α-cyclopropylstyrene, 825-76-3.

(9) M. F. Hawthorne, *J. Amer. Chem. Soc.*, **82**, 1886 (1960).

(10) O. Widman, *Ann.*, **400**, 86 (1913).

(11) T. A. Favorskaya, N. V. Shcherbinskaya, and S. E. Chernobel'skaya [*Zh. Obshch. Khim.*, **20**, 855 (1950)] report bp 88–90° (8 mm).

(12) A satisfactory elemental analysis could not be obtained. The material on standing appeared to undergo polymerization.

Epimers of 1,3,5-Cyclohexanetricarboxylic Acid

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Amoco Chemical Corp., Whiting, Indiana 46394

Received October 30, 1967

The hydrogenation of the trimethyl ester of trimesic acid with Raney nickel catalyst produced mainly *cis*-1,3,5-cyclohexanetricarboxylic acid, since after hydrolysis of the hydrogenated ester and crystallization, only a single compound, mp 216–218°, was isolated.[1,2]

This work reports the hydrogenation of the free acid in an aqueous slurry using palladium on carbon as catalyst. The composition of the product of the hydrogenation of trimesic acid was established indirectly by a procedure which involved first the esterification and then gas chromatographic analysis of the triesters. It was independently verified that no epimerization occurred during the procedure. This procedure leads to the conclusion that the hydrogenation of the acid produced the two possible epimers in 22:78 ratio (in order of elution).

The minor isomer is regarded as having the *trans* configuration (II) with two carboxyls in the equatorial position and one in the axial, while the major isomer is assumed to have all of the carboxyl groups equatorial (I). These assignments are based on the following arguments: (1) three *cis* additions of hydrogen during one act of adsorption on the catalyst producing the *cis* isomer should be more favorable than *cis* addition of hydrogen during successive acts of adsorption leading to the *trans* isomer, and (2) it has already been demonstrated[3] that the *trans*-dimethyl ester of 1,3-cyclohexanedicarboxylic acid appears before the *cis* isomer, and assuming a reasonable correlation of the molecular volumes and order of elution between the 1,3-diester and the 1,3,5-triester the *trans* epimer of the triacid would also be expected to elute before the *cis* epimer.

The pure *cis* epimer (I) of 1,3,5-cyclohexanetricarboxylic acid, mp 218–219° in agreement with the literature value, was isolated by crystallization from ethanol. It was at least 98% pure since the corresponding methyl ester showed this degree of purity by gas chromatography.

The *trans*-tricarboxylic acid could not be obtained in high degree of purity from the initial hydrogenation mixture since the *trans* acid is considerably more soluble than the *cis* isomer which greatly predominated. However, the pure *trans* epimer was isolated by epimerization of the original acid mixture.

It was found possible to effect a nearly complete conversion of the original hydrogenation mixture into pure *trans* epimer (II) by first, heating a solution of the acids in acetic anhydride containing sodium acetate, and then neutralizing the basic epimerization catalyst by refluxing with acetyl chloride, concentrating, and crystallizing from water. The *trans* epimer (II), mp 208–210°, was obtained in 96% purity as analyzed by gas chromatography following esterification. A possible explanation for the unusual selectivity of this epimerization is the conversion of the unstable *cis*(a,a,a) conformer of the triacid into the unstable *cis*-anhydride axial carboxyl followed by sodium acetate catalyzed epimerization into the *trans*-anhydride acid (III), which would undergo hydrolysis to the *trans* (e,a,a) conformer (IV) which equilibrates with the *trans* (a,e,e) conformer (II) (see Scheme I).

Equilibration of the original mixture of 22:78 *trans–cis* mixture of tricarboxylic acid obtained by hydrogenation was conveniently effected by keeping the mixture molten at 240° for 24 hr. The product of this treatment now contained the *trans–cis* acids in the ratio 56:44. The same equilibrium mixture was obtained by the same thermal treatment of the pure *trans* acid and the pure *cis* acid showing that equilibration had been obtained in this treatment.

The main question raised by these experiments concerns the reason for the formation of the equilibration mixture containing 56% *trans* and 44% *cis* isomer at 240°.

Equilibration of the acid isomers by maintaining them in a molten state for an extended period of time might be suspect of giving rise to hydrogen-bonded entities which would disturb the true thermodynamic epimer equilibrium. However, when a sample of mixed isomers of 1,3-cyclohexanedicarboxylic acid was held at 240° for 20 hr the composition became 63.8% *cis*.[4] Calculation of the equilibrium from the conformational free energy of the carboxyl group and applying the entropy of mixing term of $R \ln 2$ (based on the existence of the *trans* isomer as a racemate) favoring *trans* isomer as used by Allinger and Curby[3] gives a theoretical composition of 62% *cis*. Thus it is believed that hydrogen bonding is not significant at the high temperatures used for equilibration. Shifting of the equilibrium does not occur on cooling since the molten samples are shock chilled to their freezing point of 218°.

Calculation of a theoretical epimer equilibrium for 1,3,5-cyclohexanetricarboxylic acid may be made from the conformational free energy of a carboxyl group (1.2 kcal/mol[5] favoring equatorial conformation) by applying a comparatively large entropy term for the free energy of mixing of a compound having a symmetry number of 3 ($T\Delta S = RT \ln 3 = 1.12$ kcal/mol at 240°) which favors the *trans* epimer. This method of calculation predicts a value of 48% *trans* epimer, whereas 56% was found. It is not known why this theoretical treatment is not so applicable to epimerization of tricarboxylic acid systems as it is for dicarboxylic acids. However, the ring inversion forms for *trans*-1,3-cyclohexanedicarboxylic acid (a,e and e,a) are identical whereas the ring inversion form of *trans*-(a,e,e)-1,3,5-cyclohexanetricarboxylic acid (II), namely, *trans*-(a,a,e)-1,3,5-cyclohexanetricarboxylic acid may contribute to the energetics of equilibrium. This conformer is analogous to the diaxial carboxyl conformation of 1-*t*-butyl-3,5-cyclohexanedicarboxylic acid which exists in equilibrium with the diequatorial carboxyl and *trans* (a,e) forms.[6] At 240°, 3.8% of the 1-*t*-butyl-3,5

(1) J. M. Van der Zanden and G. De Vrees, *Rec. Trav. Chim. Pays-Bas*, **67**, 998 (1948).

(2) M. S. Newman and H. S. Lowrie, *J. Amer. Chem. Soc.*, **76**, 4598 (1954).

(3) N. L. Allinger and R. J. Curby, Jr., *J. Org. Chem.*, **26**, 933 (1961).

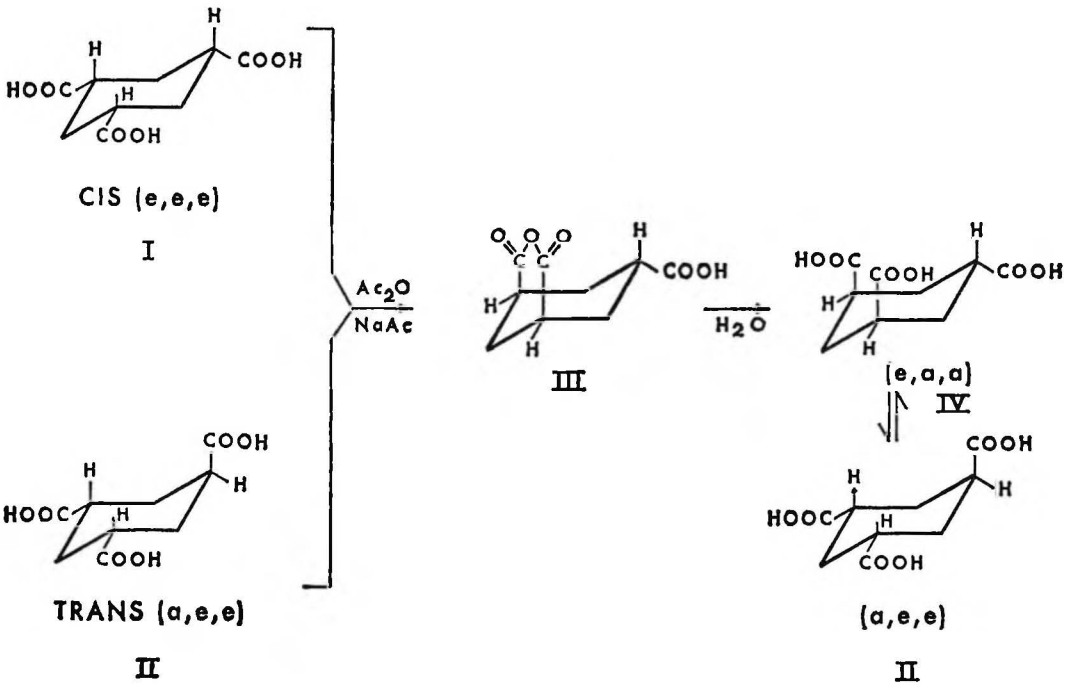
(4) A. Steitz, Jr., *Amer. Chem. Soc., Div. Petrol. Chem., Preprints*, **12**, No. 2, *D*162, 1967.

(5) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965; pp 43–44 and 57.

(6) B. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, **20**, 747 (1964).

SCHEME I

PREPARATION OF *trans*-1,3,5-CYCLOHEXANETRICARBOXYLIC ACID



(a,a)-cyclohexanedicarboxylic acid is formed as shown by gas chromatography of the equilibrated mixture after esterification. Armitage, *et al.*,[6] suggests that this third epimer of 1-*t*-butyl-3,5-cyclohexanedicarboxylic acid assumes the skew-boat conformation.

Experimental Section

Hydrogenation of Trimesic Acid.—A slurry of trimesic acid (three parts) in water (five parts) was hydrogenated at 150° and 1500 psig using as catalyst 5% palladium on carbon in the amount of 5% based on trimesic acid. Hydrogen uptake ceased in 3 hr. Catalyst was filtered from the otherwise homogeneous product. In order to preserve isomer ratio, the total solids (mp 175–206°, acid number 762 (theory 778), were recovered by evaporation of solvent rather than by crystallization. The solids were esterified with diazomethane[3] and analyzed by gas chromatography on a 10-ft column of silicone grease–Carbowax 6000 on Chromosorb W with the temperature programmed from 80 to 210°. The product consisted of 76.6% *cis* isomer, 21.4% *trans* isomer, and 2.0% dibasic acids.

***cis*-1,3,5-Cyclohexanetricarboxylic Acid.**—The hydrogenation product was dissolved in the minimum quantity of boiling ethanol, and toluene was added to decrease solubility. The crystals obtained on cooling were washed with chilled ethanol–toluene, and recrystallized in the same manner. The dried crystals melted at 218–219°; analysis showed that the product consisted of 1.5% *trans* isomer, 98% *cis* isomer, and 0.5% dibasic acids.

Anal. Calcd for $C_9H_{12}O_6$: C, 49.9; H, 5.55. Found: C, 50.2; H, 5.58.

***trans*-1,3,5-Cyclohexanetricarboxylic Acid.**—The hydrogenation product (5 g) was refluxed with 20 ml of acetic anhydride and 1 g of sodium acetate for 4 hr. The base was removed by refluxing 2 hr with 10 ml of acetyl chloride. Excess acetyl chloride was removed by distillation to an overhead temperature of 132°. The liquid mixture containing some sodium chloride crystals was poured into 400 ml of water. Evaporation to 5 ml and cooling gave a crystal crop, which was recrystallized from water, mp 208–210°. Analysis by esterification and gas chromatography showed 95.9% *trans* isomer, 2.5% *cis* isomer, and 1.7% dibasic acids.

Anal. Calcd for $C_9H_{12}O_6$: C, 49.9; H, 5.55. Found: C, 50.3; H, 5.58.

Thermal Equilibration.—Two-gram samples of the hydrogenation product and each of the pure isomers were heated in test tubes in a thermostatically controlled aluminum block at 240° for 24 hr. The molten samples were rapidly chilled to below their freezing point of 218°. The pulverized products were analyzed by esterification and gas chromatography, all products had substantially the same composition: 54.9 (± 0.3)% *trans* isomer, 43.5 (± 0.6)% *cis* isomer, and 1.6 (± 0.7)% dibasic acids.

Registry No.—I, 16526-68-4; II, 16526-69-5.

Phosphonitrilic Chloride as Activator of Carboxylic Acids. Formation of Amides and Hydrazides[1]

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Received January 2, 1968

Considerable advances have been made in the study of the chemical behavior of phosphonitrilic halides during the last decade.[2]

The simplest and best known member of this family of compounds, hexachlorocyclotriphosphatriazene **1**, reacts readily with a variety of compounds, like amines, alcohols, and phenols, to yield substitution products. The high reactivity of the halogen atoms and the observation that the high-temperature reaction of **1** with sodium benzoate resulted in the formation of benzonitrile and benzoic anhydride[3] prompted us to examine the possibility of using **1** or other phosphonitrilic chlorides as activators of carboxylic acids. It was expected that the reaction of an acid or its

(1) Work done with financial support of the Italian National Research Council (C. N. R.)

(2) See, for recent surveys, R. A. Shaw, *Chem. Ind.* (London), 1737 (1967); N. L. Paddock, *Quart. Rev.*, **18**, 168 (1964).

(3) I. I. Bezman and W. R. Reed, *J. Amer. Chem. Soc.*, **82**, 2167 (1960).

TABLE I

Acids[a]	Amines	Moles	$(PNCl_2)_3$, mol	Procedure	Solvent	Product	From	Yield,[b] %
α-Naphtylacetic	Aniline	6	0.3	A,B	THF, benzene, acetone	α-Naphtylacetanilide	CH_2Cl_2–heptane	73
α-Naphtylacetic	Cyclohexylamine	5	1.0	A,B	THF, benzene, acetone	N-Cyclohexyl-α-naphthylacetamide	Heptane	82
Palmitic	Cyclohexylamine	5	1.0	A,B	THF, benzene, THF–water 80:20	N-Cyclohexylpalmitamide	CH_2Cl_2–heptane	80
Benzoic	Aniline	6	1.0	B	THF, benzene, THF–water 80:20	Benzanilide	EtOH–water	83
Salicilic	NH_3	12	1.0	C	THF, benzene	Salicilamide	EtOH–water	60
p-Nitrocinnamic	Cyclohexylamine	7	0.5	B	THF, benzene, diethylene dioxide	N-Cyclohexyl-p-nitrocinnamide	CH_2Cl_2–heptane	70
12-Ketostearic	Cyclohexylamine	6	0.5	B	THF, benzene	N-Cyclohexyl-12-keto-stearamide	Heptane	65
Thiophen-2-carboxylic	Aniline	8	1.0	B	THF, benzene, diethylene dioxide	N-Phenylthiophen-2-carboxamide	CH_2Cl_2–heptane	75
α-Phenylcinnamic	Cyclohexylamine	12	1.0	C	THF, benzene, diethylene dioxide	N-Cyclohexyl-α-lithocolicamide	CH_2Cl_2–heptane	75
Lithocolic	Dimethylamine	6	1.0	B	THF, benzene, diethylene dioxide	N,N′-Dimethyllithocolic-amide	EtOH–water	63

[a] One mole. [b] Yields calculated on acid employed.

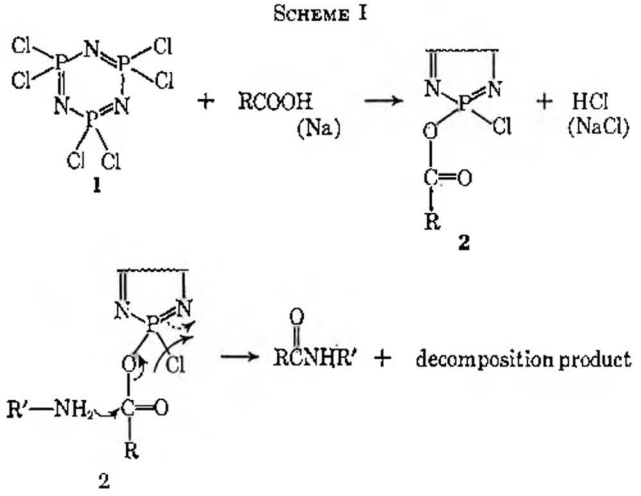
TABLE II

Acids[a]	Hydrazides	Moles	$(PNCl_2)_3$, mol	Procedure	Solvent	Product	From	Yield,[b] %
Palmitic	Hydrazine	6	1.0	A,B	THF, benzene	Palmitoylhydrazide	MeOH	76
Benzoic	Hydrazine	10	1.0	C	THF, benzene, cyclohexane	Benzoylhydrazide	MeOH–water	65
Phenylacetic	Phenylhydrazine	6	1.0	A,B	THF	Phenylacetophenylhydrazide	MeOH–water	65
α-Phenylcinnamic	Phenylhydrazine	6	1.0	B	THF	α-Phenylcinnamylphenylhydrazide	EtOH	60
Salicylic	Phenylhydrazine	10	0.5	B	THF, benzene	Salicylphenylhydrazide	EtOH	67
α-Naphthylacetic	p-Toluenesulfonylhydrazine	8	0.5	B	THF, benzene	N-p-toluenesulfonyl-N′-α-naphthyl-acetylhydrazide	EtOH	73

[a] One mole. [b] Yields calculated on acid employed.

salt with 1 would lead to an intermediate such as 2 (Scheme I); this, in turn, was expected to react with amines and hydrazines to yield the corresponding amides and hydrazides analogous to compounds of the type RCOOX=Y.[4]

SCHEME I



In fact, reaction of 1 with salts of carboxylic acids, followed by treatment of the reaction mixture with an excess of a primary or secondary amine, produced amides in very good yields. The reaction could be run in a variety of solvents (benzene, cyclohexane, tetrahydrofuran, tetrahydrofuran–water, ethyl acetate). Preformed sodium salts of carboxylic acids could be employed, but equivalent results were obtained by treating the free acid *in situ* with 1 equiv of triethylamine or a suitable primary or a secondary amine.

When a slurry of the sodium salt of the carboxylic acid was added to 0.35–1 equiv of 1 (calculated on a mole to mole basis), the precipitate of sodium chloride appeared at once.

A six- to tenfold excess of amine was then added and work-up of the reaction mixture yielded the corresponding amide.

The whole operation required no more than 20 min. Table I gives a list of amides prepared. Analogously, we prepared a number of hydrazides (Table II).

Our results indicated that 1 can be used as an activator in the conversion of the carboxylic function. The possibility of using a variety of solvents for the reaction, the simplicity of the operations involved, the high yields even with polyfunctional acids together with mild conditions, and the ready availability of the reagent 1 recommend the new route to amides and hydrazides.

Work is in progress to elucidate the mechanism of formation of the carboxy derivative from 1 as well as to widen the scope of the synthesis.

Experimental Section

Materials.—Hexachlorocyclotriphosphatriazene (1) was purchased from Albright and Wilson, England, and used without further purification. Thin layer chromatography to test the purity of the synthetic products was performed on Merck silica gel G.

Procedure A.—The sodium salt of the carboxylic acid (1 mol) was stirred in the solvent of choice (tetrahydrofuran, benzene, cyclohexane, tetrahydrofuran–water 80:20, ethyl acetate) with 0.35–1 mol of 1 at room temperature during 5–10 min; then a six- to tenfold excess of amine (or hydrazine) was added, and stirring was continued for 5–10 min.

A saturated solution of sodium bicarbonate was added and the mixture was extracted with diethyl ether. The organic layer was washed with water, dilute hydrochloric acid, and water again and dried over sodium sulfate.

The solvent was evaporated and the compound obtained was then purified by crystallization or by chromatography on silica gel.

Procedure B.—A solution of 1 mol of the acid and 1 mol of triethylamine in the solvent of choice (*vide supra*) was added

(4) J. Rudinger, *Pure Appl. Chem.*, 7, 335 (1963).

to 0.35–1 mol of **1** dissolved in the same solvent and was then treated as in procedure A.

Procedure C.—A solution of 1 mol of the acid and 1 mol of the amine to be used for the preparation of the amide in the solvent of choice (*vide supra*) was added to 0.35–1 mol of **1** dissolved in the same solvent and was then treated as in procedure A.

Registry No.—**1**, 940-71-6.

Acknowledgment.—We wish to thank Mr. G. Baccolini, who carried out some of the experiments, and Mr. G. Valentini for obtaining the elemental analyses.

Diaryliodosyl Salts[1]

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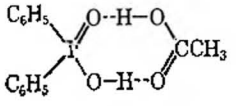
Received January 19, 1968

In 1935, Masson, Race, and Pounder[2] reported the self-condensation of iodoxybenzene in the presence of hydroxide ion to yield the first member of a new class of compounds called by the authors "diphenyliodyl hydroxide." It was isolated as an impure, unstable, amorphous solid which formed a moderately stable amorphous carbonate and a stable, crystalline acetate. Salts derived from strong acids were not isolated. Salts of carbonic and acetic acids were reported to be hydrogen-bonded cyclic complexes, such as "diphenyliodyl acetate" (I).[2,3] Strong acids, it was reasoned, do not readily undergo chelation or coordination and therefore the "diphenyliodyl salts" of strong acids undergo hydrolysis with consequent decomposition of the unstable hydroxide.

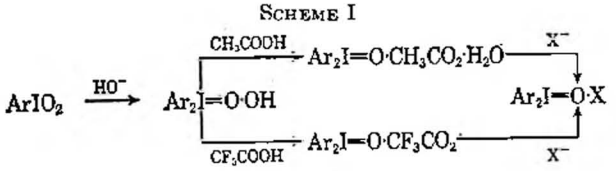


I

A study of this class of compounds which we have renamed "diaryliodosyl salts" has been initiated, and the synthesis and properties of several of these compounds are reported here.

Synthesis.—The method of preparation is a modification of that of Masson, *et al.*[2] according to Scheme I.

SCHEME I



X = F, Cl, Br, and IO_3

These compounds are colorless, nonvolatile, infusible solids. They are listed in Table I along with their respective decomposition points and yields. Solubility characteristics are described in the Experimental Section.

TABLE I

DIARYLIODOSYL SALTS

Diaryliodosyl salt	X (compd no.)[i]	Dec pt, °C	Yield,[a] %
$Ph_2I{=}O\cdot X$	$CH_3CO_2\cdot H_2O$	114[b]	50[d]
	(1)	114 dec[c]	75,[e] 50[f]
	CF_3CO_2 (2)	158 exp[i]	95[f]
	F (3)	197 exp	54[g]
	Cl (4)	181 exp	44[g]
	Br (5)	144 exp	49[g]
p-$(MeC_6H_4)_2I{=}O\cdot X$	IO_3 (6)	131–133 dec	78[f]
	CF_3CO_2 (7)	159 dec	65
	F (8)	170 exp	48[f]
p-$(FC_6H_4)_2I{=}O\cdot X$	CF_3CO_2 (9)	175 exp	14[f]
			36[h]
	F (10)	185 exp	53[g]
	Cl (11)	163 exp	44[g]

[a] Yields are of the unrecrystallized product. [b] Reported value (ref 2). [c] Observed value. [d] Reported yield (ref 2). [e] Observed yields; the higher was obtained by treating the carbonate with acetic acid, while the lower was obtained when the diphenyliodosyl hydroxide was neutralized directly with acetic acid. [f] Yield is based on starting iodoxy compounds. [g] Yield is based on parent diaryliodosyl trifluoroacetate. [h] Yield is based only on reacted *p*-fluoroiodoxybenzene; that is, on unrecovered starting material. (The *p*-fluoro group therefore not only retards the reaction but causes the iodoxy compound to be consumed in a different way.) [i] Explodes. [j] Registry no. are as follows: 2, 16317-00-3; 3, 16451-39-1; 4, 16503-27-8; 5, 16451-40-4; 6, 16317-04-7; 7, 16394-32-4; 8, 16451-41-5; 9, 16394-33-5; 10, 16451-42-6; 11, 16451-43-7.

Chemical Properties.—Diaryliodosyl salts are easily reduced to the corresponding iodonium salts by iodide, bisulfite, and hydrogen peroxide. Chloride and bromide are rapidly oxidized under acidic conditions probably according to the following equation.[2]

$$Ph_2I{=}O\cdot X + X^- + 2H^+ \longrightarrow Ph_2I^+ + X_2 + H_2O$$

4,4′-Dimethyldiphenyliodosyl fluoride and iodate are hygroscopic, forming hydrates on prolonged contact with air. The fluoride forms a monohydrate as confirmed by elemental analysis. Hydration of the iodate was not studied quantitatively. Attempted dehydration of diphenyliodosyl acetate was unsuccessful. More vigorous conditions than drying to constant weight at 25° and 2-mm pressure caused decomposition.

Ultraviolet Spectra.—Ultraviolet spectra of iodoxybenzene and diphenyliodosyl salts have previously not been reported, while those of iodobenzene[4–7] and diaryliodonium salts[7,8] have been studied in the 400–200-mμ region. Diphenyliodosyl salts and iodoxybenzene exhibit bands which are much broader than those of diphenyliodonium salts and iodobenzene; otherwise there are no distinguishing features. The spectrum of diphenyliodosyl trifluoroacetate, in water, has a band with a plateau extending from 216 to 227 mμ (log ε 4.12). Diphenyliodonium trifluoroacetate exhibits a

(1) This paper is largely based on part I of a dissertation submitted by P. Bodlaender in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, 1967.

(2) I. Masson, E. Race, and F. E. Pounder, Jr., *J. Chem. Soc.*, 1669 (1935).

(3) C. G. Le Fevre and R. J. W. Le Fevre, *ibid.*, 3373 (1950).

(4) K. Bowden and E. A. Braude, *ibid.*, 1071 (1952).

(5) H. E. Ungnade, *J. Amer. Chem. Soc.*, **76**, 434 (1952).

(6) W. F. Forbes, *Can. J. Chem.*, **37**, 1979 (1959).

(7) F. M. Beringer and I. Lillien, *J. Amer. Chem. Soc.*, **82**, 5135 (1960).

(8) H. Irving, G. P. A. Turner, and R. W. Reid, *J. Chem. Soc.*, 2082 (1960).

maximum at 227 mμ (log ε 4.19), and iodoxybenzene has a broad maximum at 224 mμ (log ε 3.94).[9-11]

Infrared Spectra.—The infrared absorption spectra of diaryliodosyl salts are similar to those of the corresponding iodonium salts except for strong, broad bands in the region 750–690 cm^{-1}; these have tentatively been attributed to I–O vibration. Intense bands originating in the iodine–oxygen system have previously been reported in this region (800–700 cm^{-1}) for inorganic iodates, iodic acid, iodine pentoxide,[12] and various organic iodoso and iodoxy compounds.[13] Absorption bands of diaryliodosyl salts in the 820–670-cm^{-1} region are given in the Experimental Section.[14]

The infrared absorption bands of the carboxylate group in diaryliodosyl carboxylates were compared with those of acetic acid dimer (hydrogen-bonded carboxylate), iodosobenzene acylates (covalently bound carboxylates),[15] and diaryliodonium and metal carboxylates (ionic).[16] It is apparent from Table II that absorption bands of the acetate and trifluoroacetate groups in the diaryliodosyl compounds are most similar to those bands obtained from ionic carboxylates. These correspond to the asymmetrical and symmetrical vibrations of the COO^- structure.

TABLE II
INFRARED ABSORPTION BANDS OF IONIC AND NONIONIC CARBOXYL GROUPS

	Absorption bands, cm^{-1}	
Ionic carboxylate	CO_2^- (asym)	CO_2^- (sym)
$CH_3CO_2^-Na^+$ [a]	1527 s	1408 s
$CH_3CO_2^-Ph_2I^+$ [b]	1545 s	1387 s
$Ph_2I{=}O\ CH_3CO_2{\cdot}H_2O$	1534 s	1380 s
$CF_3CO_2^-Na^+$ [c]	1680 s	1457 w
$CF_3CO_2^-Ph_2I^+$ [b]	1650 s	*d*
$Ph_2I{=}O{\cdot}CF_3CO_2$ [b]	1640 s	...
$(p\text{-}CH_3C_6H_4)_2I{=}O{\cdot}CF_3CO_2$ [b]	1640 s	
$(p\text{-}FC_6H_4)_2I{=}O{\cdot}CF_3CO_2$	1646 s	
Covalent carboxylate	C=O stretch	C–O stretch
$PhI(O_2CCH_3)_2$ [e]	1625 and 1640 s	1275 s
$PhI(O_2CCF_3)_2$ [f]	1700 and 1740 s	...
Hydrogen-bonded carboxylate	C=O stretch	
$(CH_3CO_2H)_2$ [g]	1735 s	

[a] The spectrum is of a finely powdered solid: C. Duval, J. Leconte, and F. Dowville, *Ann. Phys.*, 17, 5 (1942). [b] Nujol mull. [c] The spectrum is of a finely powdered solid: W. Klemperer and G. C. Pimentel, *J. Chem. Phys.*, 22, 1399 (1954). [d] A definite assignment could not be made. [e] Nujol mull.[13] [f] Nujol mull, C–O bond was not identified: N. W. Alcock and T. C. Waddington, *J. Chem. Soc.*, 4103 (1963). [g] The spectrum was taken of the vapor: L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 165.

(9) For further details, see P. Bodlaender, Ph.D. Dissertation, Polytechnic Institute of Brooklyn, 1967.

(10) Iodobenzene and diphenyliodonium iodide have been reported to exhibit maxima at 207 and 204 mμ, respectively, and a longer wavelength band at 226 mμ.[7,11] The lower wavelength bands were identified as a shifted first primary (^1L_a) band of benzene, and the 226-mμ band was interpreted as being due to an $n \rightarrow \pi^*$ excitation of the iodine chromophore. Before the 207-mμ band was reported for iodobenzene, the 226-mμ band had been assumed to be the shifted primary (^1L_a) band of benzene. In the present work the ultraviolet spectra of several diphenyliodonium salts and iodobenzene were reexamined; maxima were not found in the 220–200-mμ region. Bowden, *et al.*,[4] and Forbes,[5] who have previously published the ultraviolet spectra of iodobenzene down to 200 mμ, also did not report any peaks in the lower end of the spectrum. These bands are also missing in the spectra of iodoxybenzene and diphenyliodosyl salts. The maxima previously reported in this region probably resulted through an instrumental error.

(11) H. H. Jaffé and M. Orchin, "Theory and Application of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1964, pp 251–252, 504–505.

(12) F. A. Miller and C. H. Wilkins, *Anal. Chem.*, 24, 1253 (1952).

(13) (a) C. Furlani and G. Sartori, *Ann. Chim.* (Rome), 47, 174 (1957); (b) R. Bell and K. J. Morgan, *J. Chem. Soc.*, 1209 (1960).

(14) The I–O bands obtained from iodoxybenzene in solution are shifted considerable from those of the solid.[13b] Similar changes should therefore be expected for diphenyliodosyl salts.

(15) W. D. Johnson and N. V. Riggs, *Aust. J. Chem.*, 8, 457 (1955).

(16) F. M. Beringer and M. Mausner, *J. Amer. Chem. Soc.*, 80, 4535 (1958).

(17) Approximate decomposition points of diaryiodosyl salts were obtained. Then, new samples were introduced 5° below this point and the temperature was raised 2° per min. This procedure was repeated until reproducible decomposition points were obtained. Diaryliodonium salts were introduced 10° below their melting point as previously described.[18] A Thomas–Hoover capillary melting point apparatus was used. Ultraviolet spectra were measured on a Perkin-Elmer Model 350 spectrophotometer in the 400–200-mμ region. Infrared spectra were measured on a Perkin-Elmer Model 521 grating spectrophotometer. Elemental analyses were performed by Galbraith Laboratories and Schwartzkopf Microanalytical Laboratories.

(18) F. M. Beringer, M. Drexler, E. M. Gindler, and C. C. Lumpkin, *J. Amer. Chem. Soc.*, 75, 2705 (1953).

(19) J. G. Sharefkin and H. Saltzman, *Org. Syn.*, 43, 65 (1963).

Experimental Section [17,18]

Diphenyliodonium Trifluoroacetate.—To 25.0 g (79.0 mmol) of diphenyliodonium chloride, mp 226–227°, dissolved in 80 ml of trifluoroacetic acid (60°) there was added with vigorous stirring at 60–65° a solution of 17.45 g (79.0 mmol) of silver trifluoroacetate dissolved in 80 ml of trifluoroacetic acid. After the solution was cooled to 0°, the silver chloride was removed by filtration through Supercel, and the filtrate was reduced in volume at room temperature under vacuum until product began to precipitate. Ether (300 ml) was added in 100-ml portions with vigorous shaking to yield white granules, which were collected, washed with ether, and dried. The yield of crude product was 29.6 g (75.1 mmol, 95%), mp 120–140°. Three recrystallizations from water yielded 16.0 g of pure diphenyliodonium trifluoroacetate, mp 194°.

Anal. Calcd for $C_{14}H_{10}F_3IO_2$: C, 42.66; H, 2.56; F, 14.46; I, 32.20. Found: C, 42.79; H, 2.59; F, 14.73; I, 32.23.

Iodoxy Compounds.—Iodo compounds were oxidized to the corresponding iodoxy compounds with 40% peracetic acid (FMC Corp.) according to established procedures.[19]

***p*-Fluoroiodoxybenzene**, mp 243° (explodes), has previously not been reported.

Anal. Calcd for $C_6H_4FIO_2$: C, 28.37; H, 1.59; F, 7.48; I, 49.96. Found: C, 28.29; H, 1.57; F, 7.44; I, 49.85.

Care should be taken when working with iodoxy compounds since violent decomposition of dry samples may be initiated by the scraping action of a spatula.

Diphenyliodosyl Trifluoroacetate.—To 400 ml of 1 *M* sodium hydroxide there was added 57.2 g (200 mmol) of iodoxybenzene with vigorous stirring at 0°. After 1.5 hr, the precipitated sodium iodate was removed by filtration, and carbon dioxide was bubbled through the filtrate at 0° until the solution was nearly neutral. Then, trifluoroacetic acid was slowly added with vigorous stirring, 3 ml beyond that required for complete liberation of carbon dioxide. The white trifluoroacetate was collected by suction filtration, washed with water, dried, triturated twice with ether, and redried: yield 38.5 g (94 mmol, 94%); mp 150° dec. A 2.00-g portion was recrystallized from 25 ml of acetonitrile three times to yield 1.50 g (75%) of diphenyliodosyl trifluoroacetate, mp 158° (explodes).

Anal. Calcd for $C_{14}H_{10}F_3IO_3$: C, 41.00; H, 2.46; F, 13.90; I, 30.94. Found: C, 40.80; H, 2.40; F, 13.74; I, 30.79.

This trifluoroacetate was slightly soluble in water, extremely soluble in trifluoroacetic and acetic acids, moderately soluble in acetone and acetonitrile, and very slightly soluble in methylene chloride and benzene. Acetonitrile was the most suitable solvent for recrystallization, although prolonged heating in this solvent did cause some decomposition. All diaryliodosyl salts decompose in methanol and ethanol.[2] Infrared spectral characteristics of the Nujol mull were 695 (I=O), 725, and 670 cm^{-1} (C–H out of plane).

Diphenyliodosyl Fluoride.—Diphenyliodosyl trifluoroacetate (3.00 g, 7.31 mmol) was dissolved in 40 ml of boiling water. The solution was treated with activated carbon and filtered hot. A saturated aqueous solution of potassium fluoride was added until further addition caused no precipitation. The product was collected and triturated twice with hot water, dried, and then

washed with ether: yield 1.30 g (4.11 mmol, 56%) of **diphenyliodosyl fluoride**, mp 197° (explodes).

Anal. Calcd for $C_{12}H_{10}FIO$: C, 45.59; H, 3.19; F, 6.01; I, 40.15. Found: C, 45.48; H, 3.19; F, 5.78; I, 39.93.

This fluoride is very soluble in 40% hydrofluoric acid and acetic acid, slightly soluble in water, and insoluble in acetonitrile and methylene chloride. Acetic acid–water or acetic acid–ether mixtures are suitable for recrystallization. Infrared spectral characteristics of the Nujol mull were 744 (s), 722 (s), and 670 cm^{-1} (w).[20]

Diphenyliodosyl Chloride.—A similar procedure, replacing potassium fluoride with 0.440 g of sodium chloride, gave 1.10 g (3.31 mmol, 44%) of **diphenyliodosyl chloride**, mp 181° (explodes).

Anal. Calcd for $C_{12}H_{10}ClIO$: C, 43.34; H, 3.03; Cl, 10.66; I, 38.16. Found: C, 43.17, H, 3.14; Cl, 10.52; I, 37.93.

Infrared spectral characteristics of the Nujol mull were 767 (s), 730 (s), 718 (s), and 672 cm^{-1} (w).[20]

Diphenyliodosyl Bromide.—Similarly, 0.780 g (7.56 mmol) of sodium bromide gave 1.40 g (3.71 mmol, 51%) of diphenyliodosyl bromide: mp 144° (explodes); ir (Nujol mull), 735 (s), 722 (s), and 672 (w) cm^{-1}.

Anal. Calcd for $C_{12}H_{10}BrIO$: C, 38.23; H, 2.67; Br, 21.20; I, 33.66. Found: C, 38.20; H, 2.75; Br, 20.93; I, 33.93.

The chloride and bromide are virtually insoluble in methylene chloride and acetonitrile and are only slightly soluble in water. These salts can be recrystallized from hot water but prolonged heating caused some reduction to the corresponding iodonium salts.

Diphenyliodosyl Acetate Monohydrate.—Iodoxybenzene (23.6 g, 100 mmol) was treated with 200 ml of 1 *M* sodium hydroxide at 0° exactly as was described above for diphenyliodosyl trifluoroacetate but using acetic acid instead of trifluoroacetic acid to yield 14.0 g (37.4 mmol 75%) of product, mp 109–112° dec. Three recrystallizations from a methylene chloride–water two-phase system yielded 9.80 g (26.2 mmol, 52%) of **diphenyliodosyl acetate monohydrate**, mp 114–115° dec (lit.[2] mp 114°).[21]

Anal. Calcd for $C_{14}H_{15}IO_4$: C, 44.94; H, 4.04; I, 33.92. Found: C, 45.16; H, 4.20; I, 34.18.

Infrared spectral characteristics of the Nujol mull were 739 multiplet (s), 722 (w), and 671 cm^{-1} (w).[20]

4,4′-Dimethyldiphenyliodosyl Iodate.—*p*-Methyliodoxybenzene (25.0 g, 100 mmol) was added to 200 ml of 1 *M* sodium hydroxide with vigorous stirring at 0–5°. After 1.5 hr at 50% aqueous solution of iodic acid was slowly added until the reaction mixture was neutralized and then 10 ml beyond this point. The voluminous white precipitate was collected by suction filtration, washed with water, dried, and washed with ether. The precipitate was then vigorously triturated with four 150-ml portions of methylene chloride, leaving behind a white solid which was mostly sodium iodate together with small amounts of starting material. The clear, yellow methylene chloride solution was evaporated to 50–75 ml. Pentane was added until the solution became cloudy and then anhydrous ether until no more precipitation occurred. The precipitate from the chilled mixture was collected, washed with ether, and dried to yield 19.5 g (39.0 mmol, 78%) of crude product, mp 125° dec. This product was recrystallized once from water and twice from methylene chloride and was dried at room temperature over phosphorus pentoxide at 2 mm for 2 days: yield, 6.30 g (25%) of **4,4′-dimethyldiphenyliodosyl iodate**, mp 131–133° dec.

Anal. Calcd for $C_{14}H_{14}I_2O_4$: C, 33.62; H, 2.82; I, 50.75. Found: C, 33.12; H, 2.96; I, 50.41.

4,4′-Dimethyldiphenyliodosyl Trifluoroacetate.—From a reaction run as described above, the crude 4,4′-dimethyldiphenyliodosyl iodate was isolated and then triturated three times with 100-ml portions of cold water. The insoluble material was removed by filtration. To the filtrate trifluoroacetic acid was added slowly, with vigorous stirring, until no more precipitation occurred. The precipitate was collected, washed with water, dried, and triturated twice with ether: yield, 14.3 g (32.6 mmol, 65% based on *p*-methyliodoxybenzene); mp 150° dec. A 5.70-g portion of the product was dissolved in 250 ml of boiling water, filtered through Celite, and allowed to crystallize to yield 5.00 g. (88%) of material, mp 155° dec. Two subsequent recrystallizations from methylene chloride yielded 3.45 g (61%) of **4,4′-dimethyldiphenyliodosyl trifluoroacetate**, mp 159–160° dec.

Anal. Calcd for $C_{16}H_{14}F_3IO_2$: C, 43.86; H, 3.22; F, 13.01; I, 28.96. Found: C, 43.66; H, 3.10; F, 12.90; I, 29.15.

Infrared spectral characteristics of the Nujol mull were 695 (I=O) and 792 cm^{-1} (C–H out of plane).

4,4′-Dimethyldiphenyliodosyl Fluoride.—Crude 4,4′-dimethyldiphenyliodosyl iodate was isolated as described above. This crude solid was dissolved in a minimum of 98% aqueous hydrofluoric acid at room temperature; upon diluting this solution with water, a precipitate formed. The precipitate from the chilled mixture was collected by suction filtration, dried, washed with ether, and dried again to yield 8.36 g (24 mmol, 48% based on *p*-methyliodoxybenzene) of product, mp 160° dec. A 2.00-g portion was recrystallized once from water and once from methylene chloride and then dried for 2 days at room temperature over phosphorus pentoxide at 2 mm to yield 1.65 g (83%) of **4,4′-dimethyldiphenyliodosyl fluoride**, mp 170° (explodes).

Anal. Calcd for $C_{14}H_{14}FIO$: C, 48.86; H, 4.10; F, 5.52; I, 36.87. Found: C, 48.60; H, 3.89; F, 5.35; I, 36.71.

Infrared spectral characteristics of the Nujol mull were 702 (I=O) and 805 cm^{-1} (C–H out of plane).

This compound is hygroscopic. When exposed to the atmosphere for several days, it formed a monohydrate which did not show any change in decomposition point.

Anal. Calcd for $C_{14}H_{16}FIO_2$: C, 46.43, H, 4.45; F, 5.25; I, 35.03. Found: C, 46.29; H, 4.70; F, 5.20; I, 34.96.

Infrared spectral characteristics of the Nujol mull were 720 (I=O) and 805 cm^{-1} (C–H out of plane).

4,4′-Difluorodiphenyliodosyl Trifluoroacetate.—*p*-Fluoroiodoxybenzene (6.35 g, 25.0 mmol) was treated with 50 ml of 1 *M* sodium hydroxide according to the procedure described in the synthesis of diphenyliodosyl trifluoroacetate. The yield was 0.80 g (1.79 mmol, 14.3%) of crude product, mp 170° (explodes). Three recrystallizations from acetonitrile yielded 0.64 g (1.43 mmol, conversion 11.4%) of **4,4′-difluorodiphenyliodosyl trifluoroacetate**, mp 175° (explodes).

Of the starting *p*-fluoroiodoxybenzene, 3.79 g (14.9 mmol, 60%) of mp 243° (explodes) was recovered. The yield of crude **4,4′-difluorodiphenyliodosyl trifluoroacetate** was 35.4% based only on reacted *p*-fluoroiodoxybenzene (2.56 g, 10.1 mmol).

Anal. Calcd for $C_{14}H_8F_6IO_3$; C, 37.68; H, 1.81; F, 21.29; I, 28.45. Found: C, 37.65; H, 2.11; F, 21.88; I, 28.64.

Infrared spectral characteristics of the Nujol mull were 690 (I=O) and 820 cm^{-1} (C–H out of plane).

4,4′-Difluorodiphenyliodosyl Fluoride.—4,4′-Difluorodiphenyliodosyl trifluoroacetate (0.500 g, 1.12 mmol) was dissolved in 25 ml of boiling water. The solution was then treated with potassium fluoride as in the preparation of diphenyliodosyl fluoride. This yielded 0.210 g (0.6 mmol, 54%) of **4,4′-difluorodiphenyliodosyl fluoride**, mp 185° (explodes).

Anal. Calcd for $C_{12}H_8F_3IO$: C, 40.93; H, 2.26. Found: C, 40.69; H, 2.48.

Infrared spectral characteristics of the Nujol mull were 730 (I=O) and 830 cm^{-1} (C–H out of plane).

4,4′-Difluorodiphenyliodosyl Chloride.—4,4′-Difluorodiphenyliodosyl trifluoroacetate (0.500 g, 1.12 mmol) was dissolved in 25 ml of boiling water. The solution was treated with sodium chloride as in the preparation of diphenyliodosyl chloride to yield 0.180 g (0.5 mmol, 44%) of **4,4′-difluorodiphenyliodosyl chloride**, mp 162° (explodes).

Anal. Calcd for $C_{12}H_8F_2ClIO$: C, 39.11; H, 2.19. Found: C, 38.85; H, 2.32.

Infrared spectral characteristics of the Nujol mull were 719 (I=O) and 829 cm^{-1} (C–H out of plane).

Diphenyliodosyl Fluoride with Sodium Bisulfite.—To 10 ml. of 1 *M* soldium bisulfite solution there was added with stirring at room temperature 1.00 g (3.16 mmol) of diphenyliodosyl fluoride. After 10 min of stirring, a saturated solution of potassium iodide was added until no more precipitation occurred. The white product was collected by suction filtration, washed several times with water and sparingly with acetone, and dried to yield 1.25 g (3.06 mmol, 97%) of diphenyliodonium iodide, mp 173° dec (lit.[22] mp 172–175).

(20) A clear distinction between I–O and C–H out of plane could not be made.

(21) If water was not present during the recrystallization from methylene chloride, a yellow, very viscous, oily material would usually form. This material could be partially reconverted to the known crystalline material by adding water. It was extremely soluble in methylene chloride, partially soluble in ether, and exhibited strong oxidizing power but was not further characterized. However, similar materials were found as troublesome side products in almost all synthetic routes to diaryliodosyl salts.

(22) H. J. Lucas and E. R. Kennedy, *Org. Syn.*, **22**, 52 (1942).

Diphenyliodosyl Trifluoroacetate with Hydrogen Peroxide.—To a stirred suspension of 2.00 g (4.88 mmol) of diphenyliodosyl trifluoroacetate in 10 ml of water at room temperature was added 2.00 g (17.6 mmol) of 30% hydrogen peroxide and the reaction mixture was stirred for 10 min. From the chilled reaction mixture the product was collected by suction filtration, dried, and washed with ether, yielding 1.15 g (2.92 mmol, 60%) of diphenyliodonium trifluoroacetate, mp 190–192°, after two recrystallizations from acetonitrile. Mixture melting point determination and comparison of ir spectra showed this compound to be identical with that obtained from the metathesis reaction described above.

Registry No.—Diphenyliodonium trifluoroacetate, 16668-99-8; *p*-fluoroiodoxybenzene, 16669-00-4.

Allylic Displacements by N_2F_4

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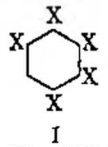
Received November 8, 1967

Previous workers, Frazer,[2,3] Petry and Freeman,[4] and others[5] have shown that NF_2 radicals derived from the dissociation of N_2F_4[6] undergo reaction with methyl iodide, trifluoromethyl iodide, acetaldehyde, and hydrocarbons by displacement reactions to give CH_3NF_2, CF_3NF_2, $CH_3C(=O)NF_2$, and RNF_2. We have extended this work to the allylic systems by demonstrating the displacement or replacement of allylic proton,[7] bromine,[8,9] and iodine by thermal free-radical reactions to form allyldifluoramines from allyl bromide and iodide, 2,3-dibromo- and 2,3-diodopropene, 1,4-cyclohexadiene, propylene, and piperylene.

These displacements seem to proceed by an S_N2 mechanism except possibly in the case of the allyl iodides where products arising from the free allyl radical indicate an S_N1 mechanism.

The reactivity of the allyldifluoromines is similar; both N_2F_4 and Br_2 add to the double bond. In the case of N_2F_4 and allyldifluoramine this gives rise to the highly energetic 1,2,3-tris(difluoramino)propane.[9]



I
(X = NF_2)

In the case of 3-difluoramino-1,4-cyclohexadiene, a second mole of N_2F_4 adds with difficulty to form isomeric pentakisdifluoraminocyclohexanes I.[7]

Historically allyl difluoramine was first found in 1959[9] during attempts to add N_2F_4 to the olefin double bond as reported by workers at Rohm and Haas.[10]

Experimental Section

Allyl Bromide and N_2F_4.[11]—Allyldifluoramine was made from allyl bromide in the vapor phase using a 0.25-in. stainless steel flow reactor[12] under conditions shown in Table I. A high bromide/N_2F_4 ratio gave maximum yields; a low ratio gave considerable quantities of tris-1,2,3-difluoraminopropane[9] owing to addition of N_2F_4 to allyldifluoramine.[13] The presence of free bromine gave rise to 1,2,3-tribromopropane and 2,3-dibromo-1-difluoraminopropane (bp 185), both identified on gc by the use of authentic reference samples.

TABLE I
ALLYLIC DISPLACEMENT CONDITIONS

Feed	Reactor	N_2F_4/feed ratio	Temp, °C	Pressure, atm	Time	Yield, mol %
Allyl bromide	Flow	1/5	230	1	1 min	52
	Flow	1/1	230	1	1 min	33
Allyl iodide	Static[a]	1	25	1	115 hr	60
2,3-Dibromopropene	Flow	3/1	200	1	0.5 min	...
2,3-Diiodopropene	Static[a]	1/7	25	0.5	110 hr	80

[a] Shielded Pyrex bulb.

Allyldifluoramine boils at 40° and weighs 1.045 g/ml at 23.5° and its vapor density was consistent with the calculated molecular weight. Table II gives gc and nmr analytical data; the infrared spectrum is given in Figure 1.

Allyl Iodide and N_2F_4.—This reaction to give allyldifluoramine was carried out in a Pyrex bulb under conditions given in Table I.

2,3-Dibromopropene and N_2F_4.—2-Bromoallyldifluoramine was made from 2,3-dibromopropene and N_2F_4 under conditions described in Table I.

The product had a boiling point of 130° and a pressure of 24 mm at 21.8°. An impure sample had a molecular weight of 208 *vs.* theoretical 200. Other analyses of samples 91 or 95% pure by gc are given in Table II.

Allene and Iodine in CCl_4 was allowed to stand at room temperature in a Pyrex bulb for a day in the presence of an incandescent light. The crude stripped product, 2,3-diodopropene, had the following analysis and was used without further purification.

Anal. Calcd for $C_3H_4I_2$: C, 12.3; H, 1.4; I, 86.4. Found: C, 15.6; H, 2.8; I, 83.6.

2,3-Diiodopropene and N_2F_4.—This reaction was carried out at the ambient conditions shown in Table I. The product, isolated by preparative gc had the properties shown in Table II. In addition to the ^{19}F nmr the proton nmr spectrum showed singlets at +0.44 and 0.80 ppm relative to benzene and a triplet at +2.62 ppm with J_{HF} of 26.3 Hz. These values are consistent with the structure assignment, $CH_2{=}CI{-}CH_2NF_2$, where the terminal olefinic protons are nonequivalent.

Propylene and N_2F_4.—This displacement was carried out at 1-min contact time and 300° in the flow reactor. Allyldifluoramine, formed in low yield, was identified in the reaction products by gc and by its conversion into 2,3-dibromodifluoraminopropane (gc spectrum) when the crude products were treated with bromine.

1,4-Pentadiene and N_2F_4.—The reaction with 3 vol. of N_2F_4 in a Pyrex bulb at 150° gave rise to HNF_2[14] in 15% yield based on diene. Distinct peaks at relative retention times

(1) Address inquiries to this author at the Enjay Chemical Laboratories, Linden, N. J.

(2) J. W. Frazer, *J. Inorg. Nucl. Chem.*, **16**, 63 (1960).

(3) J. W. Frazer, B. F. Holder, and E. F. Worden, The Preparation and Identification of N-Fluoro-N-Trifluoromethyl Diazine-N-Oxide, UCRL-6444, Lawrence Radiation Laboratory, Livermore, Calif., May 8, 1961, Report for U. S. Atomic Energy Commission, Available from Office of Technical Services, U. S. Department of Commerce, Washington, D. C.

(4) R. C. Petry and J. P. Freeman, *J. Amer. Chem. Soc.*, **83**, 3912 (1961).

(5) C. L. Bumgardner, *Tetrahedron Lett.*, 48, 3683 (1964); J. Grzechowiak, J. F. Kerr, and A. F. Trotman-Dickenson, *Chem. Commun.*, 109 (1965).

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(9) B. Freedman, L. K. Beach, and A. E. Messner (Esso Research and Engineering Co.), U. S. Patent 3,347,923 (f. Dec 1, 1959) (Oct 17, 1967).

(10) R. C. Petry and J. P. Freeman, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p 546.

(11) Purchased from Peninsular Chem Research, Gainesville, Fla.

(12) R. P. Rhodes and L. K. Beach (Esso Research and Engineering Co.), U. S. Patent 3,341,596 (f. Jan 27, 1960) (Sept 12, 1967).

(13) A. J. Passannante and L. K. Beach (Esso Research and Engineering Co.), U. S. Patent 3,342,866 (f. Jan 27, 1960) (Sept 19, 1967).

(14) Identified by its distinctive infrared spectra. See A. Kennedy and C. B. Colburn, *J. Amer. Chem. Soc.*, **81**, 2906 (1959).

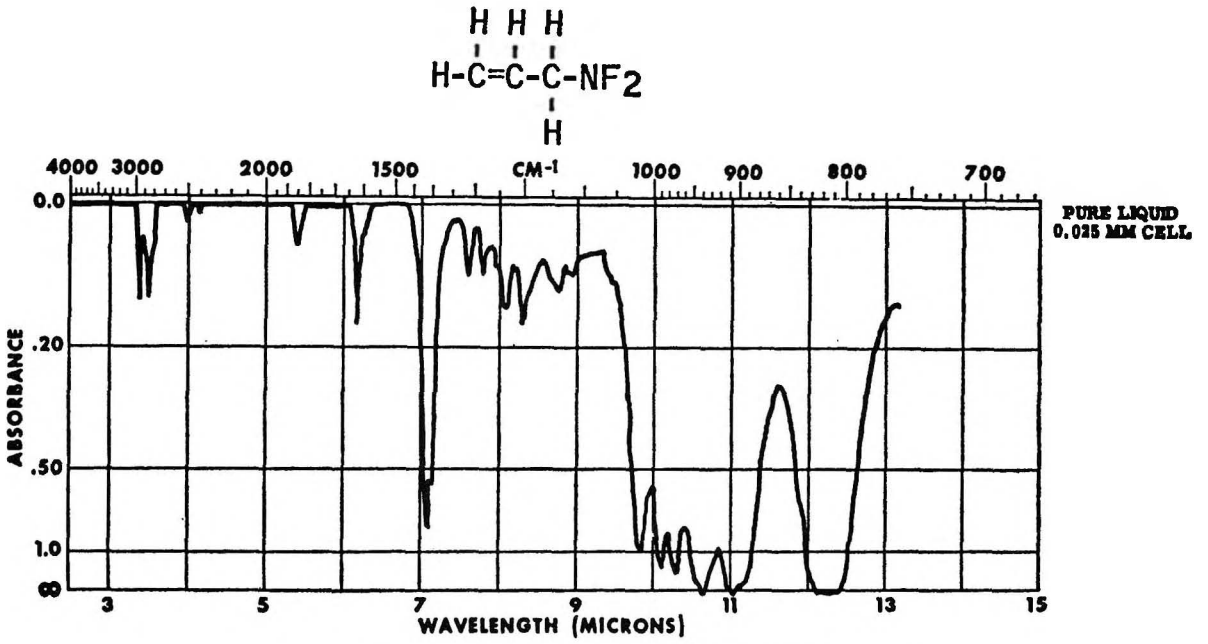

Figure 1.—Infrared spectra of allyldifluoramine.

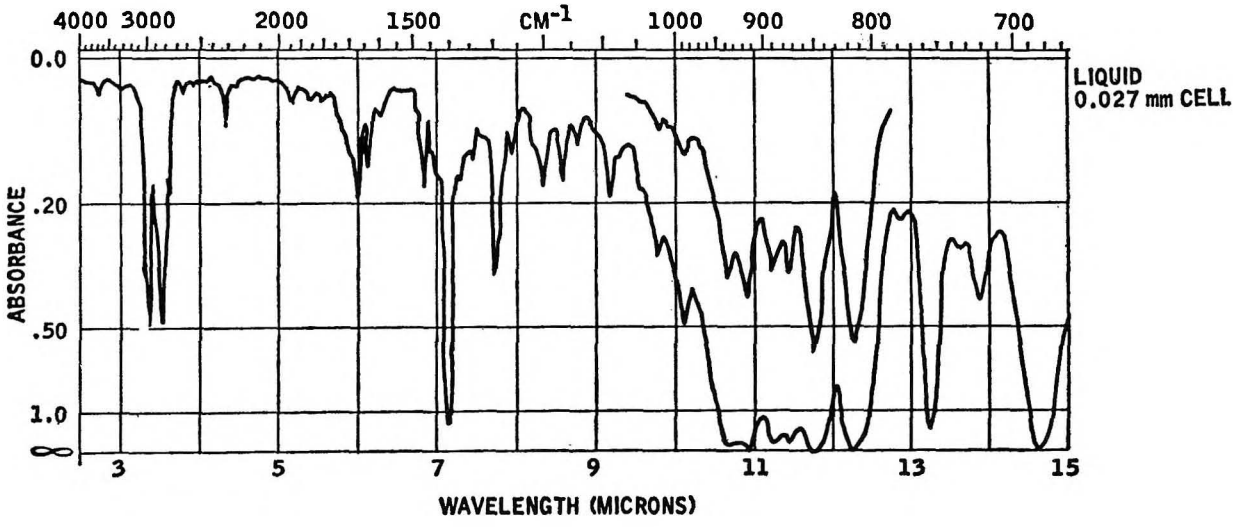

Figure 2.—3-Difluoraminocyclohexadiene-1,4.

TABLE II
PRODUCT CHARACTERIZATION

Product	Relative retention time (benzene)[a]	Elemental analyses, % C	H	N	F	Br	I	^{19}F nmr at 40 MHz Shift (TFA), ppm	J_{HF}, Hz
Allyldifluoramine	0.23	...	...	...	...	...	...	134.7 (triplet)	29[b]
2-Bromoallyldifluoramine	1.33	...	1.7[c]		19.6	43			
(theory)			(2.3)		(22.1)	(46)			
2-Iodoallyldifluoramine	2.9	17.4	1.99	6.9	17.7		56	134.4 (triplet)	26.3
(theory)		(16.5)	(1.84)	(6.4)	(17.4)		(58)		
3-Difluoramino-1,4-cyclohexadiene	4.5	55.0	5.6	9.5[d]	30.0				
(Theory)		(55.0)	(5.4)	(10.7)	(29.0)				

[a] At 75° on 0.25-in. SS 6-ft tube packed with Dow Corning 200 silicone oil, 30 g/100 g of Chromosorb. [b] Consistent with Bumgardner's observations.[5] [c] H by broad line nmr, F by wet analysis, both on 96% pure (gc) sample. Br value on 91% (gc) pure sample. [d] Low owing to leak in Coleman Analyzer.

0.8 and 1.2 relative to benzene in the gc trace indicated the possibility of the 3- and the 5-difluoraminopentadienes. These products were not investigated further.

1,4-Cyclohexadiene and N_2F_4.—The reaction of N_2F_4 with 1,4-cyclohexadiene at a 7:1 mol ratio was initially observed in a 2-cm Pyrex infrared cell at 440 mm and room temperature. The reaction began immediately on mixing the reagents and proceeded with the appearance of almost exactly 1 mol of HNF_2[14] for each mole of N_2F_4 that disappeared. In 110 hr the HNF_2 formed corresponded almost mole for mole with the cyclohexadiene originally present. Benzene was detected in increasing amounts after the 30th hour.

The principal product from larger scale reactions in Pyrex bulb was isolated in 97.6% purity (2.4% benzene impurity) by preparative gc. In addition to the analyses given in Table II the following properties were measured: mol wt, 124; vapor pressure at 23°, 15.0 mm.

The infrared spectrum of the liquid is given in Figure 2. The ultraviolet spectrum showed no diene conjugation above 2150 Å. The compound was too unstable to allow its convenient study by nmr spectroscopy.

Safety Note.—All the work with N_2F_4 reaction mixtures and products is generally quite hazardous. Extremely brisant explosions are to be expected. Plexiglas shields, shatter proof goggles, heavy leather gloves, lab coats with sleeves, and the the use of small, *i.e.*, 0.5-g, quantities of N_2F_4 are recommended for anyone comtemplating work with these and other N_2F_4 systems.

Registry No.—N_2F_4, 10036-47-2; allyldifluoramine, 16101-17-0; 2-bromoallyldifluoramine, 16101-20-5; 2-iodoallyldifluoramine, 16626-73-6; 3-difluoramino-1,4-cyclohexadiene, 16626-74-7.

Acknowledgment.—This research was supported by the Advanced Research Projects Agency, Propellant Chemistry Office, and was monitored by Army Ordnance, under Contract No. DA-30-069-ORD-2487. Thanks are owed to Dr. R. E. Swarbrick for his analytical interpretation of nmr spectra.

Steric Effects on the Reaction of Propargyl and Allenyl Chlorides with Sodium Methoxide in Methanol[1]

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Received December 27, 1967

We have observed that in a series of mixtures of substituted propargyl and allenyl chlorides (III and IV) the position of attack depends on the size of the groups attached to the propargyl position when chloride ion is displaced by sodium methoxide in methanol. A mixture of III and IV with R = methyl or ethyl (60–70% III) yielded only propargyl ethers (VI). A mixture of III and IV with R = isopropyl or *t*-butyl (98% IV) yielded a mixture of propargyl ethers (VI) and allenyl ethers (VII) in the ratios 20:80 and 10:90, respectively. Elimination to form enyne V accompanies the displacement, increasing in importance as the temperature is raised and decreasing in importance as R increases in size (methyl > ethyl > isopropyl). The results are detailed in Table I.

It may be assumed that these product proportions represent the selectivity of attack on intermediate I. The mechanism shown above is believed to be general for tertiary propargyl halides, RR'CXC≡CH, and the corresponding allenyl halides, RR'C=C=CHX, on the basis of earlier work[3] with 3-bromo-3-methyl-1-butyne and 1-bromo-3-methyl-1,2-butadiene. Other workers have noted steric effects on the position of attack on similar molecules.[4,5]

The halide mixtures were obtained by treatment of the propargyl alcohols, II, with hydrochloric acid, calcium chloride, and copper bronze[6] (see Table II). Attempts were made to increase the proportions of IV by rearrangement with a mixture of ammonium chloride, hydrochloric acid, cuprous chloride, and copper powder, but no change was observed. When the cuprous chloride and copper bronze were omitted from the reaction mixture during synthesis, the III:IV ratio increased from 60:40 to 78:22 (R = ethyl) and from 70:30 to 76:24 (R = methyl). The total chloride yield decreased under these conditions to 48% with R = ethyl and 47% with R = methyl. The reaction of II (R = methyl) with thionyl chloride in pyridine[7] gave only 29% of the allenyl chloride and so was not used further.

The reactions of potassium *t*-butoxide and sodium isopropoxide on chloride mixtures with R = methyl were examined with the hope that bulkier nucleophiles would yield allenyl ethers to some extent from these less-hindered chlorides. These reagents gave at least 93% elimination to V even at room temperature. The ether fractions were mixtures containing considerable conjugated material, probably CH_2=C(*t*-butyl)CH=CHOR which might be formed by rearrangement of the expected allenyl ethers.

Experimental Section

Infrared spectra were obtained on Perkin-Elmer Model 421 and 137 spectrophotometers (usually neat, but occasionally in carbon tetrachloride solution). Bands are designated as strong (s), medium (m), and weak (w). Nuclear magnetic resonance spectra were obtained with a Varian Associates analytical nmr Model A-60, neat or in 10% carbon tetrachloride solutions with tetramethylsilane as the internal standard, and recorded in τ values. The usual designations for singlet (s), doublet (d), triplet (t), multiplet (m), etc., are used and the figure following the letter indicates the number of protons based on the integration. Analytical glpc determinations were carried out on a Perkin–Elmer model 800 instrument with a 10-ft column of 20% 1,2,3-tris(2-cyanoethoxy)propane on 80/100 Chromsorb W at 80–105°. A silicone oil column was somewhat less satisfactory. A Nester–Faust Teflon spinning-band distillation column, Model NFT-60, was used for some of the distillations.

Substituted propargyl alcohols [$(CH_3)_3CCROHC{\equiv}CH$, **II**] were prepared from the corresponding ketones and sodium acetylide in liquid ammonia (addition 2 hr, stirring 4 hr more). Reaction mixtures were decomposed with cold aqueous ammonium chloride and extracted with ether. Yields recorded are of once-distilled product which still contained some unreacted ketone; distillation through a spinning-band column removed all but traces of carbonyl impurity. Compounds prepared (R substituent) and their physical and spectral properties are listed below.

R = CH_3: bp 143–144°; $n^{25}D$ 1.4386 (lit.[8,9] bp 142–144°; $n^{20}D$ 1.4440); ir, 3340 (s), 2120 (w), 650 (s) (C≡CH), 3500 (s), 1320 (s), 1085 (s), cm^{-1} (OH); nmr, τ 8.97 (s, 9), 8.57 (s, 3), 7.54 (s, acetylenic H), 6.93 (s, hydroxyl-H).

R = C_2H_5: bp 88°(60 mm); $n^{25}D$ 1.4428 (lit.[10] bp 94° (90 mm); $n^{20}D$ (1.4456); ir, 3340 (s), 2120 (w), 650 (s) (C≡CH),

(1) This research was supported by Grant GP-5530 from the National Science Foundation.

(2) Dr. Siebe Hoff was supported in part by National Science Foundation Grant GP-5530 and in part by a fellowship from the University of Utrecht, The Netherlands.

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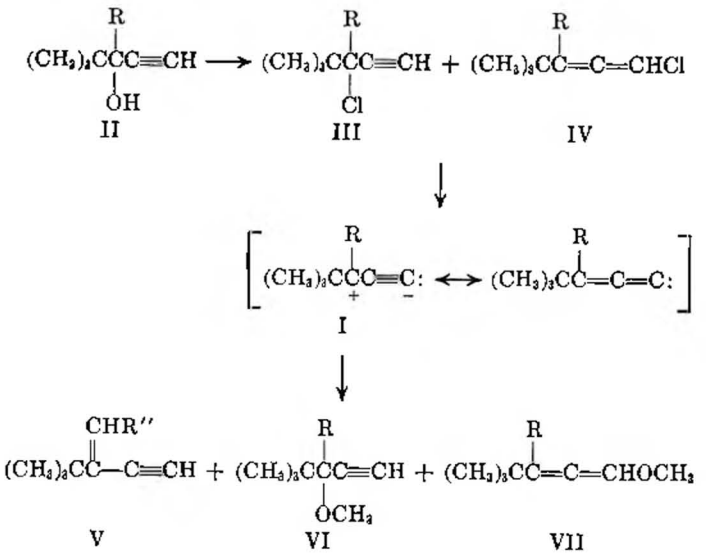


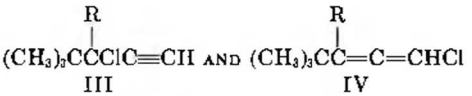
TABLE I

REACTIONS OF MIXTURES OF $(CH_3)_3CCRClC{\equiv}CH$ (III) AND $(CH_3)_3CCR{=}C{=}CHCl$ (IV) WITH 100% EXCESS OF CH_3ONa IN CH_3OH

Starting material		Conditions		Products, %[a]			
R	III:IV	Temp, °C	Time, hr	III and IV	V	VI	VII
CH_3	67:33	Room temperature	288	12[b]	40	48	
		65	15		Mainly		
C_2H_5	60:40[c]	Room temperature	288	28[b]	30	42	
		65	15		Mainly		
$CH(CH_3)_2$	2:98	Room temperature	288	Mainly	Minor	*d*	*d*
		65	15	~5	40	11	44
$C(CH_3)_3$	2:98	Room temperature	288	Mainly		Trace	Trace
		65	15	Trace		10	90

[a] The numbers represent proportions of products and errors may be as high as ±10% of the figures given. A single distillation of the reaction mixture usually gave a distillate that accounted for over 90% of starting materials but with R = $C(CH_3)_3$ the yield was about 80%. [b] This appeared to be entirely allenyl chloride IV. [c] A second experiment with III:IV = 78:22 under the same conditions gave the same product distribution but recovered IV was somewhat less. [d] The VI:VII ratio could not be determined as precisely as in the next experiment, but was approximately 20:80 in agreement with the latter.

TABLE II



					Anal., %					
					Calcd			Found		
R	Bp, °C (mm)	Yield, %	Ratio of III:IV Nmr	Glpc	C	H	Cl	C	H	Cl
CH_3	56–57 (29)[a]	68	67:33	70:30	66.43	9.06	24.51	66.57	9.15	24.43
C_2H_5	68–69 (21)	69	60:40		68.12	9.56	22.34	68.40	9.65	22.12
	63 (15)	48[b]	78:22	78:22				68.25	9.66	22.67
$CH(CH_3)_2$	65 (11)	74		2:98	69.54	9.92	20.53	69.76	10.06	19.93
$C(CH_3)_3$	56 (3)[c]	72		2:98	70.75	10.25	18.99	70.82	10.33	18.93

[a] Reported[7] for IV (R = CH_3): bp 62–63° (15 mm) and bp 91–92° (110 mm). [b] Cuprous chloride and copper bronze were omitted in this synthesis. [c] Reported[7] for IV [R = $C(CH_3)_3$]: bp 72–74° (15 mm).

3500 (s), 1320 (s), 1100 cm^{-1} (s) (OH); nmr, τ 8.97 (s), 8.91 (t), 8.45 (q), 7.57 (s, acetylenic H), 7.41 (s, hydroxyl H); the 8.97 and 8.91 peaks total 12 protons, the methylene peak at 8.45 integrates for two.

R = $CH(CH_3)_2$: bp 98° (60 mm); $n^{25}D$ 1.4487 (lit.[9] bp 174.5–176°, 65–68° (16 mm); $n^{20}D$ 1.4421–1.4423); ir, 3350 (s), 2125 (w), 600 (s) (C≡CH), 3550 (s), 1320 (s), 1110 (m), cm^{-1} (OH); nmr, τ 8.88 (s), 8.92 (d), 8.00 (q, 1) 7.60 (s, acetylenic H), 7.57 (s, hydroxyl H); the 8.88 and 8.92 peaks total 15 protons and the 7.60 plus 7.57 peaks total two protons.

R = $C(CH_3)_3$: bp 75° (14 mm); $n^{25}D$ 1.4560 (lit.[9] bp 74–75° (14 mm); $n^{20}D$ 1.4589; ir, 3350 (s), 2120 (w), 600 (s) (C≡CH), 3600 (s), 1300 (s), 1085 (s) cm^{-1} (OH); nmr, 8.82 (s, 18), 7.71 (s, acetylenic H), 7.57 (s, hydroxyl H).

Substituted propargyl and allenyl chlorides III and IV were prepared on approximately one-fourth mole scale by the method of Hennion and Boisselle[6] except that the reaction mixture was stirred for 1.5–2.5 hr and then extracted twice with ether. The work-up of the ethereal layer was essentially as described[6] except that a column packed with glass beads was used. The propargyl product with R = methyl is a semisolid and attempts at distillation through the spinning-band column were unsuccessful.

No reaction occurred when hydrogen chloride was passed through 0.3 mol of II (R = CH_3) in 250 ml of pentane at −75° for 3 hr and only very slow reaction occurred in ether at −50° or in nitromethane at −30° in similar experiments.

Reactions of Mixtures of III and IV with Sodium Methoxide in Methanol.—The chloride mixtures were dissolved in a 100% excess of 2 *N* sodium methoxide in methanol and the reaction carried out under conditions given in Table I. Reaction mixtures were poured into ice–water and extracted with ether; the ether extracts were washed with a saturated aqueous solution of sodium chloride dried over anhydrous sodium sulfate, concentrated, and

TABLE III
SPECTRAL DATA[a]

Compd	R	Infrared,[b] cm^{-1}	Nmr *	Nmr +	Nmr R
$(CH_3)_3CC(R)C\equiv CH$	CH_3	3350 (w) 2130 (w)	8.82 (s)	7.48 (s)	8.21 (s)
	C_2H_5	3330 (s) 2130 (w)	8.83 (s)	7.48 (s)	8.80 (t, CH_3)[c] 8.15 (q, CH_2)
$(CH_3)_3CC(R)=C=CHCl$	CH_3	1960 (m)	8.90 (s)	4.10 (q), J = 2.5 cps	8.17 (s)
	C_2H_5	1960 (m)	8.90 (s)	3.97 (t), J = 2.5 cps	8.80 (t, CH_3)[c] 8.15 (q, CH_2)
	$HC(CH_3)_2$	1955 (s)[d]	8.90 (s)	3.97 (s)	8.85 [d, $(CH_3)_2$] 7.70 (q, HC)
	$C(CH_3)_3$	1940 (m)[d]	8.78 (s)	4.10 (s)	8.78 (s)

[a] These spectra were determined on mixtures of III and IV; J values were often difficult to determine with any accuracy and are not then reported. Integrations were in agreement with the assignments made. [b] All of these compounds showed a strong band at 740–750 cm^{-1} attributed to the C–Cl band. [c] Bands for the ethyl groups of III and IV overlap so badly that the same average values are given for both. [d] A very weak band at 3310 cm^{-1} is attributed to 2% of III present.

distilled under reduced pressure through a 45-cm column packed with glass beads. With R = methyl or ethyl only propargyl ethers, VI, were detected either with experiments carried only part way (where essentially only III had reacted) or to completion. The starting chlorides and the methyl ethers boil so close together that efficient separation was not attained on the scale employed. Only with R = methyl was separation of quite pure propargyl ether VI possible. In all other cases the spectra and analyses were of the mixtures indicated.

R = Methyl.—The higher boiling fraction came over at 51–59° (31 mm) and contained 20% of starting chlorides (glpc and nmr spectra); spectra indicated that this recovered chloride was essentially all allenic. Careful redistillation of this fraction through the spinning-band column gave material of bp 56° (31 mm) with ir absorptions at 3340 (s), 2110 (w), 2840 (m), 1130 (s) cm^{-1}. Glpc indicated the presence of 1% of the allenyl chloride IV (R = CH_3) and this gave weak ir bands at 735 and 1945 cm^{-1}. The nmr spectrum of the ether showed peaks at τ 8.98 (s, 9), 8.70 (s, 3), 7.62 (s, 1) and 6.71 (s, 3); this is in excellent agreement with the assigned structure.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. For $C_9H_{16}O$ containing 1% $C_8H_{13}Cl$: C, 76.94; H, 11.39. Found: C, 76.94; H, 11.32.

R = Ethyl.—The higher boiling fraction, bp 67–70° (27 mm), contained 36% starting chloride, mainly allenic, on the basis of glpc and nmr spectra. Infrared absorptions were at 3335 (s), 2110 (w), 1110 (s), and 2840 cm^{-1} (m) for the ether; bands for chloride impurity as recorded for IV (R = C_2H_5). The nmr peaks for the *t*-butyl hydrogens and for the methyl hydrogens of the ethyl group overlapped in the τ 9.0 region. The acetylenic hydrogen, 7.51 (s), the methylenic hydrogens, 7.37 (q) and the methoxyl hydrogens, 6.70 (s) were in proper proportions.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.85; H, 11.76. For $C_{10}H_{18}O$ containing 35% $C_9H_{15}Cl$: C, 74.46; H, 10.98. Found: C, 74.54; H, 10.93.

R = Isopropyl.—The higher boiling fraction from the run at reflux temperature, bp 68–69° (13 mm), was free from starting chloride within the error of spectral and analytical determinations. Nmr spectroscopy indicated that it was a mixture containing 80% of the allenyl ether and 20% of the propargyl ether. Infrared absorptions of the mixtures were at 1935 (s), 3340 (m), 2850 (m), 1140 (s) cm^{-1}. In the nmr spectrum the region around τ 9.00 has a complicated band pattern because *t*-butyl and isopropyl methyls for the two compounds give bands which do not coincide; other bands for VII (R = isopropyl) are at τ 7.90 (q), 6.96 (s), and 3.52 (s) with area ratios close to 1:3:1 and for VI (R = isopropyl) are at 7.69 (s) and 6.72 (s) with a ratio of 1:3. The tertiary hydrogen on the isopropyl group was obscured.

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.40; H, 11.81.

R = *t*-Butyl.—The higher fraction from the run at reflux temperature, bp 66–68.5° (7 mm), had the following ir bands: 1940 (s), 3340 (w), 1080 (s), 735 (w) cm^{-1}. The 7.35-cm^{-1} band indicated the presence of a little unreacted chloride. Nmr peaks for VII (R = *t*-butyl) were at 9.00 (s), 6.90 (s), 3.65 (s); for VI (R = *t*-butyl) they were at 9.00 (s), 6.72 (s), 7.69 (s). The nmr spectrum suggests that the fraction was a 90:10 mixture of VII and VI. An analysis was not obtained.

The instability of the allenyl ethers to glpc separation should be mentioned.

Registry No.—Sodium methoxide, 124-41-4; methanol, 67-56-1; III (R = CH_3), 16487-11-9; III (R = C_2H_5), 16487-12-0; IV (R = CH_3), 16487-13-1; IV (R = C_2H_5), 16487-14-2; IV [R = $CH(CH_3)_2$], 16487-15-3; IV [R = $C(CH_3)_3$], 16487-16-4; VI (R = CH_3), 16487-17-5; VI (R = C_2H_5), 16487-18-6; VI [R = $CH(CH_3)_2$], 16487-19-7; VI [R = $C(CH_3)_3$], 16487-20-0; VII [R = $CH(CH_3)_2$], 16487-21-1; VII [R = $C(CH_3)_3$], 16487-22-2.

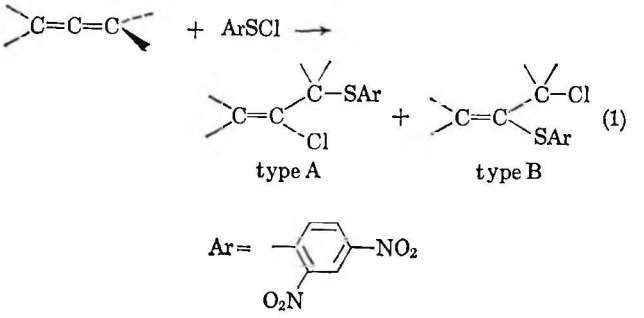
The Addition of 2,4-Dinitrobenzenesulfenyl Chloride to Allenes[1,2]

THOMAS L. JACOBS AND ROGER MACOMBER

Contribution No. 2211 from the Department of Chemistry, University of California at Los Angeles, Los Angeles, California 90024

Received February 27, 1968

In the reaction of unsymmetrical allenes with 2,4-dinitrobenzenesulfenyl chloride (DBSC), two orientations of adducts are possible at each double bond. These are of two types, as shown in eq 1. We recently



(1) This work was presented in part before the Intrascience Conference on the Chemistry of Sulfenyl Compounds, Santa Monica, Calif., Nov 1967.

(2) This research was supported in part by National Science Foundation Grant GP-5530 and in part by the Department of Chemistry under an National Science Foundation Graduate Traineeship to R. Macomber (1966–1968).

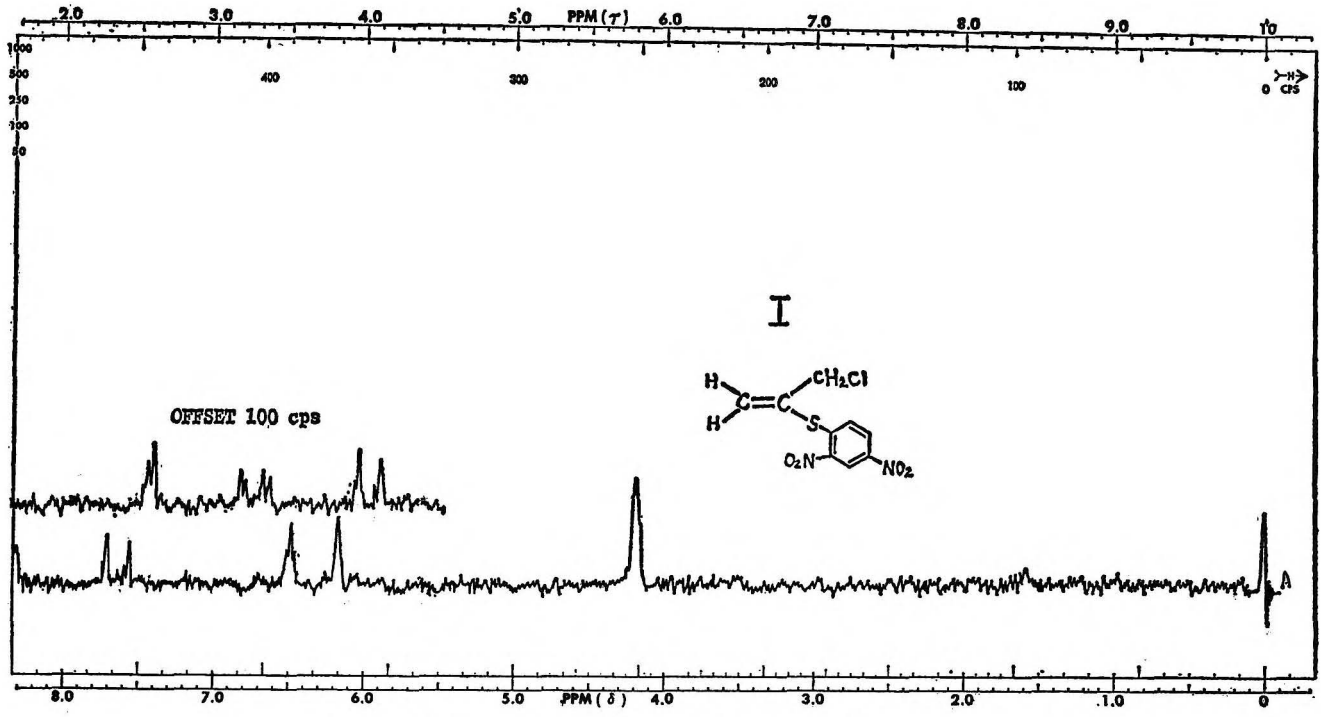


Figure 1.—The pmr spectrum of 3-chloro-2-(2,4-dinitrophenylthio)propene ($CDCl_3$ solution).

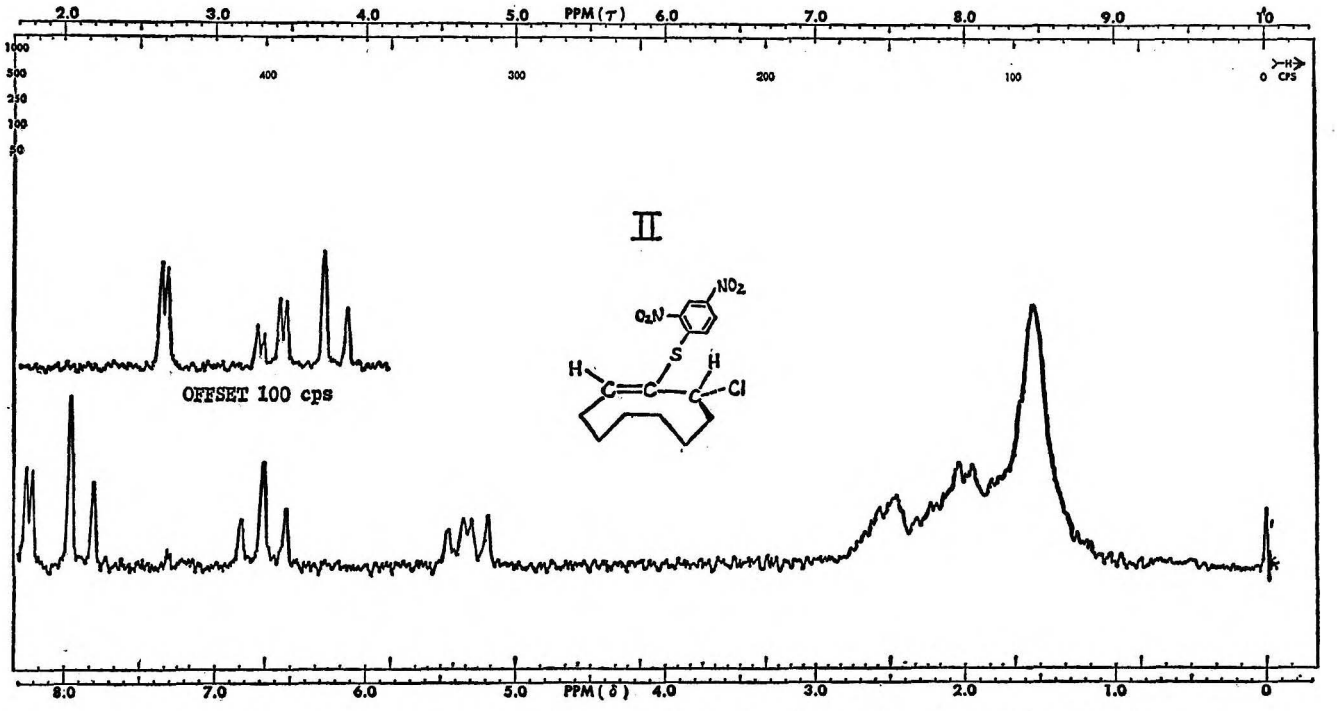


Figure 2.—The pmr spectrum of 3-chloro-2-(2,4-dinitrophenylthio)cyclononene ($CDCl_3$ solution).

reported[3] that addition of DBSC to optically active 2,2-dimethyl-3,4-hexadienol (1) yielded active 3-(2,4-dinitrophenylthio)-1,5,5-trimethyl-Δ^3-dihydropyran, a product of type B orientation. This was explained on the basis of formation of an episulfonium ion at the less hindered double bond, which opened only by direct attack of the nucleophile (in this case, oxygen). Earlier it was reported[4] that allene (1,2-propadiene) and DBSC gave the type B adduct, based on its transformation to chloroacetone. However, the product from DBSC and 1,2-cyclononadiene was assigned A type orientation[5] owing to its lack of reactivity toward alcoholic silver nitrate. We have now reexamined these last two compounds, and also the adduct from 3-methyl-1,2-butadiene, by the use of proton nmr spectroscopy, and in each case only the type B product was observed.

The adducts of DBSC with allene and 1,2-cyclononadiene were prepared as before.[4,5] The reaction of DBSC with excess 3-methyl-1,2-butadiene in carbon tetrachloride gave a 60% yield of a compound, mp 116.8–117.2°, which had the correct elemental composition for a 1:1 adduct. The pmr spectrum (in

(3) T. L. Jacobs, R. Macomber, and D. Zunker, *J. Amer. Chem. Soc.*, **89**, 7001 (1967).

(4) (a) T. L. Jacobs and R. N. Johnson, *ibid.*, **82**, 6397 (1960); (b) R. N. Johnson, Ph.D. Thesis, University of California at Los Angeles, 1960.

(5) W. R. Moore and R. C. Bertelson, *J. Org. Chem.*, **27**, 4182 (1962).

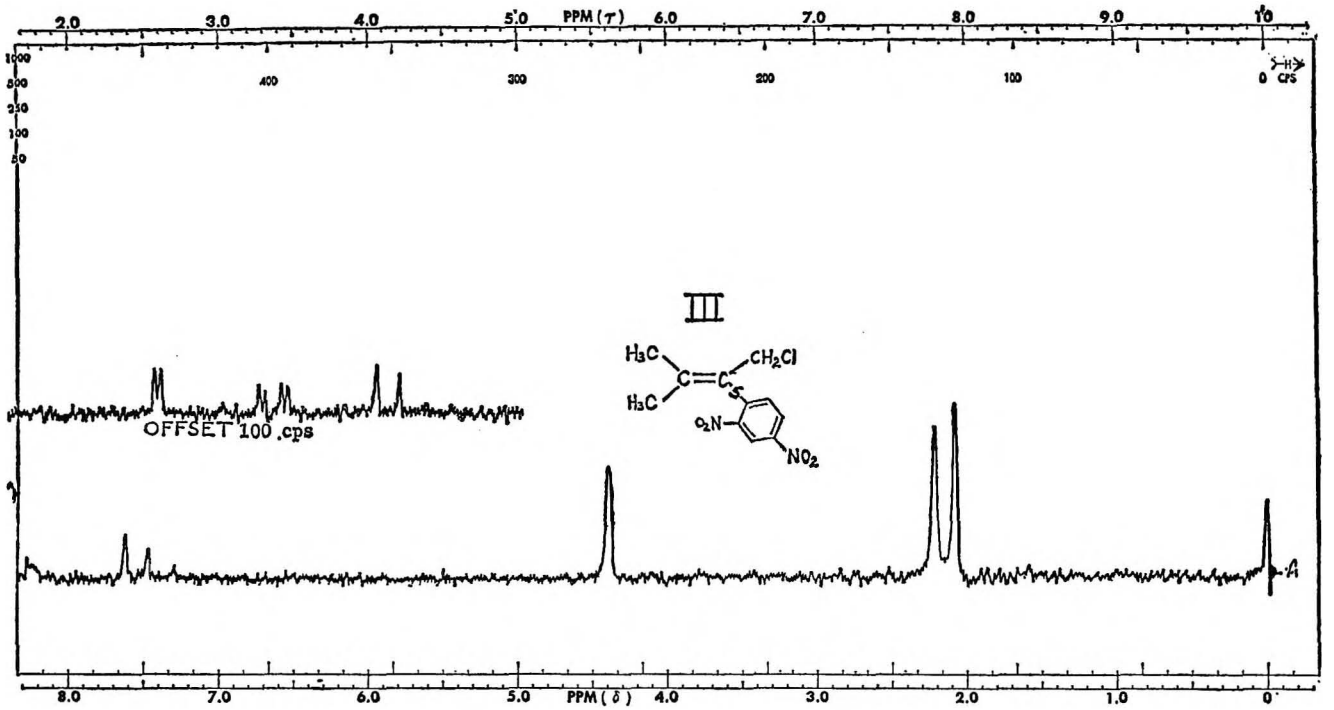


Figure 3.—The pmr spectrum of 4-chloro-3-(2,4-dinitrophenylthio)-2-methyl-2-butene ($CDCl_3$ solution).

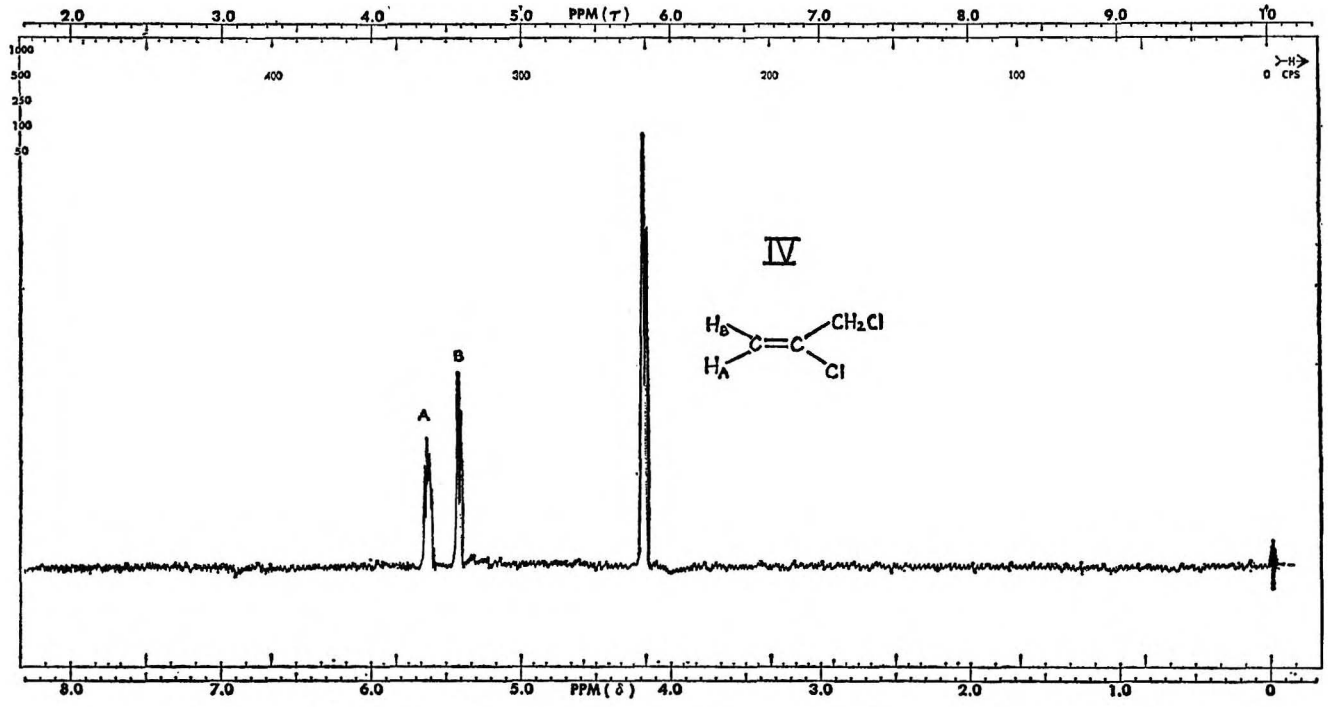


Figure 4.—The pmr spectrum of 2,3-dichloropropene ($CDCl_3$ solution).

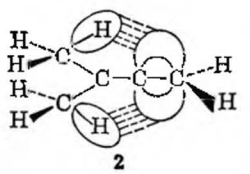
deuteriochloroform) of each is shown (Figures 1–3), together with that of 2,3-dichloropropene (Figure 4), which serves as a model compound.

Comparison of the spectrum in Figure 1 with that of the model compound indicates that the allene adduct is indeed 3-chloro-2-(2,4-dinitrophenylthio)propene, with B type orientation, as evidenced by the chlorine-substituted methylene protons at τ 5.8, and the olefinic protons at 3.5 and 3.8, deshielded 1 ppm from those expected of the type A adduct. The spectrum of the adduct from 1,2-cyclononadiene (Figure 2), shows an olefinic triplet (J = 9 cps) at τ 3.3. Recalling that the pmr spectrum of 1-chlorocyclooctene[6] exhibits an olefinic triplet (J = 8.4 cps) at τ 4.3, there remains little doubt that this adduct also has B type orientation, contrary to the previous report.[5]

Another dimension is added to this study with 3-methyl-1,2-butadiene. *A priori*, attack at the 2,3 double bond would be anticipated because the two methyl groups make it the more electron rich. Such is the observed orientation in bromination, epoxidation and addition of hydrogen chloride to this compound.

(6) M. R. St. Jacques, Ph.D. Thesis, University of California at Los Angeles, 1967.

Figure 3 indicates that in fact attack takes place at the sterically less-hindered 1,2 double bond, yielding 4-chloro-3-(2,4-dinitrophenylthio)-2-methyl-2-butene, a type B product. Although steric approach control is almost certainly important in the preference of this orientation, subtle electronic effects may also be operative. Whereas symmetry forbids overlap of the two mutually perpendicular π bonds of the allene system, there is evidence from the solvolyses of sulfonate esters of **1** that a methyl group increases the electron density in the more distant double bond.[7] This may arise from some type of "homohyperconjugation" effects involving the C–H single bonds of the methyl groups (see structure **2**). The pmr signal of the allenic protons of 3-methyl-1,2-butadiene are centered at τ 5.50 (heptet, J = 3 cps), approximately 0.2 ppm upfield from those of allene itself (τ 5.3), reflecting the increased electron density in the 1,2 bouble bond.



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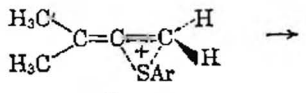
It is possible that 3-methyl-1,2-butadiene gives a mixture of adducts and that the product from attack at the 2,3 double bond was not isolated. This allene gave a crude reaction mixture which was somewhat more difficult to purify than products from any other of the allenes studied. However, the adduct isolated is certainly the major component. With all the other allenes yields were high enough to make it unlikely that type A products were formed in more than trace amounts.

It should perhaps be mentioned that if attack by DBSC on 3-methyl-1,2-butadiene occurs exclusively on one of the double bonds rather than both, a single adduct of type B orientation would be expected on the basis of the mechanism recently established,[3] which involves nucleophilic attack by chloride ion on episulfonium ion **3**. If **3** had opened to allylic cation **4**, one would expect two type B products: the one observed and **5**, because solvolyses of allylic compounds such as 3-chloro-3-methyl-1-butene seem always to give major amounts of the tertiary isomer.[8]



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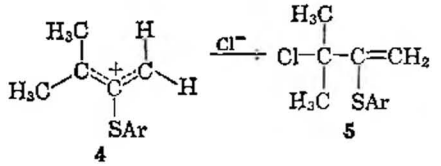

4 **5**

One point deserves further comment. Like the cycloallene adducts,[5] those from allene and 3-methyl-1,2-butadiene exhibit the same lack of reactivity toward silver nitrate. This contrasts with the high reactivity of typical allylic chlorides. Judging from the chemical shifts of the olefinic protons β to the 2,4-dinitrophenylthio moiety, it is likely that the electron density of the carbon–carbon double bond is significantly depleted. This, coupled with the cation destabilizing effect of the sulfur group also β to the incipient cationic center, may account for this anomolous unreactivity.

Registry No.—2,4-Dinitrobenzenesulfenyl chloride, 528-76-7; 3-chloro-2-(2,4-dinitrophenylthio)propene, 16626-76-9; 3-chloro-2-(2,4-dinitrophenylthio)cyclononene, 16626-78-1; 4-chloro-3-(2,4-dinitrophenylthio)-2-methyl-2-butene, 16626-77-0; 2,3-dichloropropene, 78-88-6.

(7) T. L. Jacobs and R. Macomber, *Tetrahedron Lett.*, 4877 (1967).

(8) R. H. DeWolfe and W. G. Young, *Chem. Rev.*, **56**, 794 (1956); "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 702.

Products of Acetolysis of 3-(3-Cyclohexenyl)propyl and 4-(3-Cyclohexenyl)butyl *p*-Toluenesulfonates

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Received February 27, 1968

About five years ago we examined a number of reactions which might serve as synthetic routes to bicyclo[x.3.1]alkanes.[1] As part of this effort the solvolysis of 3-(3-cyclohexen-1-yl)propyl and 4-(3-cyclohexen-1-yl)-butyl *p*-toluenesulfonates was examined, and, when the results proved unpromising, further work along this line was abandoned. Later Bartlett and his students[2] surveyed in considerable detail the structural features which influence the degree of double-bond participation in solvolysis. Taken in conjunction with the earlier work of Wilcox[3] in the 3-cyclohexen-1-ylcarbinyl system and of Winstein[4] on the 2-(3-cyclohexen-1-yl)ethyl derivatives, our data permit a view of an homologous series with a broader range of carbon chain lengths intervening between the double bond and the incipient cationic center than has previously been possible.

Synthesis of the desired alcohols was achieved in unexceptional manner by elaboration of the side chain in 3-cyclohexene-1-carboxaldehyde as is illustrated in Scheme I. The *p*-toluenesulfonates **1b** and **2b** were obtained in crude form and were used without purification when infrared spectra showed that all alcohol had been converted into the ester. Solvolyses were carried out in anhydrous acetic acid containing a quantity of sodium acetate sufficient to neutralize all strong acid produced in the solvolysis. Both **1b** and **2b** reacted slowly under these conditions and prolonged heating at 113–114° was required to complete the reaction. The product from **1b** was analyzed by glpc, and was found to contain at least 95% **1c**. Identification was made by comparison with an authentic sample. Two trace compo-

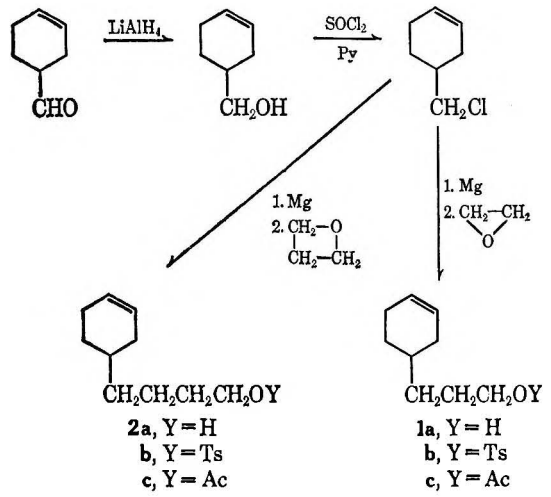
(1) The authors are pleased to make acknowledgment to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

(2) (a) P. D. Bartlett, S. Bank, R. J. Crawford, and G. H. Schmid, *J. Amer. Chem. Soc.*, **87**, 1288 (1965); (b) P. D. Bartlett and G. D. Sargent, *ibid.*, **87**, 1297 (1965); (c) P. D. Bartlett, W. D. Closson, and T. J. Cogdell, *ibid.*, **87**, 1308 (1965); (d) P. D. Bartlett, W. S. Trahanovsky, D. A. Bolon, and G. H. Schmid, *ibid.*, **87**, 1314 (1965).

(3) C. F. Wilcox, Jr., and S. S. Chibber, *J. Org. Chem.*, **27**, 2332 (1962).

(4) S. Winstein and P. Carter, *J. Amer. Chem. Soc.*, **83**, 4485 (1961).

SCHEME I



nents were not identified. The product from **2b** was similarly analyzed and found to contain not less than 96% **2c**.

Discussion

In Table I are gathered the results of studies of double bond participation of primary arenesulfonates with a double bond in a five- or six-membered ring. In the systems under consideration here, *i.e.*, those having a chain of from five to eight carbon atoms with a 1,2-disubstituted double bond at one end and a solvolyzable function on the other, it is quite clear that participation is most effective for the six-carbon chain. On the basis of the data listed the observation is valid only for double bonds in five- or six-membered rings and for acetolyses leading to a primary carbonium ion. There are, however, some published data which indicate that this suggestion may be applicable over a broader range of compounds and conditions. Thus, for example, both Δ^4-cycloocten-1-yl *p*-bromobenzenesulfonate,[5] and Δ^4-cyclohepten-1-ylmethyl *p*-toluenesulfonate[6] give cyclic products on acetolysis. Also 5-hexenyl *p*-nitrobenzenesulfonate cyclizes in part during acetolysis whereas its 4-pentenyl analog gives only open-chain products.[2c]

TABLE I

PRODUCTS OF ACETOLYSIS OF PRIMARY ARENESULFONATES WITH DOUBLE BONDS IN FIVE- OR SIX-MEMBERED RINGS

	% product		
Alkyl group	With participation	Without participation	Ref
2-(3-Cyclopentenyl)ethyl	100	0	*a*
3-(3-Cyclopentenyl)propyl	0	92–100	2d
2-(2-Cyclopentenyl)ethyl	0	100	*b*
3-(2-Cyclopentenyl)propyl	58	42	*b*
3-Cyclohexenylmethyl	0	100	3
2-(3-Cyclohexenyl)ethyl	80	20	4
3-(3-Cyclohexenyl)propyl	0	95	
4-(3-Cyclohexenyl)butyl	0	96	

[a] R. G. Lawton, *J. Amer. Chem. Soc.*, **83**, 2399 (1961). [b] W. D. Closson and G. T. Kwiatkowski, *ibid.*, **86**, 1887 (1964).

A structural basis for this empirical observation may exist in the possible conformations existing in the carbon chain in the transition state leading to double-bond participation. Bartlett and coworkers[2d] noted that 2-(3,4-dimethyl-3-cyclopentenyl)ethyl *p*-nitrobenzenesulfonate undergoes assisted acetolysis 600 times faster than 3-(3,4-dimethyl-3-cyclopentenyl)propyl *p*-nitrobenzenesulfonate. Of this rate difference a factor of 60 was attributable to an enthalpy difference, and only tenfold to the entropy difference. They suggested that in the transition state leading to double-bond participation every C–C bond with free rotation can attain a staggered conformation with the ethyl side chain, but the propyl side chain necessitates the presence of an eclipsed form. An inspection of models shows that a similar, though not always so pronounced, conformational effect is found in all of the examples of Table I. Thus when participation does occur the chain of methylene groups can be fitted into a series of nicely staggered forms at each C–C bond having free rotation. Conversely when participation does not take place some near eclipsed forms will be present in the chain.

Experimental Section

3-Cyclohexenylcarbinol.—A solution of 330 g (3 mol) of 3-cyclohexene-1-carboxaldehyde in 700 ml of anhydrous ether was added to 57 g (1.5 mol) of lithium aluminum hydride in 150 ml of ether. During the addition 200 ml of ether was added to maintain fluidity in the mixture. The reaction mixture was hydrolyzed with 3 *N* hydrochloric acid and the ether layer was dried (potassium carbonate). The product was distilled through a column packed with glass helices: bp 88–95° (25 mm); n^{21}D 1.4835; ν 3300, 3020, 1650 w, 1030, 655 cm^{-1}. A boiling point of 102° (19 mm) and n^{25}D 1.4828 has been reported[3] for this alcohol. The yield was 316 g (94%).

3-Cyclohexenylcarbinyl Chloride.—A mixture of 50 g (0.45 mol) of 3-cyclohexenylcarbinol and 42 g of anhydrous pyridine was added to 57 g (0.48 mol) of thionyl chloride over a 0.5-hr period. The reaction mixture was kept at *ca.* 60° throughout the addition and was then heated to 70–80° for 20 hr. The reaction mixture was taken up in ether, the pyridine hydrochloride was removed by filtration, and the ether solution was washed with water and dried (potassium carbonate). Distillation gave 35 g (60%) of a clear liquid: bp 67–68 (39 mm); n^{20}D 1.4831; $\bar{\nu}$ 3070, 1650 (w), 740, 652 cm^{-1}.

Anal. Calcd for $C_7H_{11}Cl$: C, 64.36; H, 8.49. Found: C, 64.42; H, 8.69.

3-(3-Cyclohexenyl)propyl Alcohol (1a).—A solution containing 100 g (0.77 mol) of 3-cyclohexenylcarbinyl chloride in 200 ml of anhydrous ethyl ether was added to 20 g (0.83 g-atom) of magnesium. The solution of the Grignard reagent was cooled to −10° in an ice–salt bath and 75 g (1.7 mol) of ethylene oxide was added over a 30-min period. The reaction mixture was allowed to warm to room temperature and to stand overnight. The mixture was hydrolyzed with dilute sulfuric acid and the ether layer dried over potassium carbonate. Distillation gave 59.5 g (55%) of **1a**: bp 110–112° (12 mm); n^{25}D 1.4792; $\bar{\nu}$ 3380, 3020, 1055, 652 cm^{-1}; nmr (CCl_4), δ 1.0–2.2 (m), 3.60 (t, J = 6.5 cps), 5.64 (s).

Anal. Calcd for $C_9H_{16}O$: C, 77.20; H, 11.40. Found: C, 77.10; H, 11.38.

3-(3-Cyclohexenyl)propyl Acetate (1c).—A mixture of 1.95 g (14 mmol) of **1a**, 2.5 g of acetic anhydride, 2 ml of anhydrous pyridine, and 70 ml of benzene were heated under reflux for 5 hr. Distillation gave 2.2 g (86%) of **1b**: bp 85° (2 mm); n^{20}D 1.4613; $\bar{\nu}$ 3020, 1740, 1240, 1045, 653 cm^{-1}; nmr, (CCl_4) δ 1.0–2.2 (m), 1.94 (s, 3, MeCO), 3.98 (t, J = 6.4 cps), 5.60 (s).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.92. Found: C, 72.51; H, 9.91.

4-(3-Cyclohexenyl)butyl Alcohol (2a).—Grignard reagent from 3.0 g (0.125 g-atom) of magnesium and 16.3 g (0.125 mol) of 3-cyclohexenylcarbinyl chloride was prepared in 100 ml of THF under nitrogen. To this solution was added 4.35 g (0.075 mol) of trimethylene oxide[7] in 20 ml of THF. The reaction solution

(5) A. C. Cope, J. M. Grisar, and P. E. Peterson, *J. Amer. Chem. Soc.*, **82**, 4299 (1960).

(6) G. LeNy, *Compt. Rend.*, **251**, 1526 (1960).

(7) S. Searles, *J. Amer. Chem. Soc.*, **73**, 124 (1951).

was heated at 45–65° for 24 hr. The Grignard complex was hydrolyzed with saturated ammonium chloride and the organic products were extracted with ethyl ether. Distillation gave 4.3 g (37%) of 2a: bp 73–75° (0.5 mm); $n^{20}D$ 1.4803; $\bar{\nu}$ 3300, 3070, 1650 (w), 1032, 730, 652.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.60; H, 11.47.

4-(3-Cyclohexenyl)butyl Acetate (2c).—A mixture of 2a (1.5 g, 9.8 mmol), 4.0 g of acetic anhydride, and 8 ml of pyridine was heated under reflux for 5 min. The mixture was poured on ice and the organic products were taken up in ether. Distillation gave 1.2 g (61%) of 2c: $n^{20}D$ 1.4638; $\bar{\nu}$ 3025, 1740, 1650 (w), and 1240; nmr (CCl_4), δ 1.2–2.2 (m), 1.92 (s, 3, CH_3CO), 4.01 (t, J = 6.3 cps), 5.63 (s).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.29; H, 10.25.

Acetolyses.—A sample of 1b was prepared in 87% yield by the method of Tipson:[8] $\bar{\nu}$ 3020, 1360, 1190, 1175, 955, 930, 653. The crude 1b (7.16 g, 24.4 mmol) was dissolved in 500 ml of anhydrous acetic acid containing 2.1 g (25.6 mmol) of dry sodium acetate. The solution was stirred at 113–114° for 94 hr. About 500 ml of water was added to the cooled solution, and the organic products were extracted with several portions of hexane. The combined hexane extracts were washed with sodium bicarbonate and then dried and concentrated. The residue weighed 4.16 g (108% calculated as 1c). Aside from a small amount of hexane, this contained 1c and two trace components (*ca.* 5% total). Analysis was made by glpc on a 6-ft Carbowax 1500 column at 156° using helium as a carrier gas. Distillation of the crude acetolysis mixture gave 3.52 g (78.5%) of 1c identical in infrared and nmr spectra with those of the sample prepared directly from 1a.

Similarly a sample (1.23 g) of 2b was heated at 113–114° for 72 hr. The organic products were isolated as described above and, after removal of the hexane, 1.0 g (128% calculated as 2c) of residual material was recovered. This was analyzed by glpc at 171° on a 10-ft UCON nonpolar column, and was found to consist of hexane, 2c, and two trace components. Exclusive of the hexane, the composition of this mixture was 96% 2c and 4% trace components. The main component was identified as 2c by use of an internal standard.

Registry No.—1a, 16626-54-3; 1b, 16626-55-4; 1c, 16626-56-5; 2a, 16626-57-6; 2b, 16626-58-7; 2c, 16626-59-8; 3-cyclohexenylcarbinyl chloride, 2555-08-0.

(8) S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

The Electronic Spectra of Some Air-Sensitive Phosphorus Ylides[1,2]

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Received January 12, 1968

Air-sensitive alkylidenephosphoranes (phosphinemethylenes, phosphorus ylides) are important in organic synthesis, but very few physical properties have been obtained[3] for these compounds. Recently, proton[4] and phosphorus[5] nuclear magnetic resonance data have been reported.

We report here the ultraviolet-visible spectra in hexane solution of seven of these air-sensitive compounds (Table I). Each of the spectra consists of two main absorptions in the region (200–600 mμ) examined, *viz.*, a structured band centered about 265 mμ and a broad peak at longer wavelength in the 340–400-mμ range. The 265-mμ peak is constant within experimental error for all the compounds in this study. It is due to the benzene absorption and has been discussed previously[6] for the somewhat analogous compound, triphenylphosphine oxide.

TABLE I

ULTRAVIOLET MAXIMA AND ^{31}P CHEMICAL SHIFTS FOR SOME AIR-SENSITIVE PHOSPHORUS YLIDES

Compound[a]	λ_{max}, mμ		δ (ppm) *vs.* 85% H_3PO_4[b]
$(C_6H_5)_3P{=}O$	266		−25.5[c]
$(C_6H_5)_3P{=}CH_2$	265	341	−20.3
$(C_6H_5)_3P{=}CHCH_3$	265	374	−14.6
$(C_6H_5)_3P{=}CHCH_2CH_3$	265	378	−12.2
$(C_6H_5)_3P{=}CH(CH_2)_2CH_3$	264	375	−12.6
$(C_6H_5)_3P{=}CH(CH_2)_4CH_3$	264	377	−12.2
$(C_6H_5)_3P{=}C(CH_3)_2$	265	386	−11.3
$(C_6H_5)_3P{=}C(CH_2)_5$	265	391	−6.4

[a] Registry no. are given in descending order: 791-28-6, 3487-44-3, 1754-88-7, 16666-78-7, 3728-50-5, 16666-79-8, 16666-80-1, 16666-81-2. [b] See ref 5. [c] In dimethyl sulfoxide. Literature values, −23.0 to −27.0: V. Mark, *et al.*, "Topics in Phosphorus Chemistry," Vol. 5, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, Inc., New York, N. Y., 1967, p 285.

The long-wavelength peak varies as the alkylidene group changes, and it is the absorption of interest. It is seen that the substitution of a methyl group for a methylene hydrogen in the parent compound, methylenetriphenylphosphorane, gives rise to a bathochromic shift of 33 mμ. Substitution of longer chain alkyl groups causes only slight further shifts of several millimicrons to longer wavelengths. Substitution by another methyl for the second methylene hydrogen causes an additional bathochromic shift of 12 mμ.

In the case of the resonance-stabilized, charge-delocalized ylides, the more extensive the conjugated system becomes, the greater is the bathochromic shift.[7]

At first glance, these data seem contradictory, *i.e.*, both increasing electron-withdrawing (by delocalization of the methylenic negative charge) character and electron-releasing (by induction of alkyl substituents) character of the groups cause shifts to longer wavelengths. However in the case of the resonance-stabilized ylides, the substituent on the methylene carbon contains a chromophore and extensive conjugation serve to lower the π^* energy levels. The phosphorus in this case probably contributes only slightly as an auxochrome by participating in the conjugation,[7] and the transition is undoubtedly $\pi \rightarrow \pi^*$ (or $n \rightarrow \pi^*$ depending on the nature of the substituent). Further evidence for this slight participation by phosphorus in the resonance-stabilized ylides is provided by their

(1) Supported by the National Science Foundation under Grant No. GP 4483.

(2) Taken from the M.S. Thesis of J. H. Ambrus, University of Maryland, 1966.

(3) A. W. Johnson, "Ylid Chemistry," Academic Press Inc., New York, N. Y., 1966, pp 76–79.

(4) H. J. Bestmann and J. P. Snyder, *J. Amer. Chem. Soc.*, **89**, 3937 (1967), and references cited therein.

(5) S. O. Grim, W. McFarlane, and T. J. Marks, *Chem. Commun.*, 1191 (1967).

(6) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p 500.

(7) H. Fischer and H. Fischer, *Chem. Ber.*, **99**, 658 (1966).

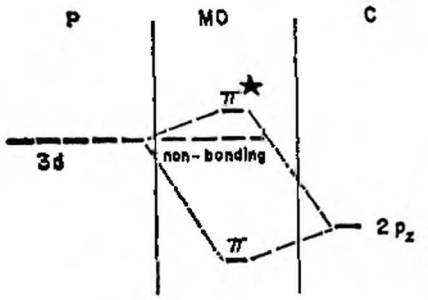

Figure 1.—Simple energy level diagram for nonconjugated phosphorus ylides.

phosphorus-31 chemical shifts, which are very similar to those of the corresponding phosphonium salts from which they are derived.[3,5]

In the colored air-sensitive ylides, the methylene carbon–phosphorus bond system must be the chromophore. A simple energy level diagram is given in Figure 1. If phosphorus is bonded to the four attached atoms by sp^3 hybrids and carbon is bonded to its three attached atoms by sp^2 hybrids and if the methylene carbon–phosphorus bond is taken as the x axis with the carbon sp^2 hybrids lying in the xy plane, then the remaining carbon p orbital has the same π symmetry as the d_{xz} orbital[3] of phosphorus and can combine to form a π bonding and an antibonding orbital. The transition could be $\pi \rightarrow$ 3d or $\pi \rightarrow \pi^*$. The $\pi \rightarrow$ d transition represents an electronic transfer from a molecular orbital mainly on carbon to an empty nonbonding 3d orbital of phosphorus. This would not be greatly different from the $\pi \rightarrow \pi^*$ transition, which is the transition from the molecular orbital mainly on carbon to the antibonding orbital composed mainly of the 3d orbital of phosphorus. The usual methods for differentiating between $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$, for example, are of limited use for discriminating between $\pi \rightarrow \pi^*$ and $\pi \rightarrow$ d. First, two methods,[8] *viz.*, the magnitude of the extinction coefficients and the shift of wavelength with change in solvent polarity, are experimentally very difficult in this case because of the great reactivity of the compounds (see Experimental Section). Second, apparently $\pi \rightarrow$ d transitions have not been discussed previously; so there is no mention of selection rules for such transitions.

Although the intensity of the long-wavelength peak in fresh solution is an order of magnitude less than the intensity of the benzene absorption, any decomposition of the ylide would result in loss of the long-wavelength peak intensity with no decrease in the benzene absorption. Because of the air-sensitive nature of the compounds, reliable values for the extinction coefficients were not obtained.

In either case, $\pi \rightarrow$ d or $\pi \rightarrow \pi^*$, substitution by alkyl groups would tend to destabilize the π bond (raise the π-energy level) of these compounds with a large proportion of carbanionic character, and thereby lower the transition energy so that increased alkyl substitution leads to bathochromic shifts.

It should be pointed out that, with free rotation about the phosphorus–methylene carbon bond, the *dxz* and *dxy* orbitals of phosphorus would become equivalent and the bonding and antibonding orbitals would contain equal amounts of these orbitals. Also, in this symmetry for phosphorus, the remaining 3d orbitals would not be degenerate. For simplicity, this is not shown in the figure.

The quantitative correlation between changes in λ_{max} and the phosphorus chemical shifts is interesting (see Table I), with both being related to the inductive effect. The most significant changes in the λ_{max} occur for one and two methyl substitutions on the methylene carbon, whereas larger alkyl groups cause a less significant change. Ths phosphorus chemical shifts have been discussed briefly previously.[5] The rather unexpected chemical shift of the cyclohexyl derivative is not understood at present.

Experimental Section

Spectra of the solutions in 1-cm quartz cells were recorded with a Cary Model 14 spectrometer.

Preparation of Phosphonium Salts.—*n*-Alkyltriphenylphosphonium bromides were prepared by the direct reaction of triphenylphosphine and the alkyl bromide in refluxing benzene. *sec*-Alkyltriphenylphosphonium salts were prepared in a Carius tube from the alkyl bromide and triphenylphosphine without solvent at 140°. All bromides gave acceptable analyses, except the cyclohexyl compound which is extremely hygroscopic. It was converted into the hexafluorophosphate for analysis.

Cyclohexyltriphenylphosphonium Bromide.—Triphenylphosphine (10 g, 0.038 mol) and bromocyclohexane (6.1 g, 0.038 mol) were placed in a 25 × 320 mm medium-walled Pyrex tube. After degassing, the contents were cooled to −78° and the tube was sealed. The Carius tube was heated in an oven at 140° for 24 hr. After cooling the tube was opened in a glove bag filled with N_2. The contents of the tube were dissolved in a minimum amount of isopropyl alcohol and then reprecipitated by the addition of diethyl ether. The solid was separated by decantation, then washed with ether and the mixture decanted again. While ether-wet, the solid was removed from the glove bag and transferred to a vacuum oven and dried at 60° (5 torr). Nitrogen was released into the oven and the flask containing the cyclohexyltriphenylphosphonium bromide, mp 273–276°, was quickly stoppered.

Preparation of Alkylidenephosphoranes.—A 100-ml, three-necked flask, equipped with Dry Ice condenser, mechanical ground glass stirrer, and stopper, was flushed with nitrogen and insulated with asbestos cloth, and 30–40 ml of ammonia was introduced. A small crystal of $Fe(NO_3)_3 \cdot 9H_2O$ was added, followed by sodium (0.12 g, 0.005 g-atom). The mixture was stirred until the blue color had disappeared and the Na had been converted into $NaNH_2$. Finely powdered phosphonium salt (0.005 mol) was added at once and the mixture was stirred for 10 min. The bright color characteristic of the alkylidenephosphoranes appeared immediately. The insulation was removed; the Dry Ice condenser was replaced by an adaptor with a three-way stopcock for N_2 inlet and NH_3 outlet to a Hg bubbler; the stopper was replaced by a dropping funnel with 50 ml of degassed hexane; and the mixture was stirred as the NH_3 evaporated. After the NH_3 had evaporated, the hexane was added and after stirring for a few minutes the mixture was allowed to settle. Several drops of the solution was added *via* syringe to the quartz cells which had previously been almost filled with degassed hexane. The spectra were recorded immediately. After a short time the long-wavelength band began to decrease in intensity and usually disappeared after several hours. For this reason, it was difficult to estimate the extinction coefficient for the long-wavelength band, although it was generally about one-tenth the intensity of the 265-mμ band when the spectra were recorded immediately after preparation of the sample.

Registry No.—Cyclohexyltriphenylphosphonium bromide, 7333-51-9.

Acknowledgment.—We are grateful to T. J. Marks for some experimental assistance.

A 5-Aza Analog of $\Delta^{6a(10a)}$-Tetrahydrocannabinol

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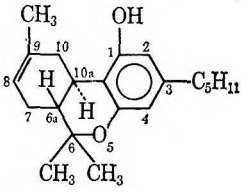
Received January 8, 1968

It has been shown that the active constituents of hashish (marijuana) are *l*-Δ^8-tetrahydrocannabinol **1**[1] and *l*-Δ^9-tetrahydrocannabinol **2**.[2] The early work of



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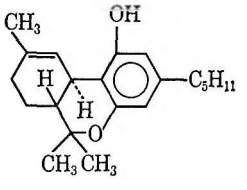
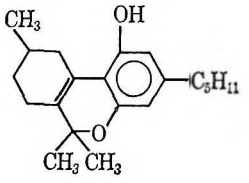


2

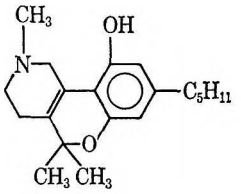
Adams and Todd and their collaborators[3] led to the synthesis of the physiologically active $\Delta^{6a(10a)}$-tetrahydrocannabinol isomer **3**.



3

Pars, *et al.*,[4] prepared the 9-aza analog **4** of the $\Delta^{6a(10)}$ isomer.

We now wish to report the synthesis of a 5-aza analog **5** of the $\Delta^{6a(10a)}$ isomer.



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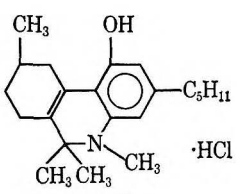
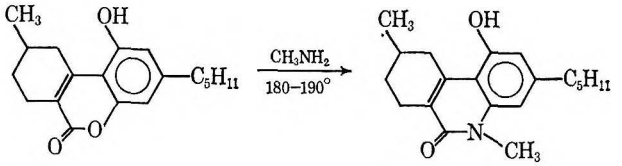


5

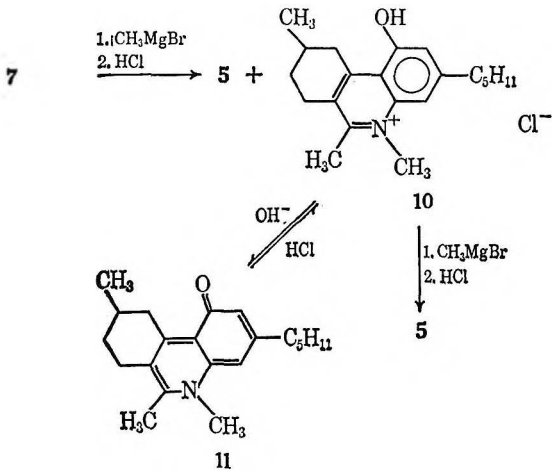
Although conversion of α- and β-pyrones into the corresponding 2- and 4-pyridones have been achieved by reaction with ammonia or aliphatic amines,[5] and similarly isoquinolines have been prepared from the corresponding isocoumarins,[6] no synthesis of tetrahydrophenanthridinones has been reported from a reaction of an aliphatic amine with the corresponding 6-dibenzopyrones. However, it has been found that heating the dibenzopyrone **6** with methylamine at 180–190° in a sealed tube for several days yielded the tetrahydrophenanthridin-6-one **7**.



6 **7**

The reaction probably proceeds through an initial formation of an amidoresorcinol **8** which then undergoes a Bucherer-type reaction to give the amino phenol **9**. Transaminating cyclization then yields **7**. A strong base is presumably required for this reaction, as it failed to take place with either ammonia or benzylamine. (See Scheme I.)

Treatment of **7** with an excess of methylmagnesium bromide yielded two products in about the same amounts, the tetrahydrophenanthridine as its hydrochloride **5** and the 6-methylphenanthridinium chloride **10**.

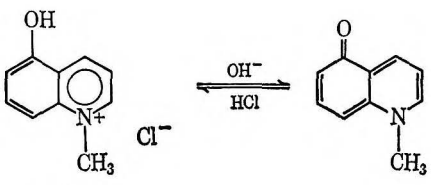


10 **11**

Further treatment of the quaternary salt **10** with methylmagnesium bromide yielded **5**.

When the yellow quaternary salt **10** was treated with alkali, a deep violet color was observed $\lambda_{max}^{CH_3OH/pH\ 11}$ 284 mμ (ϵ 35,000), 340 (3500), 470 (4900)].

The similar spectral data of the known quinolinium chloride[7] **12** [$\lambda_{max}^{EtOH/pH\ 8.5}$ 273 mμ (ϵ 33,000), 318 (1240), 332 (1150), 462 (3800)] led to the structural assignments **10** and **11**.



12

(1) Y. Gaoni and R. Mechoulam, *J. Amer. Chem. Soc.*, **86**, 1646 (1964).

(2) R. L. Hively, W. A. Moshen, and F. W. Hoffmann, *ibid.*, **88**, 1832 (1966).

(3) R. Adams and B. R. Baker, *ibid.*, **62**, 2405 (1940); R. Ghosh, A. R. Todd, and S. Wilkonsin, *J. Chem. Soc.*, 1121 (1940).

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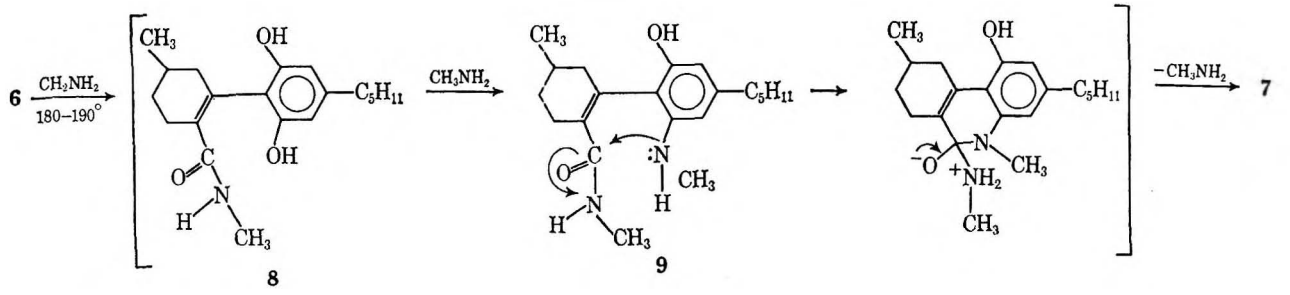
(7) S. F. Mason, *J. Chem. Soc.*, 5010 (1957); W. Schneider and A. Pothmann, *Ber.*, **74B**, 471 (1941).

SCHEME I



Experimental Section

Melting points were determined on a Thomas–Hoover Unimelt and are uncorrected. Ultraviolet spectra were determined on a Beckman Model DK-2A ultraviolet spectrophotometer in methanol solution, unless otherwise stated. Ascending thin layer chromatography was performed on Eastman silica gel chromatogram sheets, K301R. Analyses were performed by Mr. Charles Pouchert of our analytical department.

7,8,9,10-Tetrahydro-1-hydroxy-5,9-dimethyl-3-*n*-pentylphenanthridin-6-one (7).—A mixture of 0.5 g (1.67 mmol) of 7,8,9,10-tetrahydro-1-hydroxy-3-*n*-pentyl-6-dibenzopyrone[3] (6) and 2.7 g (35 mmol) of 40% aqueous methylamine was heated in a Carius tube at 190 ± 5° for 42 hr. After cooling to room temperature, methylene chloride was added and the mixture was washed with 2 *N* hydrochloric acid. The organic layer was dried over magnesium sulfate and evaporated to dryness yielding 0.5 g (95.5% theory) of the product, mp 216–219°. Recrystallization from ethyl acetate yielded fine colorless needles, mp 219–220°.

Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.83; H, 8.45; N, 4.39.

7,8,9,10-Tetrahydro-1-hydroxy-5,6,6,9-tetramethyl-3-*n*-pentylphenanthridine Hydrochloride (5) and 7,8,9,10-Tetrahydro-1-hydroxy-5,6,9-trimethyl-3-*n*-pentylphenanthridinium Chloride (10).—To a refluxing solution of 1.8 g (5.74 mmol) of 7,8,9,10-tetrahydro-1-hydroxy-5,9-dimethyl-3-*n*-pentylphenanthridin-6-one (7) in 125 ml of dry benzene, 16.7 ml (50 mmol) of a 3 *N* solution of methylmagnesium bromide in ether was added over a 5-min period. After heating under reflux for 26 hr, addition of 50 ml of 2 *N* hydrochloric acid to the cooled (0°) reaction mixture resulted in the formation of a yellow-orange precipitate. The solid (shown by tlc with 1:1 methanol–ethyl acetate on silica to contain two components) was twice recrystallized from 5% aqueous methanol, yielding 0.72 g (34.6% theory) of **5** (the faster moving component on tlc) as colorless plates: mp 233–235° dec; $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 27,400), 293 (6000); $\lambda_{max}^{CH_3OH\text{-}HCl}$ 262 mμ (ε 12,100), 304 (8500); $\lambda_{max}^{CH_3OH/pH\ 11}$ 242.5 mμ (ε 25,600); ir absorption, 3.26 (OH), 4.01 ($^+$NH), 6.11 (s, conjugated C=C), 6.35 μ (Ph).

Anal. Calcd for $C_{22}H_{34}ClNO$: C, 72.59; H, 9.42; Cl, 9.74; N, 3.85. Found: C, 72.61; H, 9.45; Cl, 9.79; N, 3.96.

Evaporation of the mother liquor to dryness gave a solid which upon recrystallization from ethyl acetate gave 0.55 g (38.4% theory) of **10** as a yellow solid: mp 138–145° after charring at 125°; $\lambda_{max}^{CH_3OH}$ 267 mμ (ε 43,500), 289 (7500); $\lambda_{max}^{CH_3OH\text{-}HCl}$ 267 mμ (ε 54,100); $\lambda_{max}^{CH_3OH/pH\ 11}$ 284 mμ (ε 35,000), 340 (3500), 470 (4900); ir absorption, 2.97 (OH), 6.18 (C=C), 6.40 μ (Ph).

Anal. Calcd for $C_{21}H_{30}ClNO$: C, 72.49; H, 8.69; Cl, 10.19; N, 4.02. Found: C, 72.59; H, 8.68; Cl, 10.20; N, 4.09.

7,8,9,10-Tetrahydro-1-hydroxy-5,6,6,9-tetramethyl-3-*n*-pentylphenanthridine Hydrochloride (5) from 7,8,9,10-Tetrahydro-1-hydroxy-5,6,9-trimethyl-3-*n*-pentylphenanthridinium Chloride (10).—A solution of methylmagnesium bromide (16.7 ml, 3 *N*, 50 mmol) in ether was added to a refluxing solution of 1.7 g (4.9 mmol) of **10** in 125 ml of dry benzene over a 5-min period. After heating under reflux for 24 hr, the cooled (0°) reaction mixture was decomposed with 50 ml of 2 *N* hydrochloric acid; the yellow precipitate which separated was taken up in methylene chloride and washed with 2 *N* hydrochloric acid. A white solid, insoluble in either phase, was filtered, yielding 0.7 g (39.3% theory) of **5**. The methylene chloride solution was dried and the solvent evaporated, yielding 0.9 g of the starting material.

Registry No.—**5**, 16666-72-1; **7**, 16666-73-2; **10**, 16666-74-3.

A Novel Synthesis of 2,3-Seco-A-nor-5α-cholestane-2,3-diol[1a]

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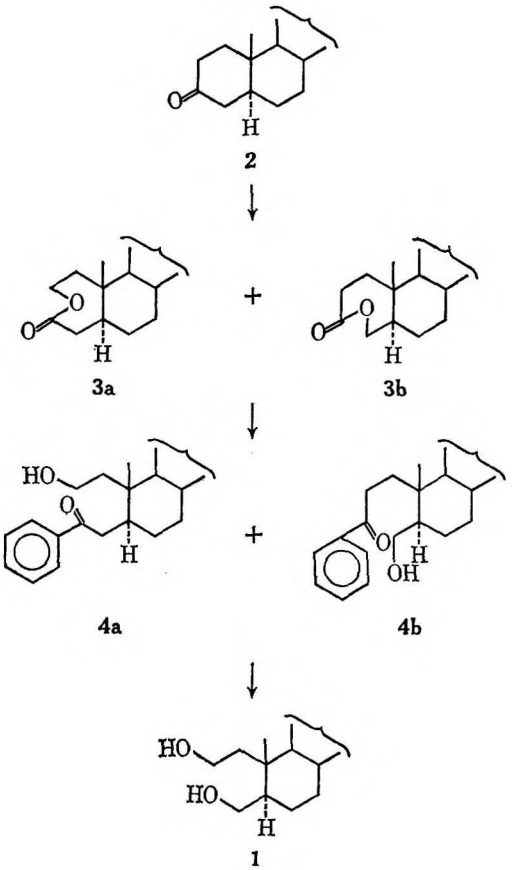
Received February 5, 1968

In connection with other work in these laboratories, it became necessary to prepare 2,3-seco-A-nor-5α-cholestane-2,3-diol [**1** (Scheme I)]. Seconordiols, useful intermediates in the synthesis of thia[2,3] and oxa[4]

SCHEME I



(1) (a) This work was supported by the Air Force Office of Scientific Research under Grant No. AF-AFOSR-1188-67. (b) National Defense Education Act Fellow, 1967–1968.

(2) R. Nagarajan, B. H. Chollar, and R. M. Dodson, *Chem. Commun.*, 550 (1967).

(3) P. B. Sollman, R. Nagarajan, and R. M. Dodson, *ibid.*, 552 (1967).

(4) *Cf.* C. Djerassi, Ed., "Steroid Reactions, an Outline for Organic Chemists," Holden-Day, Inc., San Francisco, Calif., 1963, Chapter 12.

steroids, and possible precursors to aza and phospha steroids, are obtainable at present only through lengthy reaction sequences, *e.g.*, by an eleven-step synthesis[2] from 5α-cholestan-3-one (**2**). The present paper describes a simple synthesis of seconordiol **1** by a four-step synthesis from **2**.

Baeyer–Villiger oxidation of **2**[5,6] with *m*-chloroperbenzoic acid afforded a mixture of A-homo-3-oxacholestan-4-one (**3a**) and A-homo-4-oxacholestan-3-one (**3b**). Reaction of the crude lactone mixture with phenylmagnesium bromide gave a mixture of the phenyl hydroxy ketones **4a** and **b**.[7] Oxidation with *m*-chloroperbenzoic acid,[8] followed by saponification, gave **1** in 16% yield based on **2**. No systematic attempts were made to maximize the yield.

Identification of **1** was based on its conversion to 3α- and 3β-thiacholestane oxides (**5a** and **5b**) by reaction of the dimesylate of **1** with sodium sulfide, followed by oxidation and separation of the diastereomeric sulfoxides.[2] The physical properties of **5a** and **5b** prepared from **1** are in accord with those previously described.[2]

We believe that this abbreviated synthesis, in essence amounting to the extrusion of a carbonyl group, may prove generally applicable to the synthesis of precursors to hetero steroids.

Experimental Section[9]

Oxidation of 5α-Cholestan-3-one.—A solution of 18.7 g (48.5 mmol) of 5α-cholestan-3-one and 15 g of 85% *m*-chloroperbenzoic acid in 150 ml of chloroform was stirred for 42 hr at room temperature and then heated for 2 hr at reflux. During this period the reaction mixture was protected from light. Approximately 75 ml of water and 25 ml of ether were poured into the reaction mixture and the organic layer was washed with dilute (*ca.* 5%) sulfuric acid, dilute (*ca.* 5%) aqueous sodium carbonate, and water until neutral. The organic layer was dried over anhydrous magnesium sulfate and filtered; the solvent was removed under reduced pressure. The resulting solid was recrystallized from benzene–pentane mixtures to give 15.4 g (79%) of material (mixture of lactones **3a** and **3b**) of mp 176–185° (lit.[5] mp 180–183°).

2,3-Seco-A-nor-5α-cholestane-2,3-diol.—The mixture of lactones from the oxidation of **2** (9.82 g, 24.4 mmol) was dissolved in 90 ml of anhydrous ether and 80 ml of anhydrous benzene. The solution was kept under a nitrogen atmosphere and cooled to −25° as freshly prepared phenylmagnesium bromide (approximately 24 mmol) in ether was added over a period of 2.5 hr. After stirring for 0.5 hr more, the reaction mixture was hydrolyzed with saturated aqueous ammonium chloride and warmed to room temperature, and the organic layer was separated. The ether–benzene extract was washed with dilute hydrochloric acid and water until neutral and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to yield 11.35 g of a mixture of the ketones **4a** and **4b**. The infrared spectrum of this mixture showed strong absorption at 3400 cm^{-1} (OH stretch) and at 1685 and *ca.* 1600 cm^{-1} (aryl carbonyl and aryl stretch).

The mixture of ketones (11.35 g) was dissolved in 75 ml of chloroform, and 7.5 g of 85% *m*-chloroperbenzoic acid was added. The reaction mixture was protected from light and stirred at room temperature for 46 hr. Sufficient ether and water was added to the reaction mixture to afford a clean separation. The organic layer was washed with dilute sulfuric acid (*ca.* 5%), aqueous sodium carbonate (*ca.* 5%), and water until neutral, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under reduced pressure. The glassy residue (9.31 g) was dissolved in a solution of alcoholic potassium hydroxide (2.0 g in 100 ml) and heated at reflux for 5 hr. The solvent was removed by distillation and the residue diluted with ether and water. The ether layer was washed with water until neutral, dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent under reduced pressure and recrystallization of the residue from pentane afforded 2,3-seco-A-nor-5α-cholestane-2,3-diol: mp 136.5–137.5°; $[\alpha]_D$ 17.1° (*c* 2.52, chloroform). The yield of diol based on cholestan-3-one was 16%. The nmr spectrum of **1** showed chemical shifts at 39.3 (18-Me) and 46.9 Hz (19-Me).

Anal. Calcd for $C_{26}H_{48}O_2$: C, 79.53; H, 12.32. Found: C, 79.27; H, 12.65.

3-Thia-5α-cholestane (6).—A solution of diol **1** (1.25 g, 3.18 mmol) in 10 ml of dry pyridine was cooled to −20° as methanesulfonyl chloride (1 ml) was added. The solution was allowed to stand at −20° for 4.5 hr and at 5° for 18 hr. The brown solution containing crystals of pyridine hydrochloride was poured over ice and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The crude dimesylate was dissolved in 75 ml of refluxing ethanol and 7.7 g of sodium sulfide nonahydrate dissolved in a minimal volume of water was added. The mixture was refluxed for 24 hr, after which time thin layer chromatography (silica gel plates, pentane developer, iodine stain) indicated that the reaction was complete. The ethanol was distilled and the residue was taken up in ether and water. The ether layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure to afford 3-thia-5α-cholestane (1.13 g, 91%). The product was recrystallized from methanol–ether mixtures to yield material of mp 98.5–99.5°. The nmr spectrum showed chemical shifts at 39.5 (18-Me) and 49.7 Hz (19-Me).

Anal. Calcd for $C_{26}H_{46}S$: C, 79.93; H, 11.87; S, 8.21. Found: C, 79.80; H, 12.00; S, 8.50.

3-Thia-5α-cholestane 3-Oxides.—The sulfide **6** (0.508 g, 1.30 mmol) was dissolved in 10 ml of methylene chloride and the resulting solution was held at 5° as a solution of 0.265 g of *m*-chloroperbenzoic acid in 5 ml of methylene chloride was added dropwise. The reaction mixture was stirred for 17 hr at 5° and for 3 hr at room temperature, poured into saturated aqueous sodium bicarbonate solution, and extracted two times more with sodium bicarbonate and once with water. The organic layer was separated, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under reduced pressure to yield a mixture of 3-thia-5α-cholestane 3-oxides. As determined from the relative intensities of the 18-Me group the mixture consisted of approximately 40% 3α epimer and 60% 3β epimer. The crude product weighed 0.51 g (97%).

The oxides were separated by column chromatography over 65 g of alumina. The column was developed with benzene and elution was achieved with 30% ethyl acetate in benzene. A compound identical with that reported[2] as 3-thia-5α-cholestane 3α-oxide (**5a**) was eluted first: mp 229–233°; nmr (benzene) 29.0 (18-Me), and 38.2 (Hz (19-Me); infrared (Nujol) absorption at 1020, 1030, and 1037 cm^{-1} [lit.[2] mp 227–229°; nmr 28.5 (18-Me) and 38 Hz (19-Me); infrared absorption at 1022, 1030, and 1038 cm^{-1}].

The second product eluted was identified as 3-thia-5α-cholestane 3β-oxide (**5b**): mp 230–233°; nmr (benzene) 33.5 (18-Me) and 35.3 Hz (19-Me); infrared (Nujol) absorption at 1060 cm^{-1} [lit.[2] mp 229–232°, nmr 32 (18-Me) and 35.5 Hz (19-Me); infrared absorption at 1060 cm^{-1}].

Registry No.—**1**, 16666-71-0; **4a**, 16666-68-5; **4b**, 16666-69-6; **6**, 16666-70-9.

(5) V. Burckhardt and T. Reichstein, *Helv. Chim. Acta*, **25**, 1434 (1942).

(6) S. Hara, N. Matsumoto, and T. Takeuchi, *Chem. Ind.* (London), 2086 (1962).

(7) The reaction of Grignard reagents with lactones to yield hydroxy ketones has been reviewed; see, for example, E. Muller, Ed., in Houben–Weyl's "Methoden der organischen Chemie," Vol. VI, Part 2, 4th ed, G. Thiem Verlag, Stuttgart, 1963, pp 799–802.

(8) In general, Baeyer–Villiger oxidation of primary alkyl aryl ketones yields mainly the product of aryl migration. However, examples of alkyl migration are known; *e.g.*, Baeyer–Villiger oxidation of *t*-butyl phenyl ketone and of l-apocamphyl phenyl ketone yield the product of alkyl migration [M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *J. Amer. Chem. Soc.*, **80**, 6393 (1958)].

(9) Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Nmr spectra were measured on a Varian A-60A spectrometer in *ca.* 10% solutions. Chemical shifts are reported in hertz downfield from internal TMS.

Flavonoids. VI. Synthesis and Structure of Isomeric N-Pyrrolidinomethylisoflav-3-enes[1]

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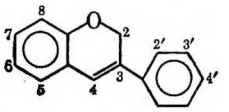
The Mannich reaction[2] provides a convenient method for the introduction of substituents into phenolic compounds, since the reactivity of the resulting dialkylaminomethyl group is such that it may be converted into a variety of other groups. We report here the application of the Mannich reaction to the synthesis of pyrrolidinomethylisoflav-3-enes, the orientation of which (readily established by nmr spectra) was found to depend upon the route of preparation.

Treatment of the hydroxycoumarin **1**[3] with formaldehyde and pyrrolidine[4] gave a 90% yield of a pyrrolidinomethylcoumarin (**2**) which reacted with methyl Grignard reagent to give crude triol **3** (Scheme I). The potential heterocyclic ring was not closed at this point, since there was no ultraviolet maximum above 300 mμ. However, when crude **3** was heated in excess hydrochloric acid, the solution exhibited a new maximum at 310 mμ,[3] and a salt precipitated. Decomposition of the salt with bicarbonate gave the isoflavene **4a**.



i

When the isoflavene **5**[3] was subjected to the Mannich reaction, the product was an isomeric pyrrolidinomethylisoflav-3-ene (**6a**). Nmr spectra[5] of the aromatic hydrogens clearly distinguished isomers **4a** and **6a**. The C-5 and C-6 protons of **4a** appeared as a pair of doublets at δ 7.04 and 6.43, with J = 8.6 cps as expected for *ortho* protons, whereas in **6a** the C-5 and C-8 protons gave sharp singlets (*para* hydrogens) at δ 6.82 and 6.36.

In both cases the signals at δ 7.04 and 6.82 were partially obscured by signals due to the 2′ and 3′ protons, but the acetoxymethyl acetates **4b** and **6b** (prepared by treating **4a** and **6a** with sodium acetate in acetic anhydride[4a]) showed quite clear-cut patterns. The C-5 and C-6 protons of **4b** were evidenced by a pair of doublets at δ 7.25 and 6.72 (J = 8 cps), whereas the *para* (5,8) hydrogens of **6b** gave singlets at δ 7.30 and 6.67. In all four compounds the pattern centered around 421 cps due to the other aromatic protons was practically identical, which is good evidence for its assignment. The peak farthest downfield in each case is assigned to the C-5 proton which lies in the deshielding region of the adjacent double bond.[6]

The 8 substitution of the 7-hydroxycoumarin **1** is consistent with the results of others,[4] and the isoflav-3-ene **4** reacts according to the pattern shown by resorcinol in, *e.g.*, acylation[7] or carboxylation[8] reactions.

Prolonged heating of isoflav-3-ene **5** with formaldehyde and pyrrolidine gave the bis adduct **7**, identified as such by integration of the nmr spectrum and analysis. The 8 position for the second pyrrolidinomethyl substituent is assigned on the basis of the *ortho–para* directing influence of the oxygen functions and on the nmr spectrum (singlet at δ 7.03; the signal at δ 6.36 present in **6a** is missing).

Experimental Section[5,9]

3-(*p*-Methoxyphenyl)-4-ethyl-7-hydroxy-8-(N-pyrrolidino)-methylcoumarin (2).—A solution of 20.0 g (67.6 mmol) of 3-(*p*-methoxyphenyl)-4-ethyl-7-hydroxycoumarin (**1**),[3] 11.2 ml of pyrrolidine, and 10.0 ml of 40% formalin in 500 ml of absolute ethanol was refluxed.[4] Tlc (1% acetic acid in 2-propanol on silica gel) indicated complete reaction at the end of 2 hr. The resulting mixture was chilled overnight and filtered to yield 24.3 g (94%) of **2**, mp 190–192° when placed in a bath preheated to 185°.

The compound could also be prepared by reaction in dimethoxyethane. Complete reaction occurred in 0.5 hr, but the yield was somewhat lower. Recrystallization could be carried out from acetonitrile, acetone, or preferably ethanol (*ca.* 40 ml/g), but with no change in melting point.

Anal. Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 73.19; H, 6.60; N, 3.92.

2,2-Dimethyl-4′-methoxy-4-ethyl-7-hydroxy-8-(N-pyrrolidino)-methylisoflav-3-ene (4a).—A solution of 15.0 g (39.5 mmol) of the coumarin **2** in 400 ml of dry tetrahydrofuran was treated with 100 ml of 3 *M* methylmagnesium bromide in ether. The solution was refluxed for 2 hr, cooled, and treated with a slurry of 100 g of NH_4Cl in 200 ml of water. The mixture was stirred for 15 min and filtered. Separation of layers and evaporation of the ether layer left an off-white solid (λ_{max} 285 mμ), which was heated with 220 ml of water and treated slowly with 1 *N* HCl until solution was complete. More HCl was added (total of 220 ml) and the yellow solution was heated on a steam bath for 1.25 hr. Overnight refrigeration yielded 15.2 g of an off-white solid which was shaken with 100 ml of sodium bicarbonate solution and 700 ml of ether until solution was complete. The ether layer was washed with water, dried, and evaporated to give a solid which was recrystallized twice from 2-propanol (9 ml/g) and once from absolute ethanol (14 ml/g) to yield a total of 11.4 g (73%), mp 150–151.5° with softening at 149°. Two more recrystallizations from ethanol gave the analytical sample (same melting point).

Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.38; H, 8.16; N, 3.65.

The infrared spectrum (CS_2) showed bands at 835 and 810 cm^{-1}. At high concentration bands were observed at 1882, 1760 (*para* disubstitution), 1852, and 1730 cm^{-1} (1,2,3,4-tetrasub-

(1) (a) Flavonoids. V: K. H. Dudley, H. W. Miller, R. C. Corley, and M. E. Wall, *J. Med. Chem.*, **10**, 985 (1967). (b) A portion of this work was presented at the 4th Annual Meeting of the Plant Phenolics Group of North America, July 1964. (c) This research was carried out under Contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health. (d) In accordance with common usage, compounds in this paper are named as derivatives of the isoflavan[3-aryl-1(2H)-benzopyran] nucleus, with the numbering shown in **i**.

(2) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942).

(3) C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **30**, 4114 (1965).

(4) (a) P. Da Re, G. Bonola, and L. Verlicchi, *J. Med. Chem.*, **7**, 162 (1964); (b) R. B. Desai, *J. Org. Chem.*, **26**, 5251 (1961).

(5) Nmr spectra were determined at 60 Mhz in deuteriochloroform solution by S. Justice of this laboratory. Values are reported in δ (parts per million) or cycles per second relative to internal tetramethylsilane.

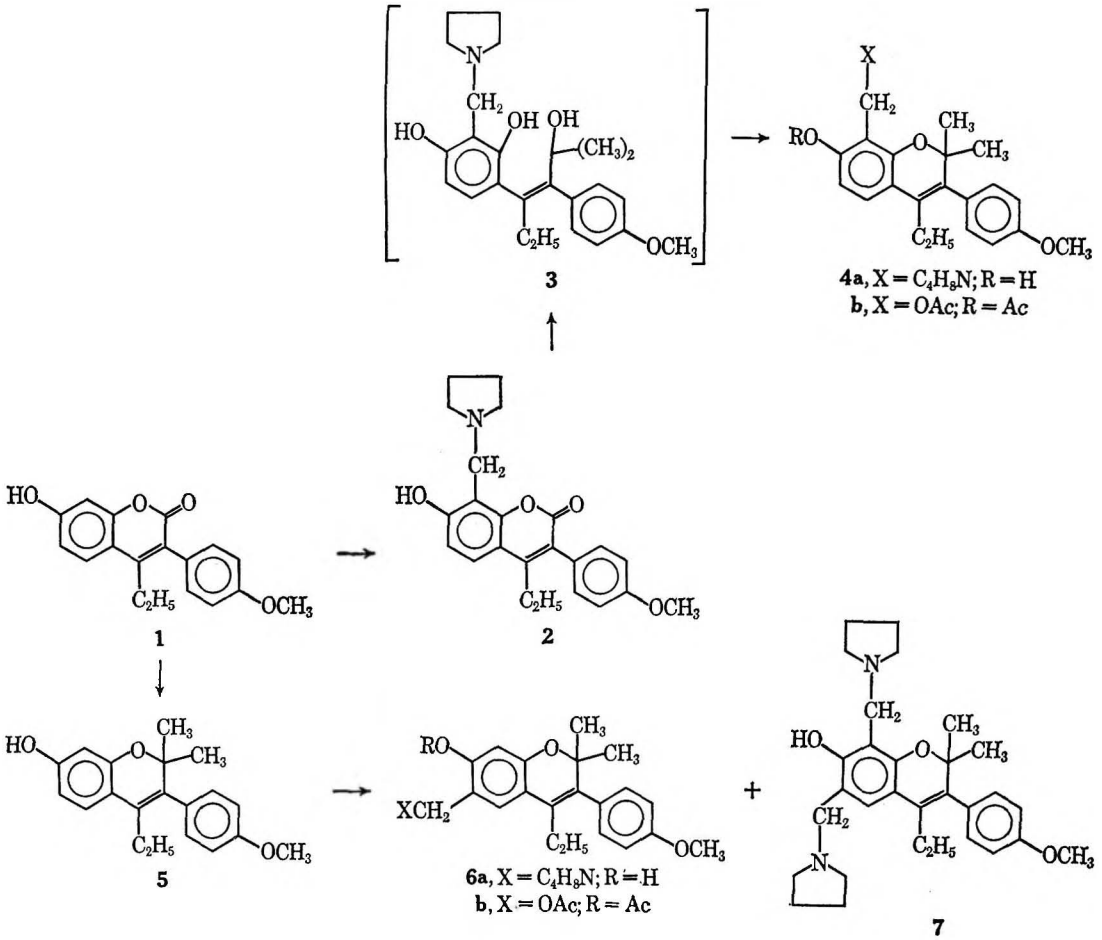
(6) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 88–89.

(7) S. R. Cooper, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 761.

(8) M. Nierenstein and D. A. Clibbens, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 557.

(9) Melting points were taken in capillary tubes (Uni-Melt apparatus) and are uncorrected. Ultraviolet spectra were recorded in methanol on a Bausch and Lomb Spectronic 505. Microanalyses were by Micro-Tech Laboratories, Skokie, Ill.

SCHEME I



stitution).[10] The ultraviolet spectrum showed λ_{max} (ϵ) 223 (27,600), 284 (12,300), and 308 mμ (9930).

2,2-Dimethyl-4′-methoxy-4-ethyl-6-(N-pyrrolidino)methyl-7-hydroxyisoflav-3-ene (6a).—A solution of 14 g (45.0 mmol) of 2,2-dimethyl-4′-methoxy-4-ethyl-7-hydroxyisoflav-3-ene (**5**)[3] in 560 ml of absolute ethanol was treated with pyrrolidine (9.0 ml) and formalin (7.5 ml of 37% solution), refluxed for 45 min (later tlc showed the reaction was over in 1 min), and evaporated almost to dryness at reduced pressure. The residue was stirred with 50 ml of methanol, filtered, washed with two 24-ml portions of methanol, and recrystallized three times from acetone (10 ml/g) to yield a total of 7.62 g (43%): mp 159–161°; mmp with **4a** 132–149°; λ_{max} (ϵ) 225 (32,200), 278 (10,500), 283 (10,660), 310 mμ (11,000).

Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.34; H, 8.05; N, 3.73.

2,2-Dimethyl-4′-methoxy-4-ethyl-7-hydroxy-6,8-bis(N-pyrrolidinomethyl)isoflav-3-ene (7).—The above reaction was repeated with 22.7 g (73 mmol) of **5**, 14.6 ml of pyrrolidine, and 12.2 ml of formaldehyde solution. The solution was refluxed for only 5 min, but, during the evaporation of the ethanol, the bath temperature was inadvertently kept above 60°. Stirring the residue with 81 ml of methanol followed by filtration yielded 7.1 g of impure **6a**, which after recrystallization from methanol had mp 158–159°. When the methanol mother liquor from **6a** was partially evaporated and treated with a little N,N-dimethylformamide and water, crystallization occurred. After recrystallization from acetone the product (**7**) weighed 9 g (26%) and had mp 153.5–154.5°, mmp with **6a** 134°, mmp with **4a** 129–132°. Passage of 1 g in benzene through a 2-g column of Florisil followed by crystallization from acetone gave the analytical sample: mp 153.5–155°; λ_{max} (ϵ) 229 (24,500), 285 (9070), 317 mμ (8500). Integration of the nmr spectrum showed the peaks at δ 1.80 and 2.65 (NC_4H_8) to have twice the relative intensity of those in compounds **4a** and **6a**, and there were two peaks for N-CH_2Ar at δ 3.70 and 3.92.

(10) K. Naskanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., and Nankodo Co., Ltd., Tokyo, 1962, p 27.

Anal. Calcd for $C_{30}H_{40}O_3N_2$: C, 75.59; H, 8.46; N, 5.88. Found: C, 75.74; H, 8.63; N, 6.30.

2,2-Dimethyl-4′-methoxy-4-ethyl-6-acetoxymethyl-7-acetoxyisoflav-3-ene (6b).—Compound **6a** (250 mg, 0.64 mmol) was refluxed for 2 hr with 4 ml of acetic anhydride and 0.25 g of anhydrous sodium acetate.[4a] The mixture was poured onto crushed ice and stirred until a solid was obtained. Purification by crystallization from methanol (20 ml/g), passage of a benzene solution through a short column of Florisil, and three more recrystallizations from methanol yielded **6b** (60%): mp 133.5–134.5°; $\nu_{max}^{CS_2}$ 1740, 1770 cm^{-1}; λ_{max} (ϵ) 229 (37,200), 274 (10,100), 310 mμ (8350).

Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.67; H, 6.69.

2,2-Dimethyl-4′-methoxy-4-ethyl-7-acetoxy-8-acetoxymethylisoflav-3-ene (4b).—Compound **4a** (250 mg, 0.64 mmol) was converted into **4b** by the above method. The crude product obtained by pouring the reaction mixture onto ice was extracted with benzene. The benzene solution was washed with water and sodium bicarbonate solution, dried, and passed through 0.5 g of Florisil to yield 222 mg (82%) of **4b**. Two recrystallizations from methanol gave the analytical sample: mp 102.5–103.5°; $\nu_{max}^{CS_2}$ 1770, 1740 cm^{-1}; λ_{max} (ϵ) 225 (29,900), 272 (10,500), 311 mμ (9090).

Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.41; H, 6.39.

Nmr Spectra.—In addition to the aromatic region (see discussion), the rest of the isoflavene nmr spectra were consistent with the assigned structures. In all the compounds the ethyl group appeared as a triplet and quartet (often obscured) at 57 and 131, the *gem*-dimethyl group at 78–82, and the methoxyl at 230 cps. In **4a**, **6a**, and **7** the α- and β-pyrrolidine protons appeared at 158 and 110, and the acetyl methyls of **4b** and **6b** were at 138 (aromatic acetate) and 123 cps (aliphatic acetate). The hydrogen-bonded hydroxyl of **4a** was a sharp singlet at 652, which shifted to 614 in **6a** and appeared as a broadened singlet at 645 cps in **7**. The shielding of the benzylic methylene was dependent upon its position; it was more shielded in the 6 position. Thus it came at 312 cps in **4b** *vs.* 303 in **6b** and at 237

in **4a** *vs.* 227 in 6a. In the bis derivative **7** there were two peaks at 221 and 235 cps.

Registry No.—**2**, 16797-56-1; **4a**, 16797-57-2; **4b**, 16797-59-4; **6a**, 16797-60-7; **6b**, 16797-61-8; **7**, 16797-62-9.

Acknowledgment.—We thank Frances Holton for experimental assistance in part of this work.

Derivatives of Morphine. VI.[1] The Structure of Dihydrodesoxycodeine E, the Product of Electrolytic Reduction of 14-Bromocodeinone

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Received March 1, 1968

Through electrolytic reduction of 14-bromocodeinone (I) in 25% sulfuric acid, Speyer and Sarre[4] prepared a phenolic dihydrodesoxycodeine (II), $C_{18}H_{23}NO_2 \cdot 0.5C_2H_5OH$, mp 139–140° dec. Their results were subsequently confirmed by Small and Cohen,[5] who proposed the name "dihydrodesoxycodeine E" to distinguish the substance from the several other known dihydrodesoxycodeines. Since II is reduced catalytically (Pd), with uptake of 1 mol of hydrogen, to the well-known tetrahydrodesoxycodeine (III), it must be one of the four possible analogs of III with a double bond in ring C (Scheme I). Of these, the Δ^5 and Δ^6 isomers are known compounds,[6] the dihydrodesoxycodeines C and B, respectively. Both are different from II, which must thus have its double bond in Δ^7 (IIb) or $\Delta^{8(14)}$ (IIa). No evidence on this point appears in the published literature, but the two possibilities should be readily distinguishable by nmr spectroscopy.

Colorless, well-crystallized preparations of II, obtained from a strongly discolored authentic sample[7] still remaining from the work of Small and Cohen[5] by recrystallization from a variety of solvents or by vacuum sublimation, and a new sample isolated by alumina chromatography from a crude product prepared recently by the method of Speyer and Sarre,[4] all showed a triplet (1 H) centered around δ ~5.7 in their nmr spectra. This triplet is very similar to that occurring at δ 5.5[8,9] in the spectrum of neopine (IV) as the X part of a deceptively simple ABX system,[8] and definitely caused by the proton at C-8. As expected, similar signals appear in the spectra of other $\Delta^{8(14)}$ compounds, such as isoneopine (V, triplet, δ 5.5),[9] desoxycodeine D ("desoxyneopine")[10] (VI, triplet, δ 5.5),[11] and neopine methyl ether[12] (VII, quartet, δ 5.45).[11]

The material available at present thus unquestionably has formula IIa rather than IIb. However, even our best samples, though homogeneous on gas chromatography, gave low, very unsharp melting points instead of mp 139–140° given in the literature. Unequivocal proof was thus needed that the substance is chemically identical with the one prepared long ago.[4,5] This proof was furnished by the complete agreement of the melting points of the methiodide and methyl ether methiodide, prepared from one of our samples, with literature values.[4] The nmr spectrum of II methiodide again showed a triplet (1 H) in the olefinic region, this time centered at δ 6.25, and analogous to signals in the spectra of the methiodides of VI[10] and VII[12] (triplets at δ 6.3 and 6.1, respectively).

These findings prove conclusively that II is indeed the $\Delta^{8(14)}$ isomer IIa. The discrepancy between the melting points found by us for II, and those recorded in the literature, appears to be based on polymorphism rather than variable solvation, since it persists after sublimation.

II is thus formed from I by removal of the carbonyl oxygen, reductive opening of the oxygen bridge, and hydrogenolysis of the bromine with allylic shift of the double bond. The last one of these changes is formally identical with that taking place during the *catalytic* (Pd on C in chloroform) reduction[13] of I to neopinone (VIII). The conversion of I to II might conceivably consist of an analogous process, accompanied by the removal of the carbonyl oxygen and opening of the ether bridge. The two processes may or may not be totally concerted; however, no information on the actual mechanism of the electrolytic process is available.

Experimental Section

Nmr spectra were taken on a Varian A-60 instrument in $CDCl_3$ with TMS as internal standard.

Dihydrodesoxycodeine E (IIa).—Both the original, brown sample and the colorless, well-crystallized (rhombic leaflets) preparations obtained from it by vacuum sublimation or recrystallization from ethanol, benzene, or ether, showed very unsharp melting points from about 90° to about 110–115° if taken on a Kofler hot stage. In capillaries, partial melting took place from ~100° up, the last crystals disappearing only at ~140°. Vapor phase chromatograms of the purified samples showed only one peak, retention time 3.55 min (3% OV-17 on Gas Chrom Q mesh 80; column 6 ft × 3 mm, 235°; inlet pressure 26 psi).[14] The old sample showed the same peak accompanied by very small peaks at 4.5 and 8.8 min.

The methiodide (mp 198–199° after recrystallization from ethanol and benzene, lit.[4] mp 199°) and methyl ether methiodide (mp 238–243°, lit.[4] mp 245°) were prepared by the method of Speyer and Sarre.[4] The sample of VI methiodide, left from the work of Small and Mallonee,[10] was labeled "mp 203–204°;" the melting point is given as "204–206° (evacuation tube)" in ref 10. However, the melting point was now found to be ~230° (hot stage); Rapoport and Bonner[15] found 233–234°.

Isolation of II.—The crude mixture of bases resulting from reduction[16] of I by the method of Speyer and Sarre[4] was chro-

(1) Paper V: U. Eisner and U. Weiss, *J. Org. Chem.*, **33**, 1264 (1968).

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(3) Laboratoire de Chimie Organique des Hormones, Collège de France, Paris 5e, France.

(4) E. Speyer and K. Sarre, *Ber.*, **57**, 1404 (1924).

(5) L. F. Small and F. L. Cohen, *J. Amer. Chem. Soc.*, **53**, 2227 (1931).

(6) *Cf.* K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Clarendon Press, Oxford, 1954, p 155, and literature quoted there.

(7) This sample and those of several reference compounds were made available from the collection of the late Dr. L. F. Small through the courtesy of Drs. E. L. May and L. S. Sargent.

(8) T. Rüll, *Bull. Soc. Chim. Fr.*, 586 (1963).

(9) S. Okuda, S. Yamaguchi, Y. Kawazoe, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **12**, 104 (1964); T. J. Batterham, K. H. Bell, and U. Weiss, *Aust. J. Chem.*, **18**, 1799 (1965).

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(11) Unpublished observations.

(12) L. F. Small, *ibid.*, **20**, 953 (1955).

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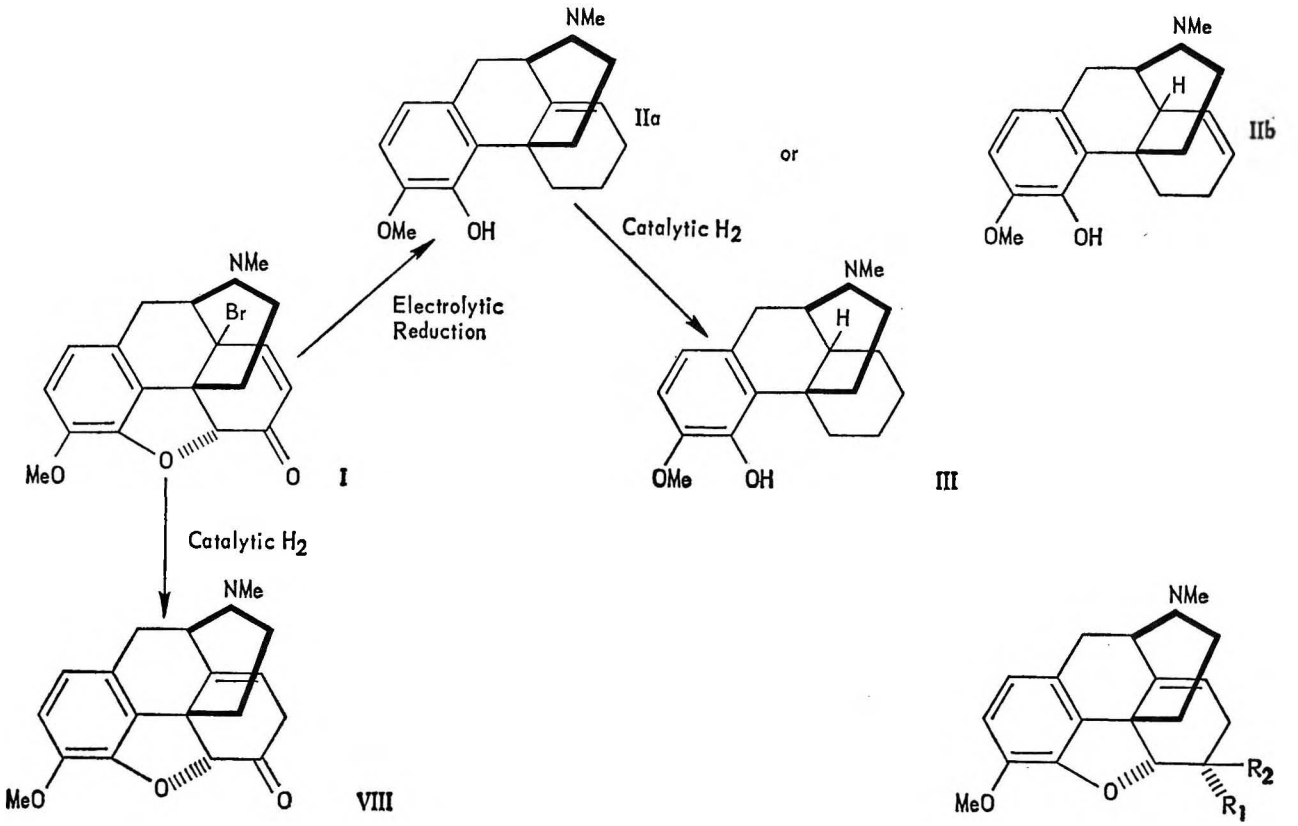
(14) The authors are indebted to Mrs. P. F. Highet for the gas chromatograms.

(15) H. Rapoport and M. Bonner, *ibid.*, **73**, 2872 (1951).

(16) The authors are much indebted to Mlle. G. Chalier, Grenoble, France, for performing this electrolytic reduction.

SCHEME I



IV: R_1=OH, R_2=H
V: R_1=H, R_2=OH
VI: R_1=R_2=H
VII: R_1=OMe, R_2=H

matographed on alumina. Elution with benzene–methylene chloride (1:1) yielded first unchanged I, 19%, followed by II, 31%. Subsequent elution with chloroform and chloroform–methanol 6:1 gave additional, more polar fractions, which were not identified; they were nonketonic (no ν (CO) between 1700 and 1721 cm^{-1}). The melting point and nmr spectrum of the sample of II obtained in this way agreed completely with those of the old samples.

Registry No.—I, 5140-31-8; IIa, 16808-39-2.

Laboratory Application of a Chemical Reactor Column. The Synthesis of Perdeuteriotropilidene

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Received February 13, 1968

Perdeuteriotropilidene, which was required in larger quantities in our program of investigations of mechanisms of oxidation reaction, was prepared in low isotopic purity (total deuterium content 90.8%, C_7D_8 55.9%) by Doering and Gaspar[1] by base-catalyzed hydrogen exchange between tropilidene and a deuterated solvent under drastic conditions. For our purposes a considerably higher deuterium content was desirable. As repeated equilibration turned out to be impractical (only about 50% tropilidene could be recovered after treating 5.0 g of tropilidene with 5.0 g of potassium dissolved in 75 g of triethylcarbinol under exchange conditions), a direct synthetic approach was sought.

Of the several methods of tropilidene syntheses available in the literature either the photochemically[2,3] or metal-catalyzed[4] reaction of benzene with diazomethane seemed most promising. The disadvantage of the photochemical method is the formation of toluene as a by-product. This drawback is removed in the catalytic process[4-7] which was explored in considerable detail by Müller and Fricke,[4] who were able to obtain yields up to 85% based on diazomethane. In their modification diazomethane was used in a benzene solution and a large excess of benzene over diazomethane (40:1) was required.

For the synthesis of perdeuteriotropilidene from ben-

(1) W. von E. Doering and P. P. Gaspar, *J. Amer. Chem. Soc.*, **85**, 3043 (1963).

(2) W. von E. Doering and L. H. Knox, *ibid.*, **72**, 2305 (1950).

(3) H. Meerwein, H. Disselnkötter, F. Rappen, H. v. Rintelen, and H. van de Vloed, *Ann.*, **604**, 151 (1957).

(4) E. Müller and H. Fricke, *ibid.*, **661**, 38 (1963).

(5) G. Wittig and K. Schwarzenbach, *ibid.*, **650**, 18 (1961).

(6) P. P. Gaspar, Doctoral Dissertation, Yale University, 1961.

(7) W. von E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

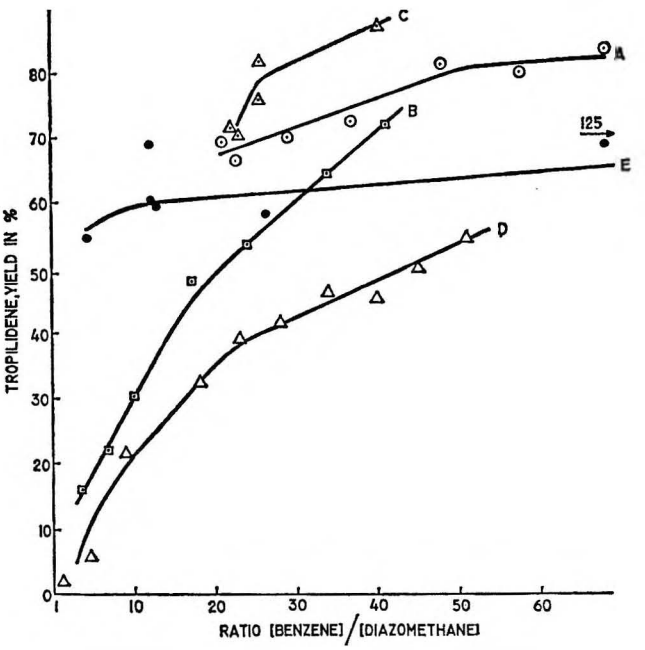

Figure 1.—Dependence of yield of tropilidene on the benzene–diazomethane ratio: (A) CH_2N_2 in benzene, CuCl catalysis, 78°; (B) CH_2N_2 in ether, CuCl catalysis, room temperature; (C) CH_2N_2 in benzene, CuCl catalysis, data from Müller and Fricke;[4] (D) CH_2N_2 in ether, photochemical reaction (yields include about 10% of toluene); (E) CH_2N_2 in ether, CuCl catalysis, 78°, in reactor column.

zene-d_6 and diazomethane-d_2 the use of benzene as solvent for the extraction of diazomethane as well as the use of a large excess of benzene in the reaction as recommended by Müller and Fricke would seem rather extravagant. The effect of the benzene–diazomethane ratio on the yields of tropilidene for benzene and ether solutions of diazomethane was therefore investigated. The results are given in Figure 1. The yields for ether solutions are consistently somewhat lower, but the general trend is the same for both solvents. Our results for benzene solutions are in general agreement with those of Müller and Fricke[4] (curve C), though slightly lower. The difference is probably due to the dependence of the reaction on the nature of the catalyst.

We investigated also the method employed by Doering and Roth[7] and Gaspar[6] in which diazomethane is introduced in a stream of nitrogen rather than in solution. However, only about a 10% yield of tropilidene was obtained when a benzene–diazomethane ratio of 10:1 was used.

The dependence of the yield of tropilidene on the benzene–diazomethane ratio is best explained by the assumption that tropilidene itself is not only capable of reacting with diazomethane[8] but is actually considerably more reactive than benzene. A large excess of benzene is therefore required to compete successfully with the already formed tropilidene for the newly introduced diazomethane. The relative reactivity of diazomethane toward tropilidene and benzene is about the same for the photochemically (curve D) and for the cuprous chloride catalyzed process (curves A, B, C).

(8) The reaction of tropilidene with diazomethane in the presence of cuprous chloride was studied by Doering and Roth.[7] Bicyclo[5.1.0]octa-2,5-diene and bicyclo[5.1.0]octa-2,4-diene are the main products.

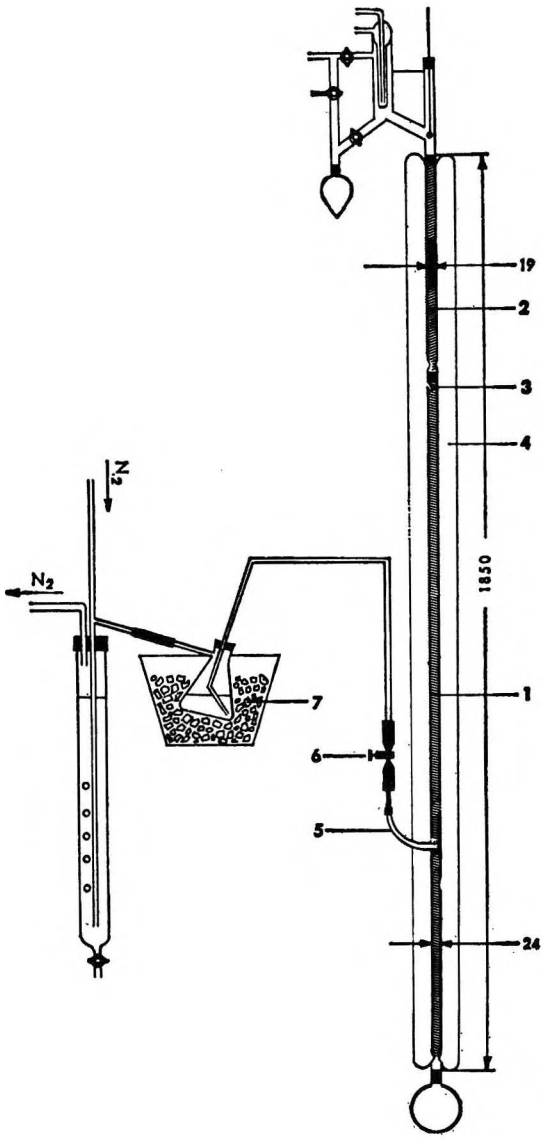

Figure 2.—Reactor column: 1, section with catalyst (CuCl on boiling chips); 2, section with "Heli-pak;" 3, thermocouple well; 4, thermal insulation (cotton wool and aluminum foil); 5, inlet of diazomethane solutions; 6, screw clamp; 7, Dry Ice bath.

The requirement of a high benzene–tropilidene ratio at the time of the reaction with diazomethane combined with a satisfactory over-all conversion of the benzene into tropilidene can be accomplished by the use of a distillation column using a packing material coated with the cuprous chloride catalyst (Figure 2). In this way a high local benzene–diazomethane concentration can be maintained in the reaction zone while the higher boiling tropilidene is concentrated in the pot protected from further reaction with diazomethane. An ether solution of diazomethane was introduced at the lower fourth of the column and the ether continuously removed from the top of the column. The reaction section of the column was kept at the boiling point of benzene to assure sufficient contact time for benzene and diazomethane. The separation of ether from diazomethane took place in the upper part of the column filled with "Heli-pak."[9] The temperature of the column head was not allowed to exceed the boiling point of ether in order to prevent losses of ben-

(9) "Heli-pak," Nichrome, 0.050 in. × 0.100 in. × 0.100 in., Podbielniak, Franklin Park, Ill.

zene. The reactor column was tested in a set of experiments using 50 ml of benzene and variable amounts of diazomethane. The results are given in Figure 1 (curve E). They show that the reaction modified in this way gives indeed good yields of tropilidene even at benzene to diazomethane ratios as low as 4.25:1. Still lower ratios could probably be used and the yields could be further improved if the effectiveness of the column were improved either by a more efficient type of column packing or by increasing the length of the column in order to decrease further the concentration of tropilidene in the reaction zone.

The perdeuteriotropilidene prepared in the reactor column contained 87.7% C_7D_8, 11% C_7D_7H, and 1.3% $C_7D_6H_2$ (by low voltage mass spectrometry), corresponding to a total deuterium content of 98.31%. The heptadeuteriotropilidene contained 75% of the protons in the CH_2 group and 25% distributed equally over the three equivalent olefinic CH groups (by nmr). No appreciable amount of isomerization took place during the reaction.

Diazomethane-d_2 used in the synthesis was prepared from N-methyl-d_3-N-nitroso-*p*-toluenesulfonamide by a modified procedure of Dahn and coworkers.[10]

The method of tropilidene synthesis as developed here and tested on the preparation of tropilidene-d_8 would in general be applicable to any catalytic carbene synthesis in which a volatile substrate available in limited amounts yields a product capable of further reaction. Substrates of this kind are known in the literature. *E.g.*, Doering and Roth[7] applied their method of cyclopropanation to *cis*-hexatriene, cycloheptadiene, and tropilidene. Working with excess diazomethane they always found higher homologous compounds besides the starting material and the monocyclopropanated products in the reaction mixture. In the case of tropilidene they were able to isolate the monocyclopropanated compound in better yield after changing the tropilidene–diazomethane ratio.

Experimental Section

Analytical Methods.—Reaction products were identified and the yields determined on an analytical F & M Scientific 5750 research gas chromatograph using a 10-ft column with 10% Carbowax 20M, 80–100 WAW at 130°. Preparative gas chromatography was carried out on a F & M Prepmaster Jr. Model No. 776 with a 0.75-in. column of 80-in. length with 20% Carbowax 20M on Chromosorb PAW 10–30 at 90°. The deuterium content in nitromethane and in methylamine was determined on a mass spectrometer of Consolidated Engineering Co. Type 21-630. The final analysis of perdeuteriotropilidene was made on an Atlas mass spectrometer, Model CH4, at 10 eV and the distribution of deuterium determined by nmr spectroscopy on a Varian HR-100 spectrometer.

Preparation of Tropilidene. A. Batch Process.—Purified[11] cuprous chloride (Fisher Scientific Co., 50–100 mg) was weighed into a flask fitted with reflux condenser, dropping funnel, and drying tube, the flask with the catalyst flame dried under a stream of nitrogen, the desired amount of benzene (1–12 ml) introduced, and the solution of diazomethane[12] (10–30 ml) slowly added under stirring with a magnetic stirrer. The addition was carried out at room temperature if ether was used as a solvent, and under reflux when benzene solutions were employed. The time required for the addition varied from 10 to 15 min. After the reaction was completed, the tropilidene–benzene ratio was determined chromatographically.

In the photochemical reaction benzene (0.5–8 ml) and diazomethane in ether (2–10 ml) were mixed in glass tubes of 8-mm o.d. and 50-cm length. The tubes were immersed in a water bath at 15° and irradiated for 3 hr at λ_{max} 3500 Å.[13]

B. Reactor Column (Figure 2).—Boiling chips coated with cuprous chloride[14] were used as packing material of the column in the reaction zone. The upper part of the column above the reaction zone was filled with "Heli-pak" [9] packing. Benzene (50 ml) was placed in the pot and heated. When the entire reaction zone was filled with benzene vapors (temperature at upper end >75°) the addition of a cooled (Dry Ice) solution of diazomethane in ether (about 0.5 *M*) was started. The rate of addition was regulated by the pressure of nitrogen and by a screw clamp; 4–6 hr was required for the addition of the diazomethane. Whenever the temperature in the reaction zone dropped the addition was interrupted. For a smaller column (16-mm diameter, 120-cm length), 30 ml of benzene was used. The yields in both columns were the same.

The product obtained by this method contained small amounts of ethanol from the preparation of diazomethane.[10] No toluene was formed, but small amounts of a higher boiling by-product could be observed when the benzene–diazomethane ratio was less than 10.

Nitromethane-d_3.—Nitromethane (30 g) was heated with deuterium oxide (38 g, Columbia Chemicals, 99.77% purity) in which 16 mg of sodium metal was dissolved (under nitrogen) in a 100-ml pressure bomb with a magnetic stirrer at 110° for 24 hr. The reaction mixture was transferred under pressure of nitrogen to a round-bottom flask and separated from polymer formed by distillation on a vacuum line and the nitromethane layer removed with a syringe. The remaining deuterium oxide was extracted with ether and the extract dried over calcium sulfate and evaporated; the combined yield was 85–90° for each step. The isotopic purity after five exchanges was 99%.

Methyl-d_3-amine Hydrochloride.—Nitromethane-d_3 (10.0 g) was added to 75 ml of dioxane (purified by distillation over sodium metal) containing 1.0 g of palladium catalyst (5%, on charcoal). The mixture was magnetically stirred under deuterium (CP grade, Matheson, 99.5%) for 4 days. After the flask was cooled with acetone and Dry Ice, 50 ml of concentrated hydrochloric acid was slowly added, the content of the flask let melt, and the solution filtered through a fritted funnel covered with Celite and evaporated to dryness. The crude deuteriomethylamine hydrochloride was used without purification for the next step. In an experiment with unlabeled nitromethane a 80% yield methylamine hydrochloride was obtained.

Diazomethane-d_2.—The crude amine was converted into the N-methyl-d_3-*p*-toluenesulfonamide (70%), N-nitroso-N-methyl-d_3-*p*-toluenesulfonylamide (85–87%), and dideuteriodiazomethane (50%) following Dahn's procedure.[10] Based on the determination of deuterium content and distribution in the product it could be estimated that the diazomethane had the following composition: 90.6% CD_2N_2, 8.3% $CDHN_2$, and 1.1% CH_2N_2. The diazomethane solution was dried over sodium metal before use.

Tropilidene-d_8.—Perdeuteriotropilidene was prepared from C_6D_6 (Merck Sharp and Dohme, Montreal, isotopic purity 99.5%) and CD_2N_2 in the reactor column. After all CD_2N_2 was introduced, the column was extracted with ether to recover the benzene and tropilidene retained by the column packing. The solution was then purified by bulb-to-bulb distillation, most of the benzene was removed on a spinning-band column (Nester–Faust), and the residue was purified in 1-ml fractions by preparative gas chromatography. The yield for the work-up procedure was 77%.

Registry No.—Perdeuteriotropilidene, 16675-63-1.

Acknowledgments.—Support of this work by the U. S. Army Research Office (Durham) is gratefully acknowledged. We also wish to express our appreciation to Professor K. L. Rinehart, Department of Chemistry,

(10) H. Dahn, A. Donzel, A. Merbach, and H. Gold, *Helv. Chim. Acta*, **46**, 994 (1964).

(11) R. N. Keller and H. D. Wycoff, *Inorg. Syn.*, **2**, 1 (1946).

(12) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1950, p 165.

(13) A Rayonet photochemical reactor of the Southern N.E. Ultraviolet Co. was used.

(14) Boiling chips (1 lb, Abrasive Grain Crystolon, Norton Co., Worcester, Mass.) were mixed with 3.0 g of cuprous chloride in hydrochloric acid, dried under vacuum with shaking, washed successively with acetic acid, water, and ethanol, and dried again under vacuum at 60°.

University of Illinois, Urbana, for final deuterium analysis of tropilidene, to Professor J. Jonas, Department of Chemistry, University of Illinois, Urbana, for the determination of the deuterium distribution, and to Professor E. T. Kaiser, Department of Chemistry, University of Chicago, for the use of the mass spectrometer.

The Reaction of 4-Chloro-8-methoxyquinoline with Hydrogen Peroxide[1a]

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Received January 9, 1967

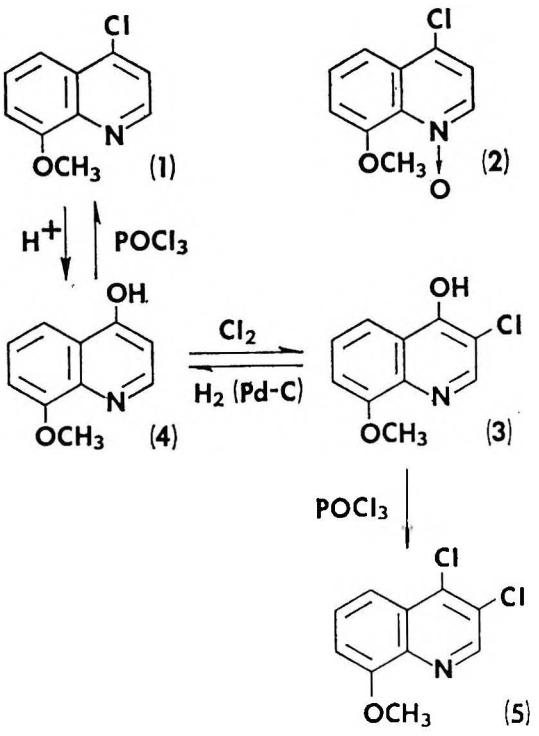
In the course of an attempt to synthesize 4-chloro-8-methoxyquinoline 1-oxide by the treatment of 4-chloro-8-methoxyquinoline (**1**) with hydrogen peroxide, the resulting product failed to show the properties expected of the desired 1-oxide (**2**), but instead appeared to be 3-chloro-8-methoxy-4-quinolinol (**3**). The proposed structure (**3**) was considered as a possible product because it had an ultraviolet spectrum nearly identical with that of 8-methoxy-4-quinolinol (**4**), and because **3** was converted into **4** by reduction with palladium on charcoal in methanol containing hydrogen chloride (Scheme I). Furthermore, **3** was prepared from **4** and chlorine in acetic acid, and treatment of **3** with phosphorus oxychloride produced 3,4-dichloro-8-methoxyquinoline (**5**) in high yield. The nmr spectrum of **5** showed no doublet downfield expected of **2**, but did show a singlet at τ 1.27, which was assigned to the proton at the C_2 position.

The bromination of 4-quinolinol[2] and 4-quinolinol 1-oxide[3] afforded the respective 3-bromo derivatives of these compounds. Brobański[4] reported that 4-chloroquinoline was converted into 4-quinolinol by acid hydrolysis. Robison and Robison[5] found that 4-chloroisocarbostyril was obtained in the reaction of 1-chloroisoquinoline with aqueous peracetic acid. Therefore, the hydrolysis of **1** in aqueous acetic acid followed by the halogenation of the resultant **4** by the chlorine produced from hydrogen chloride by hydrogen peroxide would explain the conversion of **1** into **3** instead of the desired **2**. This mechanism was demonstrated by the experiments reported here.

Experimental Section[6]

3-Chloro-8-methoxy-4-quinolinol (3).—8-Methoxy-2-carboxy-4-quinolinol was prepared according to the method of Furst and Olsen,[7] and decarboxylated[8] in refluxing Dowtherm A at 250° to yield **4** which was converted into **1** by refluxing for 1 hr in phosphorus oxychloride, mp 80–81° (lit.[8] mp 79–80°).

SCHEME I



A solution of 0.5 g of **1** and 0.5 ml of hydrogen peroxide (30%) in 10 ml of glacial acetic acid was stirred for 3 hr at 65–70°. After another 0.5 ml of hydrogen peroxide was added to the solution, it was heated at 60–70° for 3 hr. Following evaporation of the acetic acid, the residue was dissolved in dilute aqueous sodium hydroxide and washed with ethyl ether, and the aqueous solution was neutralized with dilute hydrochloric acid. A yield of 0.21 g (39%) of colorless needles was obtained, mp 273–274°. In a second trial, 0.7 g (32%) of this product was obtained from 2.0 g of **1**. The infrared spectrum of this product showed no strong absorption of the N–O stretching frequency expected of the 1-oxide near 1210 but had a hydroxyl band at 2900–3200 cm^{-1}; uv showed λ_{max} 232 mμ (ϵ 32,530), 303 (8130), 327 (12,310), 340 (10,610) (in ethanol). *Anal.* Calcd for $C_{10}H_8NO_2Cl$: C, 57.30; H, 3.85; N, 6.68; O, 15.26; Cl, 16.91. Found: C, 57.52; H, 3.92; N, 6.52; O, 15.63; Cl, 16.21.

Reduction of 3-Chloro-8-methoxy-4-quinolinol (3).—Compound **3** (0.5 g) in 30 ml of aqueous hydrochloric acid (10%) was hydrogenated over 0.5 g of palladium on charcoal (5%) under 20-psi pressure. After removal of the catalyst, the filtrate was evaporated *in vacuo*. The residue was dissolved in a small amount of water and was neutralized with dilute aqueous sodium hydroxide to yield 0.145 g (34.6%) of white needles. After recrystallization from water, the melting point was 183–184° (with **4**, mmp 183–184°). The ultraviolet spectrum of this product was identical with that of **4** in 0.1 *N* hydrochloric acid, ethanol, and 0.1 *N* sodium hydroxide. The reduction product and **4** were also indistinguishable on paper chromatograms using the solvent system of Mason and Berg[9] containing 1% ammonia (R_f 0.90) or 1% acetic acid[10] (R_f 0.90) and 6% aqueous sodium acetate (R_f 0.50).

Chlorination of 8-Methoxy-4-quinolinol (4).—A mixture containing 2 g of **4**, 70 ml of glacial acetic acid, and 0.7 g of chlorine was kept for 12 hr at room temperature. A white

(1) (a) This work was supported by Grant No. CA-07817 from the National Institutes of Health, U. S. Public Health Service. (b) Eisai Research Laboratories, Koishikawa 4, Bunkyo-ku, Tokyo, Japan. (c) American Cancer Society–Charles S. Hayden Foundation Professor of Surgery in Cancer Research. To whom all correspondence should be addressed at Abbott Laboratories, North Chicago, Ill. 60064.

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precipitate (2.5 g) was collected and washed with hot water, and 1.5 g of **4** was recovered. The insoluble material was recrystallized from aqueous ethanol and 0.6 g (25% of **4**) was obtained as white needles, mp 272–274°. The melting point of an admixture with 3-chloro-8-methoxy-4-quinolinol (**3**) was 272–274°, and this product was identical with **3** in ultraviolet and infrared spectra and on paper chromatograms.

Treatment of 8-Methoxy-4-quinolinol (4) with Hydrochloric Acid and Hydrogen Peroxide in Acetic Acid.—A solution of 1.0 g of **4**, 1 ml of hydrochloric acid (35%), and 1 ml of hydrogen peroxide (30%) in glacial acetic acid was stirred for 3 hr at 65–70°. After another 1 ml of hydrogen peroxide was added to the solution, it was heated at 60–70° for 3 hr. The oily product, which resulted from evaporation of most of the solvent, was dissolved in dilute aqueous sodium hydroxide, and the alkaline solution was neutralized with dilute hydrochloric acid. A yield of 0.44 g of tan needles was obtained, mp 268–271°, undepressed on admixture with **3**.

Hydrolysis of 4-Chloro-8-methoxyquinoline (1).—Compound **1** (0.3 g) was treated under the same conditions as used in the attempted oxidation of **1** to **2** except that hydrogen peroxide was replaced by water. The residue, upon evaporation of the acetic acid, was dissolved in dilute aqueous sodium hydroxide and washed with ethyl ether. Neutralization of the alkaline solution gave 104 mg of colorless needles, mp 180–183° (undepressed on admixture with **4**). From the ethereal solution 82 mg of the starting material was recovered, mp 78–79° (admixture with **1** gave mp 78–80°).

3,4-Dichloro-8-methoxyquinoline (5).—**3** (0.3 g) in 5 ml of phosphorus oxychloride was refluxed for 3 hr. The solution was poured into ice water and then made basic with aqueous sodium hydroxide (20%) to yield 0.3 g of colorless precipitate, mp 113–116°. After recrystallization from aqueous ethanol, 0.19 g (61%) of 3,4-dichloro-8-methoxyquinoline (**5**) was obtained as colorless crystals: mp 115.0–115.5°; nmr (τ value), 1.27 (singlet) for C_2–H, 2.31 (quartet) for C_5–H, 2.55 (triplet) for C_6–H, 3.03 (quartet) for C_7–H, and 5.97 (singlet) for C_8–OCH_3 (J_{56} = 8.3, J_{67} = 7.2, and J_{57} = 2.0 cps). *Anal.* Calcd for $C_{10}H_7NOCl_2$: C, 52.66; H, 3.10; N, 6.14; Cl, 31.09. Found: C, 52.79; H, 3.11; N, 5.86; Cl, 30.90.

Registry No.—**1**, 16778-21-5; hydrogen peroxide, 7722-84-1; **3**, 16778-22-6; **5**, 16797-43-6.

Acknowledgments.—The authors wish to thank Mr. K. Sakaguchi from the Eisai Research Laboratories for valuable assistance with the nmr analyses.

Isolation and Identification of Contaminants Found in Commercial Dihydroquinine[1]

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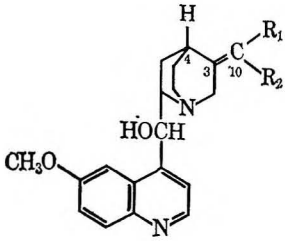
Received March 19, 1968

Dihydroquinine, which occurs naturally in Cinchona bark in very small quantities, is a useful antimalarial agent possessing slightly higher activity than quinine.[2] Commercially, it is prepared by hydrogenation of quinine with Pd–C in ethanol. In the commercial samples examined, we consistently found two minor contaminants, which constituted 2–7% of the samples. In view of the current interest in malarial chemotherapy, it seems important that the structures of these impurities be known. This manuscript describes the isolation and identification of these contaminants.

The isolation was accomplished by preparative thin layer chromatography (tlc) with methanol on silica gel H. The pmr spectra of the individual contaminants clearly distinguished these compounds from quinine and dihydroquinine, the noteworthy difference being a doublet near τ 8.6 and a quadruplet near 4.4 (area ratio 3:1, respectively). These resonances strongly suggest the presence of a vinylmethyl group, $=CHCH_3$, in both compounds.

Hydrogenation of the individual contaminants with PtO_2 in absolute ethanol resulted in a single product,[3–5] which was shown to be dihydroquinine. This identity was established by comparison of pmr, tlc, and melting point with those of authentic dihydroquinine. The evidence presented strongly suggests that these contaminants are isomeric quinines of the following structures.[6,7]



1a, α-isoquinine;[6] $R_1 = CH_3$; $R_2 = H$
b, β-isoquinine;[6] $R_1 = H$; $R_2 = CH_3$

To provide further proof for the structures of these contaminants, α- and β-isoquinines were synthesized from quinine by the procedure reported by Suszko.[8] The final products were isolated not by the literature method, which called for tedious fractional crystallizations, but by preparative tlc, which was much simpler and far more specific. The equivalence of the synthetic materials to those isolated from samples of commercial dihydroquinine was established by infrared, pmr, tlc, and melting point comparisons.

Recent pmr studies[7] on the two isomeric 3-ethylidene-1-azabicyclo[2.2.2]octanes (3-ethylidenequinuclidines, **2a** and **2b**) have established that the protons of the methyl in **2a** resonate at a lower field than do the protons of the methyl in **2b**. Since the methyl signals from the respective isoquinines are centered at τ 8.51 and 8.60, we can, by analogy, assign the lower field

(1) This work was supported by US Army Medical Research and Development Command, Office of the Surgeon General, under Contract No. DA-49-193-MD-2753. This is Contribution No. 353 to the Army Research Program on Malaria.

(2) G. A. H. Buttle, T. A. Henry, and J. W. Trevan, *Biochem. J.*, **28**, 426 (1934); P. B. Marshall, *J. Pharmacol.*, **85**, 299 (1945).

(3) The catalytic hydrogenation of the Δ_{3-10} double bond in the α- and β-isoquinines produces a center of asymmetry, C_3, and should result in a pair of diastereomers, dihydroquinine and *epi*-C_3-dihydroquinine. According to Henry,[4,5] the former has mp 173.5° and $[\alpha]D$ −235.7° (0.1 *N* H_2SO_4), and the latter has mp 169° and $[\alpha]D$ −275° (0.1 *N* H_2SO_4). The dihydroquinine which we isolated from commercial samples has mp 169–171° and $[\alpha]^{21}D$ −221 ± 6° (0.1 *N* H_2SO_4); the dihydroquinine which we obtained from the hydrogenation of α- and β-isoquinines has mp 173–175° and $[\alpha]^{21}D$ −234 ± 5° (0.1 *N* H_2SO_4). A comparison of the $[\alpha]D$ values for our dihydroquinine samples does suggest that the materials from the reduction of the isoquinines are mixtures of dihydroquinine and *epi*-C_3-dihydroquinine.

(4) T. A. Henry, "The Plant Alkaloids," The Blakiston Co., Philadelphia, Pa., 1949, p 429.

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(6) The assignments of α to the C_4H–$C_{10}H$ transoid and of β to the C_4H–$C_{10}H$ cisoid are based on the assignments made for the 3-ethylene-1-azabicyclo[2.2.2]octanes.[7]

(7) J. C. Nouls, G. Van Binst, and R. H. Martin, *Tetrahedron Lett.*, **41**, 4065 (1967); G. Van Binst, J. C. Nouls, J. Stokes, C. Danheux, and R. H. Martin, *Bull. Soc. Chim. Belges*, **74**, 506 (1965).

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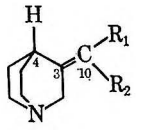
methyl resonance to the α-isoquinine (**1a**) and the higher field methyl resonance to the β-isoquinine (**1b**).



2a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$

The formation of these isoquinines during the hydrogenation of quinine with Pd–C resulted from a catalytic isomerization of the Δ_{10-11} (quinine) to Δ_{3-10} (α,β-isoquinine). Once formed, these isoquinines cannot be reduced to dihydroquinine under the conditions normally employed for the commercial preparation of the latter compound. However, we found that, by substituting PtO_2 for Pd–C, these isoquinines are readily reduced to dihydroquinine.[3]

Experimental Section

Infrared spectra were determined as Nujol mulls on a Perkin-Elmer 137 spectrometer. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter. Pmr spectra were recorded as $CDCl_3$ solutions on a Varian HA-100 spectrometer equipped with a C-1024 time-averaging computer; chemical shifts are reported on a τ scale from internal tetramethylsilane (τ = 10.00 ppm). Melting points were obtained on a Fisher-John melting point apparatus. Tlc solvent systems are (a) methanol, (b) methanol–triethylamine 25:1 v/v, and (c) acetone–water 9:1 v/v.

Isolation of α- and β-Isoquinines.—Commercial dihydroquinine[9] (45 mg dissolved in 2 ml of chloroform) was applied to a 200 × 200 × 1 mm SiO_2–H plate, which was developed with methanol. The respective α- and β-isoquinine bands from numerous plates were isolated, combined, and extracted with methanol. The methanol solutions were filtered and evaporated to dryness, and the residues were extracted with chloroform. The chloroform solutions were concentrated to minimal volumes and the materials were rechromatographed until each isomer was chromatographically pure. The α-isoquinine, **1a**, had mp 178–181°, $R_{f(a)}$ 0.50. The β-isoquinine, **1b**, had mp 167–170°, $R_{f(a)}$ 0.55.

Hydrogenation of α- and β-Isoquinines.—The isoquinines were individually hydrogenated with PtO_2 (1:1 isoquinine–PtO_2) in absolute ethanol at room temperature, 1 atm, for 1 hr. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue, which was shown to be chromatographically homogeneous and identical with dihydroquinine, was crystallized from ethyl acetate. The product[3] melted at 173–175° and was identical with authentic dihydroquinine according to mixture melting point, pmr, and infrared comparisons.

Synthesis of α- and β-Isoquinines.—The procedure employed was that reported by Suszko[8] except for the method of isolation of the isoquinines. Quinine was heated in 18 *N* sulfuric acid at 145° for 6 hr. The solution was cooled and made alkaline with sodium hydroxide. Carbon dioxide was added until a pH of 8 was obtained. The precipitate was collected, washed with water, and dried. The material was dissolved in methanol and treated with an ethereal solution of diazomethane for 16 hr. The isolation of the respective isoquinines was achieved by preparative tlc. The procedure gave an over-all yield of 24% α-isoquinine,[10] mp 177–179°, $[\alpha]^{22}D$ −184 ± 4° (c 0.26, EtOH), and 1% β-isoquinine,[8] mp 166–170°, $[\alpha]^{22}D$ −185 ±4° (c 0.21, EtOH). The equivalence of these samples to those isolated from commercial dihydroquinine samples was established by tlc, pmr, infrared, and hydrogenation comparisons.

Registry No.—**1a**, 16935-07-9; **1b**, 16934-08-0; dihydroquinine, 522-66-7.

(9) Samples of commercial dihydroquinine were generously provided by Dr. Thomas R. Sweeney of the Walter Reed Institute of Research, Department of the Army, Washington, D. C.

(10) Although the melting points for these isoquinines agree with those for samples isolated from commercial dihydroquinine, they do not agree with those cited by Henry[4] (α = 196.5°, β = 183–185°) or by Suszko[8] (β = 186–187°). When Suszko's procedure for the isolation of the isoquinines was followed exactly, the recrystallized material obtained was shown by tlc to be a mixture of four components, α- and β-isoquinines, dihydroquinine, and an unknown. This may explain why the physical constants they reported differ from ours, which were obtained on materials that are chromatographically homogeneous and are supported by unambiguous spectral data.