VOLUME 38 APRIL 6, 1973 NUMBER 7 JOCEAH

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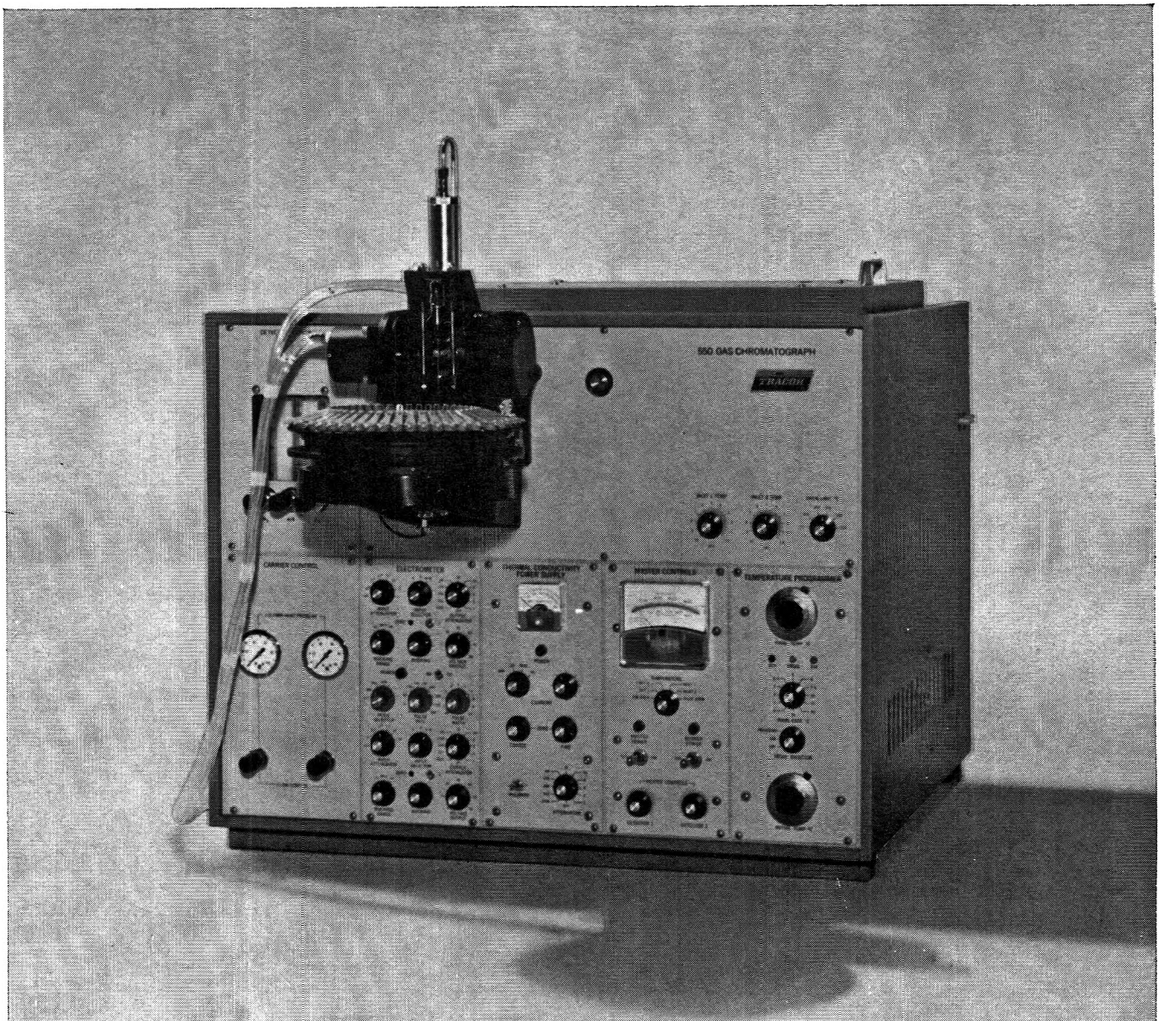

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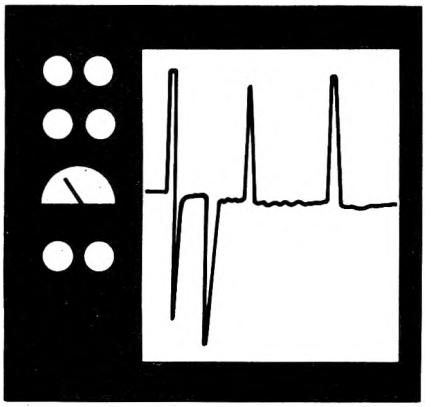

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NOTES

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THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 7 APRIL 6, 1973

Elucidation of Structure and Stereochemistry of Myriocin. A Novel Antifungal Antibiotic[1]

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Received November 2, 1972

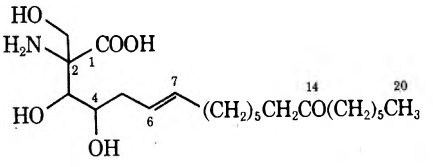
An antifungal principle myriocin was isolated from *Myriococcum albomyces*. The structure of this compound was elucidated using spectral and analytical data of its derivatives. The chemical reactions utilized in degradation work involved ozonolysis and periodic acid oxidation. Structure 1 was assigned to myriocin based on the available chemical data. The chemical and the physical evidence led to the stereochemical expression 28.

In the course of a screening program directed toward the discovery of novel antimicrobial agents, antifungal activity was detected in the fermentation broth of *Myriococcum albomyces*, a thermophilic fungus of the ascomycete class. The active principle, responsible for the antifungal activity, was isolated from the broth of the microorganism grown in submerged culture, and was named myriocin.[2]

Myriocin (1) analyzed for $C_{21}H_{39}O_6N$ (401), having mp 180–181°, $[\alpha]^{24}D$ 10.3° (*c* 0.386, CH_3OH). An infrared spectrum (Nujol) showed broad hydroxylic absorption, 1702- and 1665-cm^{-1} bands, establishing the presence of a carbonyl. A mass spectrum showed no molecular ion peak. The highest ion peak was located at $M^+ - 18$ (*m/e* 383), with a base peak at $M^+ - (127 + 18)$ (*m/e* 256). The compound gave a positive ninhydrin test, suggesting the possible presence of an α-amino acid function. The antibiotic could not be satisfactorily esterified with diazomethane, and, owing to its insolubility in most organic solvents, including DMSO, no satisfactory nmr spectrum could be obtained.

When myriocin was heated in *tert*-amyl alcohol at reflux temperature overnight, it was dehydrated to give anhydromyriocin (2). This product was characterized by a new band at 1773 cm^{-1} in its infrared (Table III), suggesting a γ-lactone carbonyl. An nmr spectrum (220 MHz, Table II) showed a symmetrical multiplet, integrating for two vinylic protons, at δ 5.72.

Acetylation of myriocin (1) as well as anhydromyriocin (2) in pyridine–acetic anhydride yielded the triacetate 4, corresponding to $C_{27}H_{43}O_8N$ (509). The formation of γ-lactone during the acetylation can be rationalized by the participation of the corresponding mixed anhydride of the acid followed by ring closure as shown in formula 5 (R = H). A mass spectrum ex-



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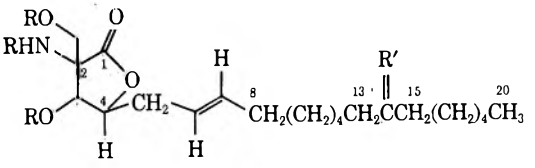
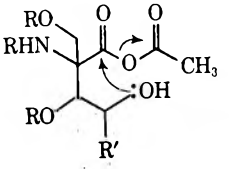


2, R = H; R′ = O

3, R = $COCH_3$; R′ = 

4, R = $COCH_3$; R′ = O



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hibited a molecular ion M^+ (*m/e* 509), $M^+ - 60$ (*m/e* 449), $M^+ - 127$ (*m/e* 382), and $M^+ - (60 + 127)$ (*m/e* 322). The nmr spectrum of the triacetate 4 showed the signals which are listed in Table II. The interesting

(1) A preliminary account of this work was presented at the VIIth International Congress of Chemotherapy, Prague, Aug 1971.

(2) D. Kluepfel, J. F. Bagli, H. Baker, M. Charest, A. Kudelski, S. N. Sehgal, and C. Vézina, *J. Antibiot.*, **25**, 109 (1972).

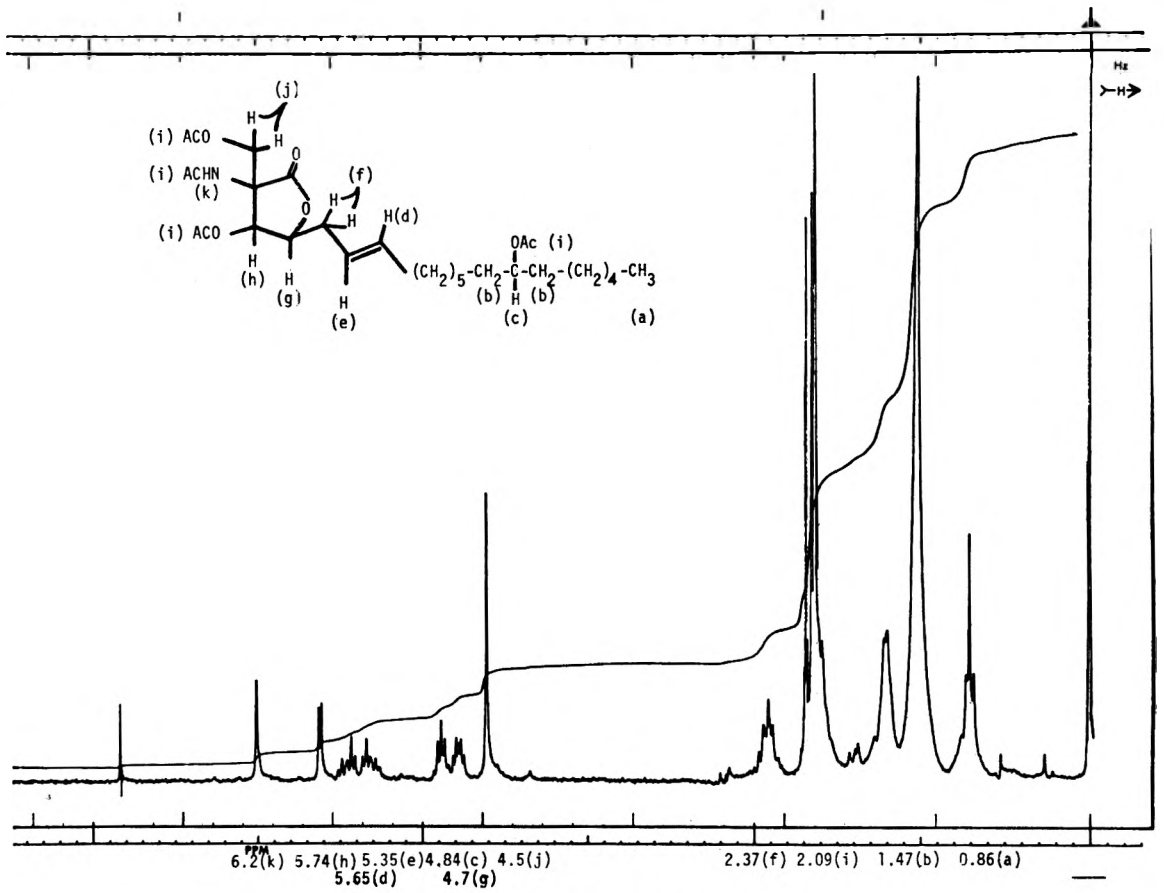


Figure 1.—Nmr (220 MHz) of tetraacetate **4**.

feature in the nmr of compound **4** was a cluster of signals integrating for six protons and appearing as a badly resolved triplet, centered at δ 2.4. Acetylation of a sodium borohydride reduction product of myriocin yielded a tetraacetate **3**, whose nmr spectrum showed a decreased intensity signal (integrating for 2 H) at δ 2.4. The acetylation of a product obtained from the catalytic hydrogenation of the parent antibiotic was characterized by the absence of vinylic proton peaks and by a signal at δ 2.4 now integrating for four protons. Finally, an acetylation, preceded by both catalytic as well as hydride reduction, yielded a product for which the peaks at δ 2.4 and 5.5 (vinylic protons) were completely absent while an appropriate increase in the number of protons at higher field was noted. These results are summarized in Table I.

TABLE I
NUMBER OF PROTONS CORRESPONDING TO THE SIGNALS AT δ 2.4 AND 5.5 IN THE NMR SPECTRA OF VARIOUS REACTION PRODUCTS

Experiment	δ 2.4 signal	δ 5.5 signal
1 —(1. Ac_2O)→ triacetate **4**	6 H	2 H
1 —(1. $NaBH_4$, 2. Ac_2O)→ tetraacetate **3**	2 H	2 H
1 —(1. cat./H_2, 2. Ac_2O)→ triacetate	4 H	
1 —(1. $NaBH_4$, 2. cat./H_2, 3. Ac_2O)→ tetraacetate		

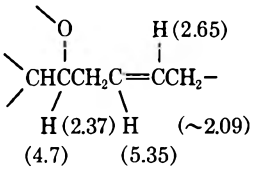
Assuming that the δ 2.4 multiplets represent the protons on carbon atoms α to a ketone, and those α to >C=C<, the above evidence clearly established the presence of $-CH_2COCH_2-$ and $CH_2HC{=}CH-$ moieties in the acetylation products. The 1702-cm^{-1} band present in the parent antibiotic is therefore attributable to a ketone. The above experiments suggested the downfield shift for one allylic methylene relative to the other, and this was indeed confirmed by a detailed analysis of the nmr (220 MHz) of the tetraacetate **3** (Figure 1).

The relevant signals of the nmr spectrum (220 MHz) of the tetraacetate **3** are listed in Table II. In addition to those listed, the spectrum exhibited a broad singlet at δ 1.47 which integrated for four protons, and a quintuplet at δ 4.84 attributable to a carbinolic proton. In a double-resonance experiment, irradiation at δ 1.47, the frequency of the former, reduced the quintuplet to a singlet. This experiment established the presence of the $-CH_2CH(OCOCH_3)CH_2-$ grouping, thus confirming the presence of the ketone and the nature of the substitution on carbons α,α' to the ketone (*vide supra*) in the parent antibiotic. The spectrum also showed a quintuplet at δ 2.37 (2 H), whose relationship to protons of chemical shift at δ 5.35 and 5.65 (vinylic, 2 H) and at 4.7 (1 H) was deduced from the double-resonance experiments as described below. Irradiation at δ 2.37 collapsed the quintuplet (4.7) to a poorly resolved doublet; at the same time, the 5.35 signal collapsed to a doublet. Furthermore, irradiation of the allylic signal at δ 2.09 (partially buried under the acetate peak) reduced the δ 5.65 multiplet to a doublet. The above experiments permit the following assignments and established the presence of the structural feature **6** in the tetraacetate **3**.

TABLE II
NMR DATA

Compd	NH	C-2 (CH_2OR)	C-3	C-4	C-6 and -7	C-20[a]
2		3.61 (q)	4.15 (d)	4.66 (m)	5.72 (m)	0.9
3	6.2 (s)	4.50 (s)	5.74 (d)	4.7 (q)	5.35, 5.65 (m)	0.86
4	6.3 (s)	4.51 (s)	5.79 (d)	4.74 (m)	5.5 (q)	0.88
8	6.46 (s)	4.48 (s)	5.70 (d)	5.24 (q)		
13		4.12 (q)	5.32 (d)	4.70 (m)	5.56 (m)	0.87
15	7.05 (s)	3.98 (s)	5.31 (d)	4.70 (m)	5.56 (m)	0.87
17	6.84	3.88	4.62 (m)[b]		5.56 (m)	0.88
18	6.59	4.43 (s)	4.57 (m)[b]		5.59 (m)	0.9
19		4.0 (q)	5.17 (d)	4.58 (m)	5.58 (q)	0.88
20		4.48 (q)	5.08 (d)	4.48[b]	5.58 (q)	0.90

[a] These signals always appeared as a badly resolved triplet. [b] C-4 signals in this case were overlapping with C-2 CH_2OH.



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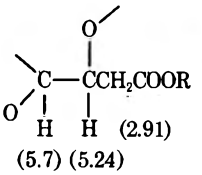

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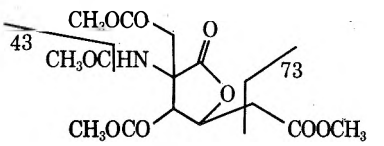

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The trans geometry of the double bond follows from (a) presence of a 950–970-cm^{-1} band in the ir spectra of the various derivatives (Table III) as well as of myriocin

TABLE III
IR DATA

Compd	Hydroxyl region	>C=O stretching region	Vinylic hydrogen bending
1	Broad	1702, 1665	962
2	3475	1775, 1705	975
4	3340[a]	1785, 1755, 1712,[b] 1665	950
3			
8	3400,[a] 3350[a]	1780–1725, 1675	
13	3375	1775, 1700, 1648, 1598	
15	3400	1775, 1700, 1635, 1595, 1509	

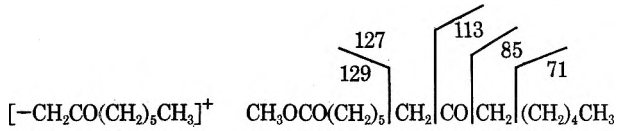
[a] N–H stretching. [b] The bands appeared as a shoulder on a broad absorption.

(1) and (b) J = 16 Hz in the nmr spectrum of tetraacetate **3**.

Ozonolysis of the triacetate **4**, followed by oxidative work-up with hydrogen peroxide and the esterification of the resulting acidic mixture, yielded two major products. A crystalline solid was obtained, whose elemental analysis led to the empirical formula $C_{14}H_{19}O_9N$. An ir spectrum showed a broad carbonyl 1760–1725 cm^{-1}, as well as a band at 1675 cm^{-1}. A mass spectrum showed a molecular ion M^+ (*m/e* 345), $M^+ - 43$ (*m/e* 302), and $M^+ - 73$ (*m/e* 272). An nmr spectrum (Figure 2) exhibited a doublet at δ 2.91 (2 H, J = 7 Hz), a quartet at 5.24 (1 H), and a doublet at 5.7 (1 H, J = 6 Hz). Irradiation at δ 2.91 led to the collapse of the δ 5.24 quartet to a doublet (J = 6 Hz). Conversely, the δ 2.91 doublet collapsed to a singlet when the quartet at 5.24 was irradiated. In addition, irradiation at δ 5.7 transformed the quartet to a triplet. These results are best accommodated by the partial formula **7** and the structure of the ozonolysis product may be expressed as **8**.

The second product of the ozonolysis appeared from its ir and nmr data to be a long-chain fatty acid ester. A mass spectrum showed a molecular ion at *m/e* 256, and a strong peak due to fragment *m/e* 129 ($M^+ - 127$). In the mass spectra of myriocin (**1**) and that of the triacetate **4** strong peaks were present for a fragment (*vide supra*) from the loss of mass 127. Considering the presence of a saturated ketone in a straight chain the *m/e* 127 can arise from a fragment $[C_8H_{15}O]^+$, which may be expanded to expression **9** for this fragment.

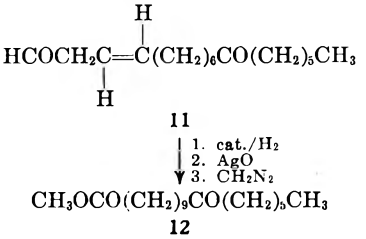
This, coupled with *m/e* 113, 85, and 71, led to the structure **10** for this product. The above assignment



9 10

was confirmed by comparison of the tlc, glc, and mass spectrum of this product with those of an authentic sample[3] of 8-ketotetradecanoic acid methyl ester.

Treatment of myriocin (**1**) with 4 equiv of periodic acid in a mixture of ether–water led to the isolation of an aldehyde in excellent yield. The ir of this product showed characteristic bands at 2710, 1710, and 970 cm^{-1} (vinylic proton bending). The nmr (100 MHz) exhibited a triplet at δ 9.65 and a multiplet at 3.09. The triplet above collapsed to a singlet when the decoupler frequency was applied at δ 3.09. The uv spectrum showed no absorption in the neutral medium; however, in the basic medium a band developed at 233 nm (ϵ 5100). This is attributable to a double bond shift from $\beta\gamma \rightarrow \alpha\beta$ position of a carbonyl. The aldehyde was assigned structure **11**. This assignment was un-



(3) F. L. Breusch and A. Kirkali, *Fette, Seifen, Anstrichm.*, **65**, 995 (1963).

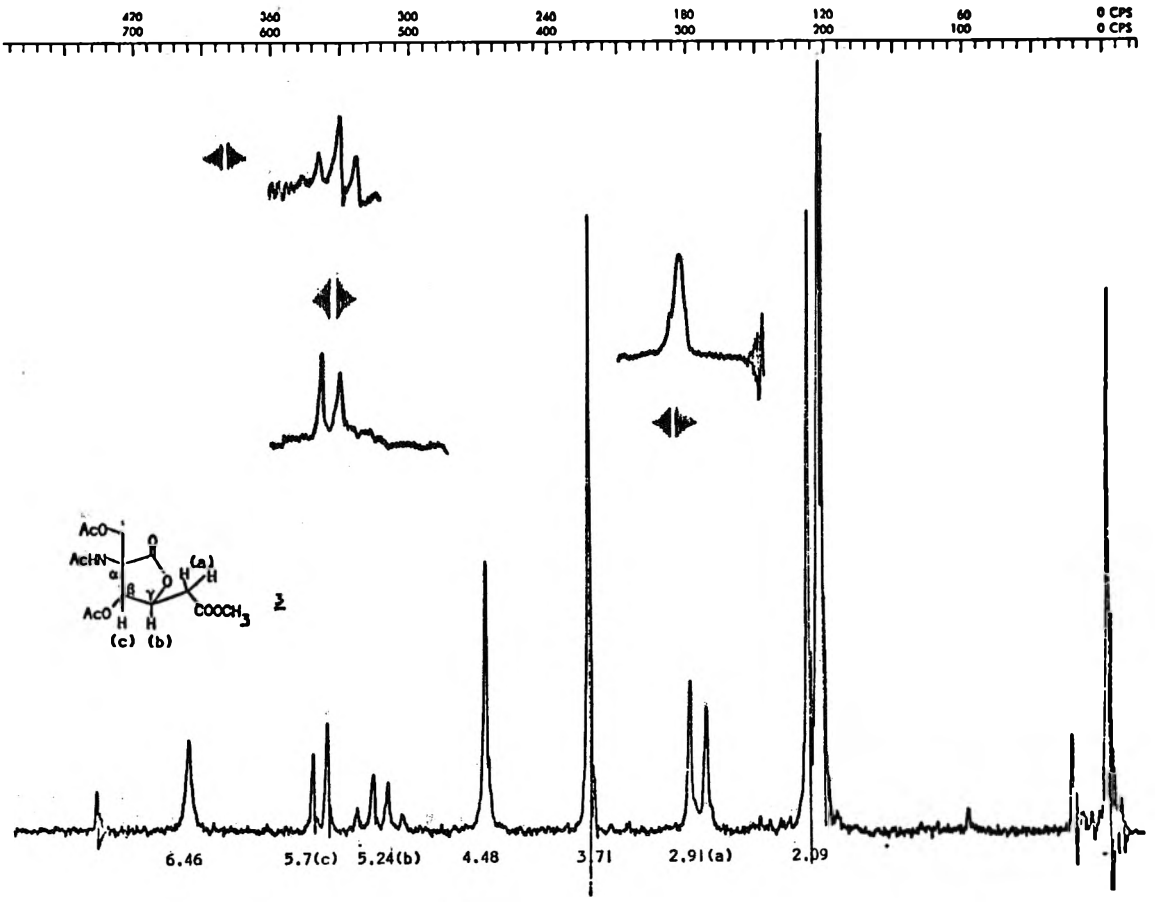


Figure 2.—Nmr (100 MHz) of the methyl ester **8**, showing the results of the spin decoupling between δ 5.7, 5.24, and 2.91 signals.

ambiguously established as follows. Catalytic reduction of the aldehyde **11**, followed by the silver oxide oxidation, yielded a saturated carboxylic acid. This was esterified with diazomethane to yield the corresponding methyl ester **12**. Both the acid and the methyl ester were found to be identical in all respects with an authentic sample[4] of 11-ketoheptadecanoic acid and its methyl ester.

The above experimental and analytical data are best accommodated in the expression **2** for anhydromyriocin and consequently the structure **1** for myriocin.

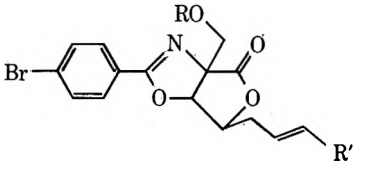
Stereochemistry.—Myriocin has three asymmetric centers, *viz.*, C-2, C-3, and C-4. The following experimental evidence led to the assignment of stereochemistry at these positions.

Treatment of myriocin with *p*-bromobenzoyl chloride in pyridine yielded a product homogeneous by tlc, which partially crystallized. The nmr spectra (Table II) of the crystals (minor product) and the oil (major product) were different, as shown below. It was evident from these spectra that they were both monobenzoates.

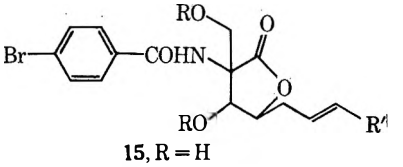
Nmr differences between two products of benzoylation

Benzoate	NH	C-2 CH_2OH (2 H)	Aromatic (4 H)
Oil	Absent	δ 4.1 (q)	δ 7.68 (q)
Solid	Present δ 7.05	δ 3.98 (s)	δ 7.60 (s)

Acetylation of the purified benzoates yielded two products. A major product was obtained whose nmr spectrum showed one acetyl methyl (δ 2.03), and its mass spectrum showed a molecular ion M^+ (*m/e* 590). In contrast, the spectrum of the minor component showed two acetyl groups (δ 2.08 and 1.88) and a molecular ion at *m/e* 650. Based on the above data, the major, oily benzoate and its acetate were assigned structure **13** and **14**, respectively. The minor benzoate and the corresponding acetate are therefore expressed as **15** and **16**.



13, R = H
14, R = $COCH_3$

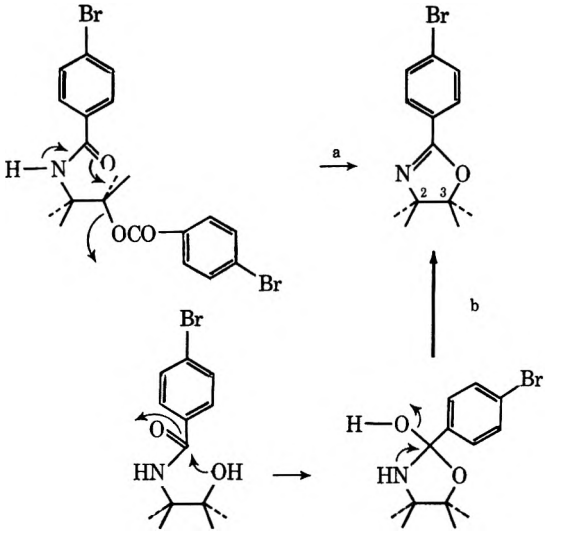


15, R = H
16, R = $COCH_3$
R' = $-(CH_2)_6CO(CH_2)_5CH_3$

Under the conditions of benzoylation (pyridine–*p*-bromobenzoyl chloride), myriocin is first transformed *via* the mixed anhydride of the type **5** leading to anhydromyriocin. This compound undergoes N-benzoylation to give the minor monobenzoate **15**. The formation of oxazoline **13** can result from the eventual benzoylation of the C-3 hydroxyl followed by nucleophilic

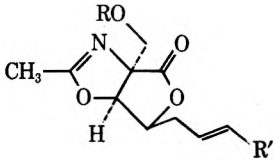
(4) F. L. Breusch and A. Kirkali, *Fette, Seifen, Anstrichm.*, **67**, 4 (1965).

participation of the *N*-benzoyl carbonyl and the ejection of -OCOPh-*p*-Br. Such a pathway to the generation of oxazolines is well documented.[5a]

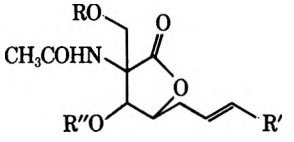


The above mechanistic pathway (a) would imply trans stereochemistry of C_2N and C_3O in anhydromyriocin (**2**). An alternate pathway (b) involving the attack by oxygen electrons[5b] is unlikely under the basic conditions employed. The lack of benzoylation of the primary alcohol may be attributed to steric reasons.

Further evidence for the trans stereochemistry of C–N and C–O bonds at carbon atoms 2 and 3 is afforded by the acetylation of myriocin under conditions of selective N-acetylation[6] in methanol–acetic anhydride. This experiment led to the isolation of the two major and two minor products. Based on the ir (Table III) and the nmr (Table II) data the major products were assigned structures **17** and **18**, whereas the minor products were assigned structures **19** and **20**.



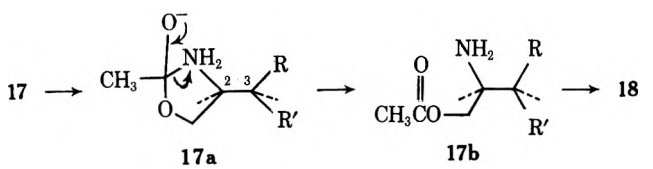
19, R = H
20, R = $COCH_3$



17, R = H; R″ = H
18, R = $COCH_3$; R″ = H
21, R = $COCH_3$; R″ = Ms

R′ = $-(CH_2)_6CO(CH_2)_5CH_3$

In contrast to the benzoylation described above, *N*-monoacetate **17** is now formed predominantly. The small tendency of the acetylation of the C-3 hydroxyl group followed by ring closure *via* pathway a described above explains the formation of oxazolines **19** and **20** as minor products. The second major product **18** can be rationalized through N → O acetyl migration *via* intermediate **17a** and **17b** followed by reacetylation[7] of the NH_2 group.



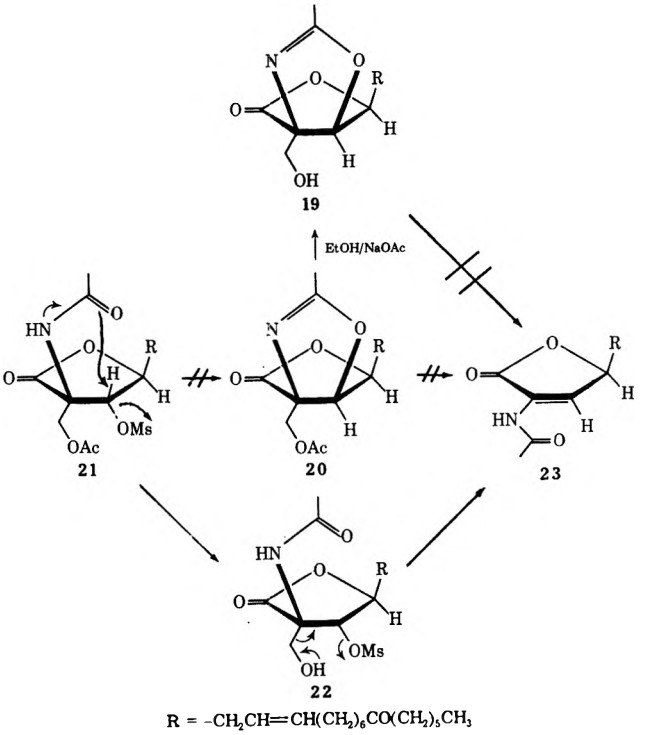
17a **17b**

If R in formula **17a** was a hydroxyl a similar N → O acetyl migration involving C-3 hydroxyl would lead to acetylation of this secondary hydroxyl group. The observation that no such C-3 acetate was formed and that the oxazolines **19** and **20** cannot be formed by pathway b under the conditions of the experiment suggests that the C-2–N and C-3–O bonds are trans to each other.

Therefore, the formation of oxazoline **13** as a major product (under conditions that promote both N- and O-esterification) and the oxazolines **19** and **20** as minor products (under conditions that promote preferential N-esterification) led us to infer that they are formed *via* the pathway suggested. Consequently the trans stereochemistry of the C–N and C–O bonds at C-2 and C-3 follows.

Mesylation of the diacetate **18** in methylene chloride–triethylamine[8] or in pyridine with methanesulfonyl chloride led to the formation of mesylate **21**. Treatment of mesylate **21** in ethanol and sodium acetate[5a] at reflux temperature overnight led in good yield to the isolation of a product that analyzed for $C_{22}H_{35}NO_4$.

The infrared spectrum showed a new band at 1742 cm^{-1} attributable to a butenolide with the concomitant loss of the saturated lactone band at 1775 cm^{-1}. The nmr spectrum exhibited a vinylic proton doublet (J = 2 Hz) at δ 7.4, and a doublet of triplets at 5.02 attributable to a carbinolic proton. The relationship between these two protons was established by double-resonance studies. The doublet at δ 7.4 collapsed to a singlet when observed during the irradiation at the resonance frequency of the proton at δ 5.02. Conversely, the doublet of triplets reduced to a triplet when observed



R = $-CH_2CH{=}CH(CH_2)_6CO(CH_2)_5CH_3$

(5) (a) L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 109 (1967); (b) S. Konstas, I. Photaki, and L. Zervas, *Chem. Ber.*, **92**, 1288 (1954).

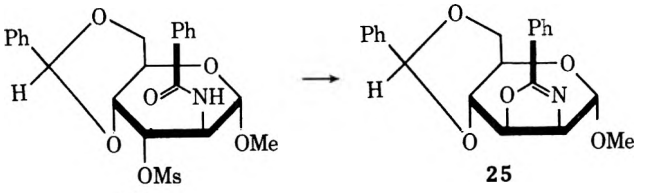
(6) Y. Inouye, K. Onodera, S. Kitaoka, and S. Hisano, *J. Amer. Chem. Soc.*, **78**, 4722 (1956).

(7) An alternative possibility of the formation of *N,N*-diacetyl compound as a precursor where one acetyl group migrates N → O cannot be discounted.

(8) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

during the irradiation at δ 7.4. This compound was assigned structure **23**.

It has been reported[9] that the α-D-altroside derivative **24** in refluxing ethanol and sodium acetate leads to oxazoline **25**. If one assumes a similar loss of the



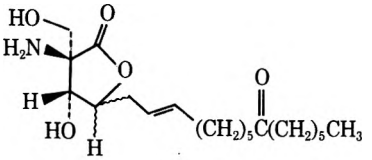
24 **25**

mesylate group in the genesis of compound **23** this would imply (a) trans stereochemistry of the methansulfonyl group relative to the –NHAc group and (b) that compound **20** is an intermediate in the formation of butenolide **23**.

However, when the oxazoline **20** was refluxed overnight in ethanol and sodium acetate, it led to the isolation of alcohol **19** as a major product. This experiment provides evidence that (1) under these conditions the methanolysis of the primary acetate occurs with ease and (2) alcohol **19** is not an intermediate in the formation of olefin **23**. It therefore follows that the mesylate **21** is hydrolyzed to the primary alcohol **22**, which undergoes a 1,3-diol cleavage to eliminate formaldehyde leading to the generation of the butenolide **23**.

Solvolytic[10] fragmentation of this type may or may not proceed *via* a concerted cyclic pathway. However, assuming (*vide supra*) the cis stereochemistry of the mesylate and the hydroxymethyl group in intermediate **22** a six-membered cyclic transition state leading to olefin **23** appears a probable pathway.

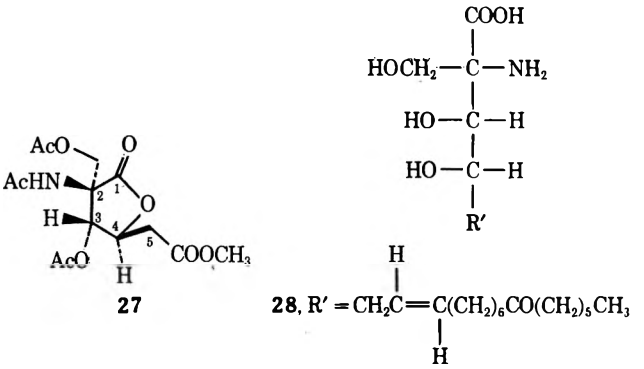
The above chemical evidence allows the expression of anhydromyriocin as shown in **26**.



26

NOE Spectrum Analysis.—In order to provide direct evidence in support of the above assignments at C-2 and C-3, and to determine the stereochemistry of substituents at C-4, we have made use of the intramolecular proton nuclear Overhauser effect (NOE), which provides a sensitive means for determining relative internuclear distances.[11] The investigation of the methyl ester **8** revealed the following. Irradiation of the resonance frequency of the methylene singlet at C-5 led to a 20 ± 3% enhancement of the integrated intensity of the NH signal, and a 15 ± 5% increase in the area of the C-3 proton. Similar experiments between the C-3 and the C-4 protons were not possible owing to the close proximity of their chemical shift. A small NOE of *ca.* 5% was detected between the C-3 proton and the methylene group attached to C-2.

Since only a large NOE can yield meaningful results, the above data demonstrates unambiguously that the C-5 methylene and the NHAc proton are on the same side of the ring. The interpretation of the NOE between C-5 methylene and the proton at C-3 warrants further discussion. Recent results[12] on the derivatives of penicillin indicate that, for a given conformation of the five-membered ring, both cis and trans methyl groups led to a significant NOE for an adjacent proton (the NOE for cis methyl was greater than that for the trans methyl). In another conformation of the same group of compounds, only the cis methyl group led to a large NOE. Recent work[13] on acetonides and related compounds also suggests that in a five-membered ring a methyl group produces a significant increase in the area of the adjacent proton, on the same side of the molecule. It therefore follows that C-5 methylene and C-3 proton in ester **8** bear a cis relationship to each other as shown in **27**. Consequently, the opening of the lactone ring of the anhydromyriocin **26** would lead to myriocin,[14] the asymmetric centers of which can be represented as shown in the expression **28** or its mirror image.



27 **28**, R′ = $CH_2C{=}C(CH_2)_6CO(CH_2)_5CH_3$

Experimental Section[15]

Myriocin (1).—The compound obtained from microbial fermentation was purified by repeated crystallizations from methanol, mp 180–181°, $[\alpha]^{24}D$ +10.3° (*c* 0.386, CH_3OH). The infrared spectrum (Table III) was recorded in KBr and showed broad hydroxylic absorption characteristic of a carboxylic acid.

Anal. Calcd for $C_{21}H_{39}O_6N$ (401): C, 62.81; H, 9.79; N, 3.49. Found: C, 62.95; H, 9.67; N, 3.32; $M^+ - 18$ (*m/e* 383), $M^+ - (127 + 18)$ (*m/e* 256).

Anhydromyriocin (2).—A solution of myriocin (1) (0.275 g) in *tert*-amyl alcohol (33 ml) was refluxed overnight. The solvent was removed and the residue (0.22 g) was purified by chromatography on silica gel (22 g) using 10% methanol–chloroform. A pure fraction recrystallized from chloroform–petroleum ether (bp 30–60°) to give lactone 2, mp 76–77°, $[\alpha]^{24}D$ +33.4° (*c* 0.718, CH_3OH). The infrared and the nmr spectra are recorded in Tables III and II, respectively.

(9) W. Mzu Reckendorf, *Chem. Ber.*, **98**, 93 (1965).

(10) C. A. Grob, *Bull. Soc. Chim. Fr.*, 1350 (1960).

(11) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect: Chemical Applications," Academic Press, New York, N. Y., 1971.

(12) (a) R. A. Archer and P. U. DeMarco, *J. Amer. Chem. Soc.*, **91**, 1530 (1969); (b) R. D. G. Cooper, P. U. DeMarco, J. C. Cheng, and N. D. Jones, *ibid.*, **91**, 1408 (1969).

(13) K. Nakaniski, D. A. Schooley, M. Koreeda, and I. Miura, *ibid.*, **94**, 2865 (1972).

(14) Since the submission of this paper, we have noted that thermozymocidin, a natural product [F. Aragozzini, *et al.*, *Experientia*, 881 (1972)] recently reported, appears to be identical with myriocin in its gross structure.

(15) The infrared spectra were recorded for solids in chloroform and for oils as film on a Perkin-Elmer model, and ultraviolet spectra were done in ethanol on a Unicam spectrophotometer. Unless otherwise mentioned, all routine nmr spectra were recorded on a 60-MHz Varian A-60A spectrometer. Decoupling experiments were carried out either at 100 MHz on a Jeol JNM-4H-100 instrument or at 220 MHz on a Varian HR-220, through the facilities of the Canadian 220 MHz NMR Centre, Sheriden Park, Ontario. The Merck silica gel (mesh 0.05–0.2 mm) was used for column chromatography. Organic extracts were dried over anhydrous magnesium sulfate, and the solvents were always removed under vacuum. Mass spectra were recorded on a Hitachi RMU-60 spectrometer.

Anal. Calcd for $C_{21}H_{37}O_5N$ (383): C, 65.76; H, 9.72; N, 3.65. Found: C, 65.79; H, 9.79; N, 3.40.

Anhydromyriocin hydrochloride was prepared by passing dry HCl gas in a solution of anhydromyriocin (0.3 g) in dry ether (37 ml) at 0°. After saturation the solvent was removed and the residue was crystallized from methanol–ether twice to give a pure sample (0.150 g), mp 180–185°.

Anal. Calcd for $C_{21}H_{38}NO_5Cl$: N, 3.35; Cl, 8.41. Found: N, 3.69; Cl, 8.41.

Acetylation of Myriocin. A. In Pyridine.—A sample of myriocin (132 mg) was acetylated with pyridine (2 ml) and acetic anhydride (2.8 ml) overnight at room temperature. The reaction mixture was worked up in the usual manner to yield a crude product (0.151 g). Purification by chromatography gave a sample of homogeneous triacetate **4** as an oil. The nmr and the ir are shown in Tables II and III.

Anal. Calcd for $C_{27}H_{43}O_8N$ (509): C, 63.63; H, 8.51; N, 2.75. Found: C, 63.63; H, 8.80; N, 2.91.

B. In Methanol.—To a suspension of myriocin (1) (10 g) in methanol (150 ml) at 65° was added acetic anhydride (200.3 ml). The mixture was stirred at that temperature for 30 min. The solvent was removed and the residue was flushed with methanol. The residue was taken in chloroform, washed with water, and dried and the solvent was removed to yield the crude mixture (11.5 g). This was chromatographed on silica gel (700 g) in 7% methanol–chloroform. A compound (3.29 g) was isolated from the later (71–94) fractions. Crystallization from methanol–ether gave pure *N*-acyl derivative **17** (3 g), mp 106–107°. An analytical sample from the same solvent had mp 106–107°.

Anal. Calcd for $C_{23}H_{39}O_6N$ (425): C, 64.91; H, 9.24; N, 3.29. Found: C, 64.84; H, 9.33; N, 3.08.

An ir spectrum showed absorptions at 3400 (broad band), 1773, 1705, and 1653 cm^{-1} (carbonyl region). The relevant nmr signals are listed in Table II.

Fractions 28–47 (5.4 g) were rechromatographed. The earlier fractions (13–20) of this chromatogram were pooled with the analogous fractions from the first purification to yield a product (0.75 g). Three crystallizations from ether–petroleum ether gave a pure sample, mp 72–73°. This was assigned structure **20**.

Anal. Calcd for $C_{25}H_{39}O_6N$ (449): C, 66.79; H, 8.75; N, 3.12. Found: C, 66.59; H, 8.86; N, 3.34.

An ir spectrum showed absorptions at 1778, 1750, 1705, and 1662 cm^{-1}. The nmr signals are listed in Table II.

Further elution gave a product (3.1 g) which slowly crystallized from ether–petroleum ether, mp 55–57°.

Anal. Calcd for $C_{25}H_{41}O_7N$ (467): C, 64.21; H, 8.84; N, 3.00. Found: C, 64.29; H, 8.92; N, 2.71.

An ir spectrum showed bands at 3300, 1778, 1750, 1705, and 1662 cm^{-1}. The nmr signals (Table II) and the above data led to the assignment of diacetate **18** for this product.

Finally, the later fractions (59–70) were pooled with similar material from the previous chromatogram and repurified to yield a product (0.58 g). Its structure **19** follows from the data below. Two crystallizations from ether–petroleum ether gave 0.35 g of product, mp 70–71°.

Anal. Calcd for $C_{23}H_{37}O_5N$ (407): C, 67.78; H, 9.15; N, 3.44. Found: C, 67.74; H, 9.32; N, 3.40.

An ir had broad absorption in the OH region, and carbonyl bonds at 1776, 1708, and 1660 cm^{-1}.

Reduction Experiments with Myriocin. A. Sodium Borohydride.—Myriocin (0.125 g) was dissolved in methanol (15 ml), and sodium borohydride (50 mg) was gradually added. After 20 min the reaction was quenched with saturated ammonium chloride solution (1.4 ml) and the product was extracted with chloroform to yield a residue (0.145 g). This was acetylated with pyridine–acetic anhydride to yield the tetraacetate **3**. An ir spectrum showed bands at 3400 (NH stretching), broad carbonyl absorption with peaks at 1775, 1748, 1700 and 1675, and a broad peak at 1225 cm^{-1} (sp^2 C–O stretching). The nmr signals are listed in Table II.

B. Catalytic Reduction.—Myriocin (0.1 g) was dissolved in methanol (12 ml) and hydrogenated in the presence of 5% palladium on charcoal (0.08 g). After filtration and removal of the solvent, a crude product (0.095 g) was obtained. This was acetylated in pyridine–acetic anhydride to yield the dihydro triacetate (0.057 g). An ir spectrum exhibited bands at 3400 (NH stretching), 1776, 1750, 1687 (broad, carbonyl), and 1212 cm^{-1} (ester). An nmr showed signals at δ 6.22 (1 H, s, NH), 5.76 (1 H, d, J = 5 Hz, carbinolic), 4.68 (1 H, m), 4.51 (2 H, s, carbinolic), 2.38 (4 H, m), 2.08, 2.03, 2.0 (s, 3 H each, acetyl methyl), 0.88 (3 H, t, terminal methyl).

C. Product of Borohydride and Catalytic Reduction.—A sample of myriocin (0.147 g) was reduced with sodium borohydride as described above. The product (0.15 g) was subjected to catalytic reduction to yield 0.16 g of tetrahydromyriocin. This was acetylated in the usual manner to yield a tetraacetate (0.085 g). An ir showed bands at 3410, 1750 (broad carbonyl absorption with shoulders at 1775 and 1723), 1680, and 1225 cm^{-1}. An nmr exhibited signals at δ 6.36 (1 H, s, NH), 5.82 (1 H, d, J = 5 Hz, carbinolic), 4.8 (1 H, m), 4.53 (2 H, s, carbinolic), 2.1 (12 H, m, acetyl methyl), and 0.88 (3 H, t, terminal methyl). Absence of signals at ~2.4 was conspicuous.

Ozonolysis of Acetate 4.—The acetate **4** (0.62 g) was dissolved in chloroform (15 ml) and ozonized for 1 hr at −50°. The solvent was removed and the crude ozonide was subjected to oxidation. It was dissolved in acetic acid (40 ml), and 30% hydrogen peroxide (10 ml) was added to it. The mixture was kept at ~80° (bath temperature) for 24 hr. The solvent was removed and the residue was esterified with diazomethane. Chromatography of the product on silica gel and elution with 5% ethyl acetate–benzene gave a product (0.15 g). Purification of this product *via* base-catalyzed hydrolysis, isolation of the acid, and reesterification gave a compound identical in its mass spectrum and glc (12 ft, 5.1% XE60, T_c 215°, retention time 6.2 min) with 8-ketotetradecanoic acid methyl ester.[3] An ir spectrum showed bands at 1737 and 1712 cm^{-1}. Further elution with 70% ethyl acetate–benzene yielded a product (0.338 g) which was recrystallized from methanol–ether once, to yield a sample of lactone **8** (0.225 g), mp 174–175°. An analytical sample obtained from the same solvent had mp 174–175°.

Anal. Calcd for $C_{14}H_{19}O_9N$ (345.3): C, 48.69; H, 5.55; N, 4.06. Found: C, 48.78; H, 5.54; N, 4.55.

The nmr and ir data are listed in Tables II and III, respectively.

Periodic Acid Oxidation of Myriocin.—Myriocin (1) (0.2 g) was suspended in ether (3 ml). To this suspension was added with vigorous stirring a solution of periodic acid (0.5 g) in water (2 ml). The reaction mixture was stirred for 15 min. The reaction mixture was diluted with ether, washed with a solution of thiosulfate and with water, and dried, and the solvent was removed. The crude product (0.132 g) was triturated and washed with ice cold petroleum ether to yield a product (0.102 g) homogenous by tlc. The ir showed an aldehydic proton stretching at 2710, a carbonyl band at 1710, and vinylic proton bending at 970 cm^{-1}. A uv spectrum showed no characteristic band in neutral medium. In basic medium a band at 223 nm (ϵ 5100) developed. The nmr showed the following signals: δ 0.88 (3 H, t, terminal $-CH_3$), 3.09 (2 H, m, $-CH_2$ α to aldehydic carbonyl), 5.53 (2 H, m, vinylic protons), 9.65 (1 H, t, HC=O).

Transformations of the Aldehyde 11.—A sample (0.309 g) of aldehyde **11** was dissolved in methanol (19 ml) and hydrogenated in presence of 5% palladium on charcoal (0.150 g). The product (0.301 g) was isolated in the usual manner. An ir showed absence of 970 cm^{-1} (vinylic proton bending). The above product was dissolved in ethanol (7.5 ml). To this solution was added a solution of silver nitrate (0.75 ml, 50%), followed by addition of sodium hydroxide solution (0.75 ml, 23%). The mixture was stirred overnight at room temperature and then filtered through Celite. The ethanol was removed and the residue was taken in ether. The ether extract was washed with sodium hydroxide (10%). The aqueous liquor was acidified with dilute hydrochloric acid, the acid thus obtained was extracted with ether and dried, and the solvent was removed to yield a crude product (0.163 g). This was pooled with the acid (0.07 g) obtained from another experiment. The mixture was esterified with diazomethane to yield crude ester (0.22 g) and was put on a silicic acid column (70 g) and eluted with 2% ethyl acetate–benzene to give pure ester **12** (0.09 g). A glc of this ester showed identical retention time with that of methyl 11-ketoheptadecanoate.[4] A sample (0.082 g) of the above ester was hydrolyzed with methanolic sodium hydroxide to yield the corresponding acid (0.062 g). A crystallization from ether–petroleum ether gave crystals (0.05 g), mp 78–79°, mmp with authentic 11-ketoheptadecanoic acid 78–79° (reported[4] 78–79°).

Benzoylation of Myriocin (I).—To a solution of myriocin (0.45 g) in dry pyridine (10 ml) was added *p*-bromobenzoyl chloride (1.8 g). The reaction mixture was heated to 100° for 24 hr. The mixture was cooled and diluted with methanol and the solvent was removed. The residue was taken in ether, washed with

hydrochloric acid (3%), sodium bicarbonate, and water, and dried and the solvent was removed. The residue (0.575 g) was passed through a column of silica gel (50 g) to yield a product (0.290 g) homogenous by tlc. On keeping, some crystals appeared which were separated with ice-cold hexane. Based on the nmr (Table II) and ir data (Table III) the crystalline benzoate was assigned structure **15**, and the oily benzoate was assigned structure **13**. The acetylation of the mixture of benzoates (0.210 g) obtained above in acetic anhydride (3.9 ml) and dry pyridine (1.7 ml) yielded after the usual work-up the crude acetate (0.2 g) as two spots on tlc. Chromatographic separation on silica gel yielded the major product (0.129 g) in the pure form, which was assigned the structure **14**. An ir showed no absorption in the NH region, and bands at 1775, 1750, 1700, 1633, and 1590 cm^{-1}. The nmr showed signals at δ 7.21 (4 H, q, aromatic), 5.55 (2 H, q, vinylic), 5.22 (1 H, d, carbinolic at C-3), 4.5 (3 H, m, carbinolics C-2 hydromethyl and C-4), 2.03 (3 H, s, acetyl methyl), and 0.88 (3 H, t, terminal methyl). A mass spectrum exhibited M^+ (*m/e* 590), $M^+ - 127$ (*m/e* 463), *m/e* 184 $(-COC_6H_4Br)^+$.

The minor products of acetylation of benzoate from two experiments were pooled and purified by repeated chromatography. The structure **16** for this product follows from the following data. An ir spectrum showed bands at 3400 (NH), 1776, 1750, 1705, 1670, and 1590 cm^{-1}. An nmr had signals at δ 7.61 (4, H, s, aromatic), 6.81 (1 H, s, NH), 5.83 (1 H, d, carbinolic at C-3), 5.50 (2 H, m, vinylic), 4.75 (1 H, m, carbinolic at C-4), 4.61 (2 H, s, carbinolic C-2 hydroxymethyl), 2.08, 1.88 (3 H each, s, acetyl methyl), and 0.88 (3 H, t, terminal $-CH_3$). A mass spectrum exhibited the following peaks: M^+ (*m/e* 650), $M^+ - 60$ (*m/e* 590), $M^+ - 127 + 60$) (*m/e* 463), $M^+ - (184 + 127 + 60)$ (*m/e* 279), and *m/e* 184 $(COC_6H_4Br)^+$.

Mesylation of Diacetate 18.—To a solution of diacetate **18** (0.117 g) in methylene chloride (4 ml) was added triethylamine (0.152 g) followed by methanesulfonyl chloride (0.126 g). The mixture was stirred overnight at room temperature. The reaction mixture was diluted with methylene chloride and washed with sodium bicarbonate, followed by dilute hydrochloric acid and water. The organic liquor was dried and the solvent was removed to yield the crude product (0.155 g). Chromatographic purification gave a pure sample of **21** (0.075 g).

Anal. Calcd for $C_{26}H_{43}NO_9S$ (545): C, 57.0; H, 7.89; N, 2.57; S, 5.86. Found: C, 56.84; H, 7.99; N, 2.59; S, 5.85.

An ir showed bands at 3400 (NH), 1780, 1750, 1690 (carbonyl); nmr δ 6.62 (1 H, s, NH), 5.55 (3 H, m, 2 H vinylic and 1 H C-3 carbinolic), 4.75 (1 H, m, C-4 carbinolic), 4.56 (2 H, d, C-2, CH_2O-), 3.05 (3 H, s, CH_3SO_2), 2.08 (6 H, s, $2CH_3CO-$), 0.89 (3 H, t, terminal $-CH_3$).

Sodium Acetate Treatment of the Mesylate 21.—The mesylate **21** (0.535 g) was dissolved in absolute ethanol (12 ml) in the presence of sodium acetate (0.3 g) and the mixture was refluxed overnight. The reaction mixture was cooled, diluted with ether, washed with water, and dried and the solvent was evaporated. The resulting residue after one crystallization from ether–petroleum ether gave a solid (0.270 g, 73%), mp 87–91°. An analytical sample had mp 94–96°.

Anal. Calcd for $C_{22}H_{35}O_4N$ (377): C, 69.99; H, 9.35; N, 3.71. Found: C, 70.16; H, 9.38; N, 3.64.

An ir showed bands at 3385, 3300 (NH), 1742, 1698, and 1650 cm^{-1} (carbonyl); nmr δ 7.95 (1 H, broad, NH), 7.4 (1 H, d, J = 2 Hz, vinylic), 5.45 (2 H, q, vinylic), 5.02 (1 H, d of t, J = 2 Hz, carbinolic), 2.2 (3 H, s, CH_3CO), 0.9 (3 H, t, terminal $-CH_3$); uv λ_{max}^{EtOH} 246 nm (ϵ 5400).

Treatment of Oxazoline 20 with Sodium Acetate.—To a solution of **20** (30 mg) in absolute ethanol (2.2 ml) was added sodium acetate (60 mg). After refluxing overnight the product was put through a small column of silica gel to yield a product (10 mg) which showed a major spot corresponding to alcohol **19** and a minor spot corresponding to diol **17**. These were separated on a thick layer plate[16] and were shown to be identical with **19** and **17** by comparison of mass spectra with those of the authentic samples.

Registry No.—**1**, 35891-70-4; **1** (tetrahydro tetraacetate), 38223-34-6; **2**, 35891-69-1; **2** (HCl), 38223-36-8; **3**, 38223-37-9; **3** (dihydro), 38223-38-0; **4**, 38223-39-1; **8**, 38223-40-4; **11**, 38223-41-5; **13**, 38223-42-6; **14**, 38223-43-7; **15**, 38223-44-8; **16**, 38337-05-2; **17**, 38223-46-0; **18**, 38223-47-1; **19**, 38223-48-2; **20**, 38223-59-5; **21**, 38223-60-8; **23**, 38223-61-9.

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(16) The authors wish to thank Dr. G. Schilling for carrying out this separation and performing the mass spectral comparison.

The Isolation and Structural Elucidation of Eupaserrin and Deacetyleupaserrin, New Antileukemic Sesquiterpene Lactones from *Eupatorium semiserratum*[1,2]

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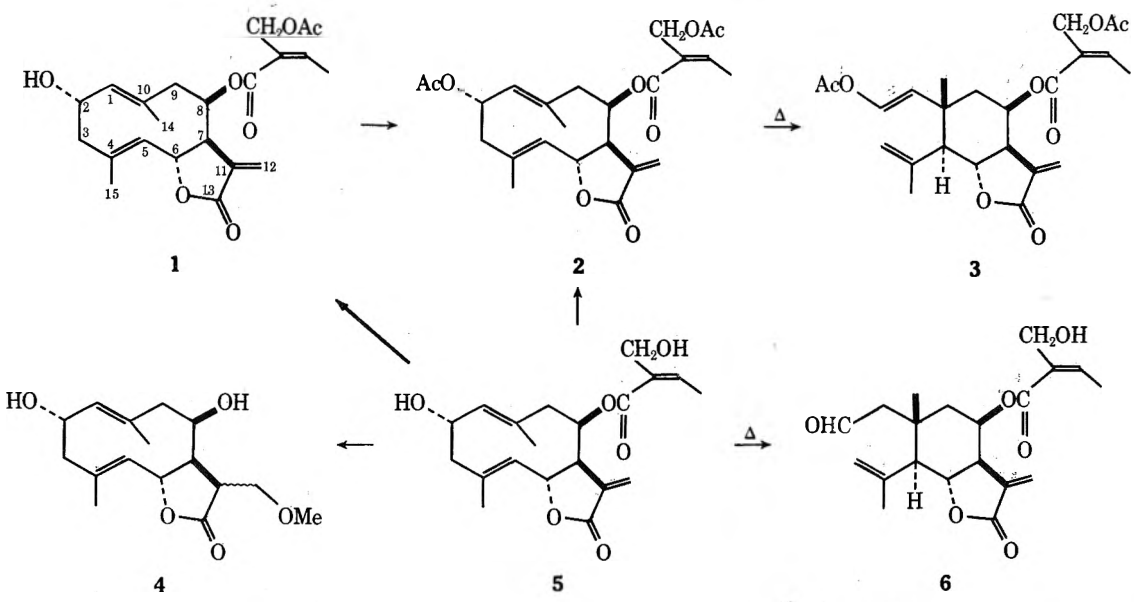
Evidence is presented for the assignment of structures for eupaserrin (**1**) and deacetyleupaserrin (**5**), two antileukemic sesquiterpene lactones from *Eupatorium semiserratum* DC. Elemental analysis and high resolution mass spectrometry supported a $C_{22}H_{28}O_7$ molecular formula for eupaserrin (**1**) and a $C_{20}H_{26}O_6$ molecular formula for deacetyleupaserrin (**5**). Acetylation of **5** gave **1** and acetyleupaserrin (**2**), whereas alkaline hydrolysis of **5** gave sarracinic acid. Chemical and spectral evidence indicated the presence of α-methylene-γ-lactone, α,β-unsaturated ester, secondary hydroxyl, and two vinyl methyl groupings in **1** and **5** and suggested that both **1** and **5** were germacranolide dienes. Pyrolysis of **5** gave an oily aldehyde lactone (**6**), and pyrolysis of **2** gave an enol acetate (**3**). Chemical and spectral arguments are advanced for assignment of structure and stereochemistry for **2** and **3** and therefore **1** and **5**.

In the course of a continuing search for tumor inhibitors from plant sources, an alcoholic extract of *Eupatorium semiserratum* DC (Compositae)[3] was found to show significant inhibitory activity *in vivo* against the P-388 leukemia in the mouse and *in vitro* against cells derived from human carcinoma of the nasopharynx

(1) Tumor Inhibitors. LXXXIV. Part LXXXIII: S. M. Kupchan, G. Tsou, and C. W. Sigal, *J. Org. Chem.*, **38**, 1420 (1973).

(2) This investigation was supported in part by grants from the National Cancer Institute (CA-11718) and the American Cancer Society (IC-57), and a contract with the Division of Cancer Treatment, National Cancer Institute (NIH-2099).

(3) Leaves, stems, flowers, and fruits were collected in Florida in Sept 1967. We thank Dr. Robert E. Perdue, Jr., USDA, Beltsville, Md., for supplying the plant material.



(KB).[4] Consequently, a systematic study aimed at the isolation of the active principles was undertaken. It is the purpose of this paper to present in detail the fractionation of the active extract of *E. semiserratum* and the isolation and structural elucidation of the active constituents eupaserrin (**1**) and deacetyleupaserrin (**5**).[5]

Fractionation of the ethanol extract, guided by assay against KB, revealed that the activity was concentrated, successively, in the chloroform layer of a chloroform–water partition, in the aqueous methanol layer of a 10% aqueous methanol–petroleum ether partition, and in the propylene glycol layer of a propylene glycol–benzene partition. Aqueous sodium bicarbonate was added to the propylene glycol layer and the combined fraction was extracted with ethyl acetate. By this process all of the activity was concentrated in the final ethyl acetate layer (fraction H). Rapid column chromatography of the ethyl acetate soluble material on silica gel gave two cytotoxic fractions (I and J). Careful rechromatography of fraction I on alumina and elution with chloroform gave crystalline eupaserrin (**1**). Rechromatography of the more polar fraction J on silica gel gave, on elution with 5% methanol in chloroform, deacetyleupaserrin (**5**) as a colorless brittle foam, which resisted all attempts at crystallization.

The molecular formula for eupaserrin (**1**), $C_{22}H_{28}O_7$, was assigned on the basis of high resolution mass spectrometry and elemental analysis. The ultraviolet high end absorption, infrared bands at 5.66 and 6.14 μ, and nmr signals at τ 3.70 and 4.40 (a pair of doublets, J = 3.5 and 3.0 Hz, respectively) suggested the presence of an exocyclic methylene γ-lactone. In addition, the presence in the nmr spectrum of **1** of a three-proton singlet at τ 8.02, a three-proton doublet at τ 7.88 (J = 7 Hz), which was shown to be coupled to an olefinic one-proton quartet at τ 3.48 (J = 7 Hz), and an AB quartet with ν_A τ 5.16 and ν_B 5.51 (J = 12 Hz) indicated the likelihood of an acetylsarracinate residue. These signals in the nmr spectrum were almost identical in chemical shift and multiplicity with those assigned to the acetylsarracinate moiety in liatrin.[6] In addition, infrared bands at 5.78, 5.82, and 8.00 μ and a large peak in the mass spectrum at m/e 141 ($C_7H_9O_3$) of **1** attested to the presence of the acetylsarracinate residue. Subtracting this residue from the molecular formula left $C_{15}H_{19}O_4$ for the sesquiterpene skeleton and, since two oxygen atoms were accounted for by the γ-lactone moiety and one more by the ester linkage, only one oxygen atom remained unassigned. The infrared spectrum of **1** showed a sharp peak at 2.90 μ indicating the presence of a hydroxyl group, and indeed acetylation of **1** with acetic anhydride in pyridine gave in good yield amorphous acetyleupaserrin (**2**). The nmr spectrum of **2** was very similar to that of eupaserrin (**1**) except for the presence of a new acetyl methyl at τ 7.90 and a one-proton doublet of triplets at τ 4.38 (J = 5, 9 Hz), which in the case of **1** had appeared at τ 5.28 (J = 6, 9 Hz). This result indicated that the remaining oxygen was present as a secondary alcohol adjacent to three other protons. The nmr spectrum of eupaserrin (**1**) also showed the presence of two tertiary vinyl methyl groups as broad singlets at τ 8.46 and 8.20, which were shown to be coupled to a two-proton multiplet at τ 5.0. The combined data suggested that eupaserrin (**1**) is bicyclic, since this would account for all of the degrees of unsaturation allowed by the molecular formula. The γ-lactone accounted for one ring, and, since the nmr of **1** clearly showed signals for two vinyl tertiary methyl groups, it was apparent that eupaserrin (**1**) was probably a member of the germacranolide diene class of sesquiterpenes.

The molecular formula for deacetyleupaserrin (**5**), $C_{20}H_{26}O_6$, was assigned on the basis of high resolution mass spectrometry. The nmr spectrum of **5** was very similar to that of eupaserrin (**1**) except that it lacked the acetyl methyl singlet at τ 8.02. In addition, an AB quartet with ν_A τ 5.16 and ν_B 5.51 (J = 12 Hz) in the spectrum of **1** was replaced by an apparent triplet centered at τ 5.80 (J = 13 Hz) in the spectrum of **5**. These results indicated that **5** was probably the deacetyl derivative of **1**. In fact, acetylation of **5** with

(4) Cytotoxicity and *in vivo* activity were assayed as in *Cancer Chemother. Rep.*, **25**, 1 (1962).

(5) Eupaserrin and deacetyleupaserrin showed significant antileukemic activity against the P-388 leukemia in mice at 30 and 18 mg/kg, respectively, and cytotoxicity against KB cell culture (ED_{50} = 0.23 and 0.29 μg/ml, respectively).

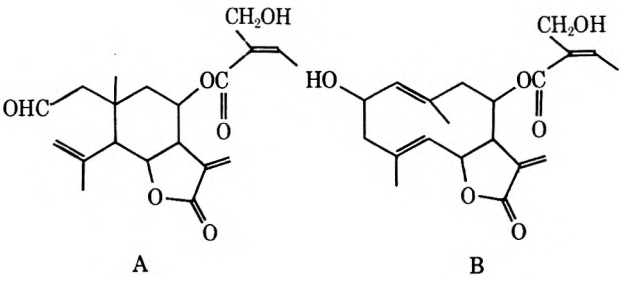
(6) S. M. Kupchan, V. H. Davies, T. Fujita, M. R. Cox, and R. F. Bryan, *J. Amer. Chem. Soc.*, **93**, 4916 (1971).

acetic anhydride in pyridine gave a mixture of eupaserrin (1) and acetyleupaserrin (2). Alkaline hydrolysis of deacetyleupaserrin (5) gave sarracinic acid;[6-8] thus the side-chain ester of 5 and, therefore, 1 was firmly established as the sarracinate and acetylsarracinate, respectively.

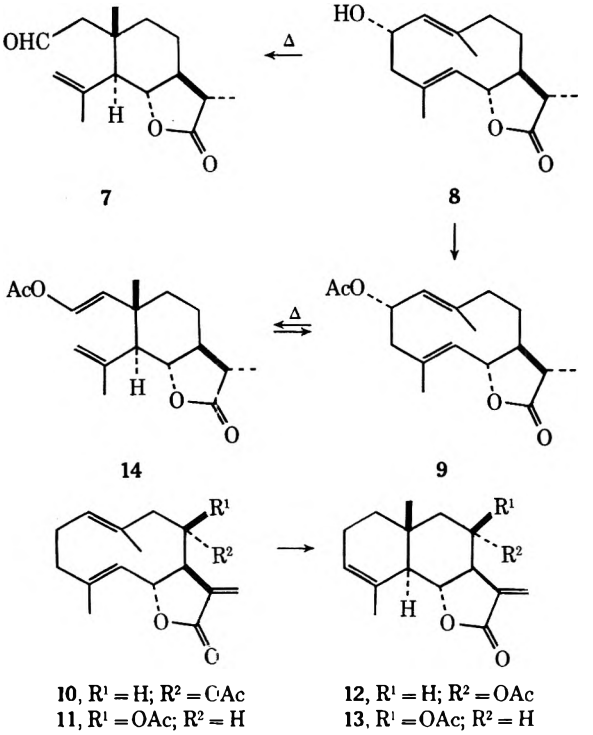
Careful inspection of the nmr spectra of 1 and 5 combined with several decoupling experiments revealed additional structural features of the two molecules. For example, irradiation of a multiplet centered at τ 7.0 in the spectrum of 1 caused the two one-proton doublets at τ 3.70 and τ 4.40, characteristic of the C-13 protons of an exocyclic conjugated methylene lactone,[9] to collapse to singlets. Thus the multiplet at τ 7.0 could be assigned to the C-7 proton. In addition, irradiation of the C-7 proton also caused a one-proton multiplet at τ 4.2 to collapse to a triplet which could thus be assigned as the C-8 (or C-6) proton signal. Furthermore, irradiation of the signal at τ 4.2 caused two one-proton doublets of doublets at τ 7.13 (J = 14, 6 Hz) and 7.63 (J = 14, 2 Hz) to collapse to doublets (J = 14 Hz), which could thus be assigned to an isolated methylene group with no other adjacent protons. Although the signal for the C-6 proton was not readily apparent in the nmr spectrum of 1, in deacetyleupaserrin (5) it appeared clearly as a doublet of doublets at τ 4.90 (J = 8, 10 Hz). Irradiation of the C-6 proton caused a sharpening in the multiplet at τ 6.96 which was assigned to the C-7 proton. Irradiation of the C-7 proton not only collapsed the C-8 multiplet at τ 4.16 to an apparent triplet but also caused the C-6 doublet of doublets to collapse to a doublet (J = 8 Hz).

On treatment with sodium methoxide in methanol, deacetyleupaserrin (5) gave the oily methanol adduct 4. In the nmr spectrum of 4, the C-6 proton was evident as a triplet at τ 4.90 (J = 9 Hz), but the C-8 proton multiplet, which appeared at τ 4.16 in 5, now appeared at τ 5.64. The large change in position of the C-8 multiplet indicated that the sarracinate ester moiety of 5 and therefore also of 1 must be located at C-8.

It has been shown that germacranolide dienes such as dihydrotamaulipin A (8)[10] undergo a Cope rearrangement on heating at 180–200° for a short period of time. It appeared that both 1 and 5 were probably germacranolide dienes of this type, and consequently deacetyleupaserrin (5) was subjected to the Cope rearrangement conditions. When 5 was heated at 180° for 3 min, the major product isolated was characterized as the oily aldehyde lactone 6. The nmr spectrum of 6 exhibited a one-proton triplet (J = 2 Hz) at τ 0.12 characteristic of an aldehyde proton, which was shown to be coupled to a two-proton doublet at τ 7.45 (J = 2 Hz). The appearance of a three-proton singlet at τ 8.73, a new vinyl methyl singlet at τ 8.07, and two new vinyl protons at τ 4.85 and 5.19 indicated that a Cope rearrangement[10-13] had taken place in the desired manner and allowed us to postulate a partial structure A for the



aldehyde lactone, and thus B for deacetyleupaserrin. This result placed the secondary hydroxyl group of eupaserrin (1) and deacetyleupaserrin (5) at C-2. In order to determine the relative stereochemistry of the C-2 hydroxyl, it was necessary to repeat the pyrolysis reaction with acetyleupaserrin (2), which gave a 1:1 mixture of the enol acetate 3 and starting material 2. The trans nature of the enol acetate double bond was indicated by the presence in the nmr spectrum of 3 of two one-proton doublets at τ 2.97 (J = 13 Hz) and 4.58 (J = 13 Hz) for the C-2 and C-1 vinyl protons, respectively. The corresponding coupling constant for enol ester cis double bonds has been found to be on the order of 7 Hz.[14] By analogy with similar studies on dihydrotamaulipin A (8) and dihydrotamaulipin A acetate (9),[10] the hydroxyl group at C-2 of eupaserrin (1) and deacetyleupaserrin (2) could now be assigned the α configuration as shown. In addition, the nmr spectrum of 3 clearly showed the C-5 proton as a sharp doublet at τ 7.54 (J = 12 Hz), which was coupled to a one-proton triplet at τ 5.42 (J = 12 Hz). The τ 5.42 peak, which could now be assigned to the C-6 proton, was also coupled to a doublet of multiplets at τ 7.12 (J = 12 Hz), which could thus be assigned to the C-7 proton. Comparison of the coupling constants and chemical shifts for the C-5, C-6, C-7, and C-8 protons in the aldehyde lactone 6 and the enol acetate 3 with the litera-



(7) C. C. J. Culvenor and T. A. Geissman, *J. Org. Chem.*, **26**, 3045 (1961).
(8) J. D. Edwards, Jr., T. Matsumoto, and T. Hase, *ibid.*, **32**, 244 (1967).
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(13) N. H. Fisher and T. J. Mabry, *Chem. Commun.*, 1235 (1967).
(14) (a) W. Brügel, Th. Ankel, and F. Krückeberg, *Z. Electrochem.*, **64**, 1121 (1960); (b) J. J. Riehl, J.-M. Lehn, and F. Hemmert, *Bull. Soc. Chim. Fr.*, 224 (1963); (c) T. Schaefer, *J. Chem. Phys.*, **36**, 2235 (1962).

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA[a]

Compd	C-1	C-2	C-5	C-6	C-7	C-8	C-9	C-13	C-14	C-15
1	5.0 m	5.28 dt (6, 9)	5.0 m	5.0 m	7.0 m	4.2 m	7.13 dd (14, 6) 7.63 dd (14, 2)	3.70 d (3.5) 4.40 d (3)	8.46 br s	8.20 br s
2	4.95 m	4.38 dt (5, 9)	4.95 m		7.0 m	4.13		3.69 d (3) 4.38 d (3)	8.32 br s	8.12 br s
3	4.58 d (13)	2.97 d (13)	7.54 d (12)	5.42 dd (12, 12)	7.12 br d (12)	4.20 m		3.83 d (3) 4.50 d (3)	8.72 s	8.12 br s
4	5.00 m	5.17 dt (6, 10)	5.00 m	4.90 t (9)		5.62 m		6.32 br d (4) 3.56 s (C-13 OCH3)	8.31 br s	8.24 br s
5	5.00 m	5.28 dt (5.5, 9)	5.00 m	4.9 dd (8, 10)	6.96 m	4.16 m	7.10 dd (14, 4) 7.62 dd (14, 2)	3.70 d (3.5) 4.47 d (3)	8.44 br s	8.20 br s
6	7.45 d (2)	0.12 t (2)	7.18 d (12)	5.42 t (12)	7.05 br d (12)	4.20 m	7.82 d (3)	3.83 d (3) 4.78 d (3)	8.73 s	8.07 br s
7[b]	7.53 d (3)	0.18 t (3)	7.53 d (12)	5.89 br dd (12, 10)				8.78 d (7)	8.90 s	8.16 br s
8[b]	5.1 m	5.40 m	5.1 m	5.45 m				8.76 d (6.5)	8.52 br s	8.28 d (1.1)
9[b]	5.09 br	4.37 dt (5.5, 10)	5.09 br	5.46 dd (7.5, 10)				8.78 d (7)	8.44 br s	8.25 br s
10[c]			5.15 br d (10)	5.44 dd (8, 10)	7.45 br m	4.8–5.2 obsc		3.77 d (3.5) 4.45 d (3)	8.58 br s	8.30 br s
11[c]			5.22 dd (1.3, 10)	4.87 dd (8.1, 10)	7.07 br m	4.28 m		3.72 d (3.5) 4.41 d (3.1)	8.48 br s	8.24 d (1.3)
12[c]				6.02 dd (10.8, 11.3)	7.20 m	4.70 m		3.89 d (3.1) 4.49 d (2.9)	9.01 s	8.13 br s
13[c]				5.60 dd (11, 11)	7.20 m	4.30 m		3.85 d (3.3) 4.56 d (3.1)	8.92 s	8.11 br d (1.5)
14[b]	4.51 d (13)	2.95 d (13)	7.77 d (10)	5.89 br dd				8.78 d (6.5)	8.88 s	8.22 br s

[a] Spectra were determined on a Varian HA-100 spectrometer in deuteriochloroform solutions unless otherwise indicated. Values are given in τ units relative to tetramethylsilane as internal standard. Multiplicity of signals is designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplets; m, multiplet; obsc, obscured; br, broad. Numbers in parentheses denote coupling constants in hertz. [b] Reference 10. [c] Reference 15.

ture values for the corresponding compounds from dihydrotamaulipin A (**8** → **7**) and dihydrotamaulipin A acetate (**9** → **14**),[10] as well as the rearrangement products of tulipinolide (**10** → **12**) and epitulipinolide (**11** → **13**)[15] allowed us to assign the relative stereochemistry of all four centers (see Table I). In particular, a comparison of the relevant data for **6** with **7** and **3** with **14** offered convincing proof of the relative stereochemistry at C-2, C-5, C-6, and C-7 of these compounds. Furthermore, the chemical shift and multiplicity of the C-8 proton in eupaserrin (**1**) and its derivatives (**5**, **2**, **6**, and **3**) were very similar to those observed in epitulipinolide (**11**) and its derivative (**13**). This was in marked contrast to the corresponding data for tulipinolide (**10**) and its derivative **12** and strongly suggests that eupaserrin (**1**) and, therefore, deacetyleupaserrin (**5**) have the β configuration at this center as depicted above.[16]

Experimental Section

Melting points were determined on a Mettler Model FP2 hot stage and are corrected. Ultraviolet absorption spectra were determined on Beckman Model DK-2A and Coleman Hitachi Model EPS-3T recording spectrophotometers. Infrared spectra were determined on Beckman Model IR-9, Perkin-Elmer Model 257, and Perkin-Elmer Model 337 recording spectrophotometers. Nuclear magnetic resonance spectra were determined on a Perkin-Elmer Model R-20 spectrometer at 60 MHz and on a Varian HA-100 spectrometer in deuteriochloroform solution with tetramethylsilane as an internal standard. Mass spectra were obtained from Hitachi Perkin-Elmer Model RMU-6A (RMU-6E) and AEI Model MS-902 spectrometers. Values of $[\alpha]_D$ were determined on a Perkin-Elmer Model 141 automatic polarimeter. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. Analytical thin layer chromatography (tlc) was carried out with 5% methanol in chloroform on silica gel plates (supplied by E. Merck), which were visualized with either concentrated sulfuric acid–vanillin–ethanol (20:1:3) spray or 2% ceric sulfate spray, unless otherwise specified. Evaporations were carried out under reduced pressure at less than 40°. Petroleum ether refers to the fraction with bp 60–68°.

Isolation Procedure.—The dried ground stems, leaves, flowers, and fruit of *Eupatorium semiserratum* (2.85 kg) were continuously extracted with hot ethanol for 48 hr, and the ethanol extract was evaporated under reduced pressure to yield a dark green residue (A, 510 g). Fraction A was partitioned between chloroform (2 l.) and water (1 l.). The chloroform layer was evaporated to give a green residue (D, 169 g) and the aqueous layer gave a dark tar (B, 213 g). Fraction D was partitioned between petroleum ether (4 l.) and 10% aqueous methanol (1.5 l.). Evaporation of the petroleum ether fraction gave a green tar (E, 61 g) and the 10% aqueous methanol layer gave a dark tar (F, 99 g). Fraction F was partitioned between benzene (2 l., G, 16 g) and propylene glycol (0.5 l.), and then the propylene glycol layer was diluted with saturated sodium bicarbonate solution (1.2 l.) and water (2 l.) and extracted with ethyl acetate (1 l.). Evaporation of the final ethyl acetate layer gave a dark brown gum (H, 39 g), which contained almost all of the original KB activity. Fraction H was chromatographed on 200 g of silica gel. Eupaserrin (**1**) and deacetyleupaserrin (**5**) were eluted with chloroform (fractions I and J). Fraction I was rechromatographed on alumina (50 g) to give on elution with chloroform a fraction, which was crystallized from ether–methanol, affording eupaserrin (**1**, 190 mg): mp 153–154°; $[\alpha]^{25}D$ +71.2° (c 0.94, MeOH); uv λ_{end}^{EtOH} 210 nm (ϵ 27,270); ir λ_{max}^{KBr} 2.9, 5.66, 5.78, 5.82, 6.14, and 8.00 μ; mass spectrum *m/e* 404.1830 (M^+, calcd for $C_{22}H_{28}O_7$, 404.1841), 386, 246, 202, 141, and 99; R_f 0.55.

Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.27; H, 7.10.

Rechromatography of fraction J on silica gel (200 g) on elution with 5% methanol in chloroform gave deacetyleupaserrin (**5**, 6.6 g), as an amorphous brittle white foam. Although **5** appeared to be homogeneous by tlc, it could not be crystallized and did not give satisfactory analytical data. Deacetyleupaserrin appeared to be quite unstable and even freshly prepared samples quickly decomposed on standing. Spectral data were obtained on freshly prepared samples: $[\alpha]^{25}D$ +75.0° (c 0.92, MeOH); uv λ_{end}^{EtOH} 209 nm (ϵ 23,200); ir $\lambda_{max}^{CHCl_3}$ 2.78, 2.90, 5.66, 5.82, 6.04, 8.12, and 8.73 μ; mass spectrum *m/e* 362.1710 (M^+, calcd for $C_{20}H_{26}O_6$, 362.1730), 264, 246, 202, and 99; R_f 0.37.

Acetyleupaserrin (2).—Eupaserrin (**1**, 195 mg) was dissolved in pyridine (4 ml), and acetic anhydride (2 ml) was added at 0°. The reaction mixture was stirred for 1.5 hr at room temperature, then diluted with water, and extracted with chloroform. The chloroform extract was dried over magnesium sulfate and evaporated to afford a yellow oil (220 mg). The total crude product was applied to 10 ChromAR 7GF (20 × 20 cm × 0.25 mm) tlc

(15) R. W. Doskotch and F. S. El-Feraly, *J. Org. Chem.*, **35**, 1928 (1970).

(16) We have also isolated eupaserrin (**1**) from *Eupatorium cuneifolium Willd.*

plates and developed with 1:1 ether in benzene. The major band was removed from the plates and eluted with chloroform to afford acetyleupaserrin (2) as a viscous colorless glass. Various attempts at crystallization of 2 were unsuccessful and so it was characterized as a foam: $[\alpha]^{25}D$ +83° (c 0.95, $CHCl_3$); ir λ_{max}^{KBr} 5.68, 5.78, 5.82, 6.10, 8.10, 8.62, and 8.77 μ; mass spectrum m/e 446.1931 (M^+, calcd for $C_{24}H_{30}O_8$, 446.1939), 386, 246, 228, 213, and 141; R_f 0.70.

Acetylation of Deacetyleupaserrin (5).—To a solution of deacetyleupaserrin (5, 300 mg) in acetic anhydride (10 ml), powdered potassium carbonate (20 mg) was added and the mixture stirred at room temperature for 2 hr. The reaction mixture was poured into ice–water, stirred for a further 3 hr, and extracted with chloroform. The organic extract was washed with aqueous sodium bicarbonate and then water, dried over sodium sulfate, and evaporated to give a colorless residue (300 mg), which yielded two major components on preparative tlc. The band of higher R_f, eluted with 10% methanol in chloroform, was crystallized from methanol to yield eupaserrin (1, 85 mg): mp 153–154° (mixture melting point, tlc, ir, and nmr identical with those of the material described above). The lower R_f band was extracted in the same manner to give acetyleupaserrin (2, 122 mg) as a colorless foam (tlc, ir, and nmr identical with those of the material described previously).

Hydrolysis of Deacetyleupaserrin (5).—Deacetyleupaserrin (5, 300 mg) was dissolved in 5 N aqueous sodium hydroxide (25 ml) and heated under nitrogen at 60° for 30 min. The reaction mixture was then acidified with concentrated hydrochloric acid, saturated with sodium chloride, and extracted with ether (6 × 80 ml). The ether layer was extracted with 5% sodium carbonate solution (3 × 10 ml), which was acidified, saturated with sodium chloride, and extracted with ether (3 × 30 ml). The final ether layer was washed with saturated sodium chloride solution, dried over sodium sulfate, and evaporated to give a foam (84 mg). This material was applied to ten Cellulose F precoated plates (20 × 20 cm × 0.2 mm) and developed with 20:80 2 N aqueous ammonia in *sec*-butyl alcohol. The acidic band (visualized with bromophenol blue) was scraped from the plates and extracted with methanol. Evaporation of the methanol afforded 16 mg of oily crystals which were recrystallized from ether–petroleum ether to give sarracinic acid, mp 51.4–52.1°. The infrared spectrum of this sample was identical with that of an authentic sample and the mixture melting point was undepressed.

Methanolysis of Deacetyleupaserrin (5).—To a solution of sodium methoxide (65 mg) in 4 ml of anhydrous methanol was added deacetyleupaserrin (5, 200 mg). The reaction mixture was stirred for 1 hr at room temperature, heated for 10 min at 60°, cooled and acidified with dilute hydrochloric acid, and then extracted with chloroform. The chloroform extract was dried over magnesium sulfate and evaporated to give 200 mg of yellow foam. This material was applied to eight ChromAR 7GF plates (20 × 20 cm × 0.25 mm) and developed with 5% MeOH in chloroform. The major band was removed and eluted with chloroform to afford 86 mg (50%) of the methanol adduct 4 as a viscous oil: $[\alpha]^{25}D$ +72.5° (c 0.99, $CHCl_3$); ir $\lambda_{max}^{CHCl_3}$ 2.78, 2.90, 5.70, 6.05, 8.55, 8.85, 9.00, and 10.30 μ; mass spectrum m/e 296.1614 (M^+, calcd for $C_{16}H_{24}O_5$, 296.1617), 278, 264, 246, 233, 195, 152, 122, 113, 107, 95; R_f 0.31.

Pyrolysis of Deacetyleupaserrin (5).—Pyrolysis of deacetyleupaserrin (5, 85 mg) at 180–200° for 3 min under aspirator pressure gave quantitatively a yellow glass. This material was separated on four silica gel plates (20 × 20 cm × 0.25 mm) using 5% methanol in chloroform to give 69 mg (81%) of the aldehyde lactone 6 as a colorless foam: $[\alpha]^{25}D$ +9.3° (c 0.71, $CHCl_3$); ir $\lambda_{max}^{CHCl_3}$ 2.90, 3.68, 5.67, 5.83, 6.12, 8.70, and 9.90 μ; mass spectrum m/e 362.1719 (M^+, calcd for $C_{20}H_{26}O_6$, 362.1722), 347, 344, 300, 298, 264, 246, 202, 163, 135, 107, 99; R_f 0.59.

Pyrolysis of Acetyleupaserrin (2).—Pyrolysis of acetyleupaserrin (2, 90 mg) at 200° for 4 min under aspirator pressure gave an approximately 1:1 mixture of starting 2 and the enol acetate 3. The crude product was applied to five silica gel plates (20 × 20 cm × 0.25 mm) and eluted with 1:1 ether in benzene giving in the band of higher R_f enol acetate 3 as a colorless foam (31 mg, 34%). The lower R_f band, corresponding to acetyleupaserrin (2), was eluted to give 2 as a pale yellow glass (28 mg, 31%), which was shown to be identical with 2 described above. The enol acetate 3 was unstable and was characterized by nmr (see Table I); ir λ_{max}^{KBr} 2.90, 3.25, 5.67, 5.75, 5.82, 6.00, 6.08, 8.15, and 8.65 μ; mass spectrum m/e 446.1942 (M^+, calcd for $C_{24}H_{30}O_8$, 446.1939), 386, 288, 246, 213, 141, 99, and 81; R_f (ChromAR, 1:1 ether–benzene) 0.25.

Registry No.—1, 38456-36-9; 2, 38400-51-0; 3, 38456-37-0; 4, 38456-38-1; 5, 38456-39-2; 6, 38456-40-5; sarracinic acid, 7689-64-7.

Novel Tricyclic Compounds from Alkylated Hydroquinones and C-10 Terpenes

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The novel hydroxylated 7-oxatricyclo[6.4.0.$1^{2,6}$]trideca-8,10,12-trienes 9 and 10 and the spiro[cyclohexane-1,2′-chroman] 11 have been synthesized in 5–31% yields *via* the acid-catalyzed condensation of alkylated hydroquinones with linalool 6 and myrcene 7. Their structures were assigned on the basis of nmr and mass-spectral data and were mechanistically rationalized. Yields of the type 9 structures were substantially increased with *d*-limonene (15) or α-phellandrene (16), supporting the idea that a cyclized monoterpene is involved in the formation of both 9 and 10.

The acid-catalyzed condensation of open-chain monoterpenes with phenolic compounds in general leads to alkenyl-substituted chromans, but in several cases tricyclic compounds have been reported as a result of further cyclization under the acidic conditions. Green and McHale cited the formation of tricyclic chromanols[1] from trimethylhydroquinones and geraniol and linalool, but their materials were not characterized unequivocally. More recently, Ichikawa and Kato[2] isolated the tricyclic compound 1 as a by-product in the synthesis of chromanol 2, and Kane[3] characterized the product from phloroglucinol dimethyl ether and citral (mixture of neral and geranial) as the tetracyclic 3a. Tricyclic chromanols 3b, 3c, and 3d have also been synthesized in cannabinoid studies. Mechoulam and Yagen[4] prepared 3b from olivetol and geraniol *via* the stereoselective cyclization of cannabigerol, while Crombie and Ponsford[5] obtained

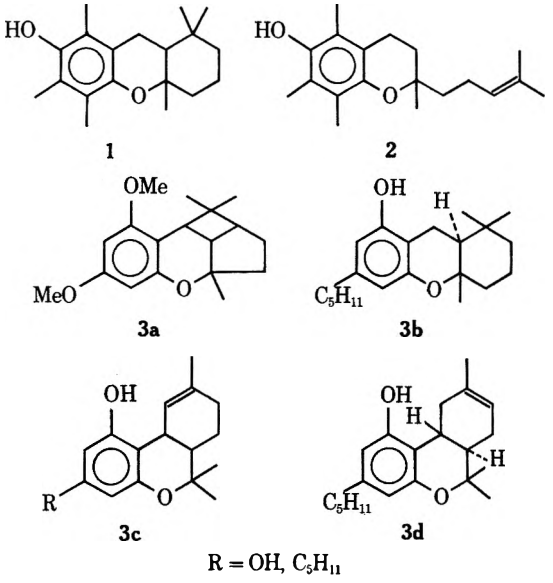
(1) J. Green and D. McHale, British Patent 949,715 (1964).
(2) T. Ichikawa and T. Kato, *Bull. Chem. Soc. Jap.*, **41**, 1224 (1968).
(3) V. V. Kane, *Tetrahedron Lett.*, 4101 (1971).
(4) R. Mechoulam and B. Yagen, *ibid.*, 5349 (1969).
(5) L. Crombie and R. Ponsford, *J. Chem. Soc. C*, 788, 796 (1961); *Tetrahedron Lett.*, 4557 (1968).

TABLE I

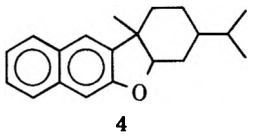
CONDENSATIONS WITH OPEN-CHAIN TERPENES IN ACETIC ACID (ZINC CHLORIDE CATALYST) OR NEAT (BORON TRIFLUORIDE ETHERATE)

Reactants and conditions	Crystalline product	Yield,[a] %	Mp, °C	$E^{1\%}_{1\,cm}$ (λ_{max})
TOHQ,[b] 6, reflux, 7 hr	10e	5 (10)	154–155	146 (301)
TOHQ, 7, 50–60°, 2 hr	11e	7 (15–20)	151–153	129 (300)
TBHQ, 6, reflux, 7 hr	9d	5 (10–15)	172–173	170 (300)
TBHQ, 7, 50–60°, 4 hr[c]	9d	4 (10–15)	173–174	170 (300)
TBHQ, 7, 50–60°, 4 hr[c]	11d	8 (15–20)	127–136	153 (298)
Methyl HQ, 7, neat	9b	3 (16)	154–156	182 (298)
Trimethyl HQ, 7, neat	11c	31 (80)	100–102	110 (292)
Trimethyl HQ, 7[d]	10c	(50)[e]	80–81[e]	72 (284)[e]
Hydroquinone, 7, 90°, 1 hr, neat	11a	10 (15)	113–115	141 (298)

[a] Estimated overall yields, including filtrate residues, are given in parentheses. [b] TOHQ = *tert*-octylhydroquinone; TBHQ = *tert*-butylhydroquinone. [c] Comparable yields were obtained at 20°, 3 days (exothermic rise to 50°), when BF_3 etherate was substituted for zinc chloride. [d] Compound 7 was used as the HCl adduct with $SnCl_2 \cdot 2H_2O$ as catalyst; product 10c was estimated to have 75% purity based on its $E^{1\%}_{1\,cm}$ value. [e] These data are on the acetate of 10c prior to saponification.



related *cis*- and *trans*-**3c** from citral and olivetol or phloroglucinol. Petrzilka, *et al.*,[6] obtained (−)-Δ^8-6a,10a-*trans*-tetrahydrocannabinol (**3d**) from *p*-mentha-2,8-dien-1-ol and olivetol. Much earlier Salfield[7] had reported the preparation of the tetracyclic **4** from the condensation of β-phellandrene with β-



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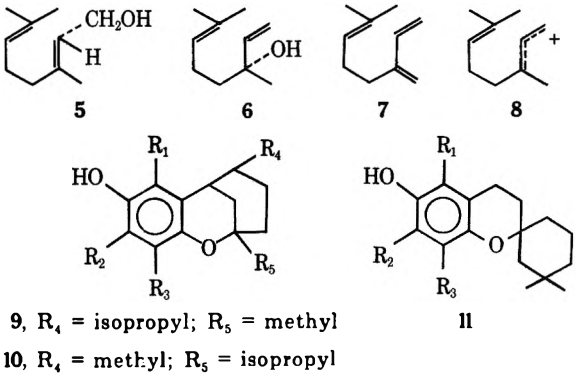
naphthol. In the absence of nmr data, particularly concerning the presence or absence of the angular H adjacent to oxygen, this structure assignment is in doubt.

In an attempt to prepare some alkenyl-substituted chromanols of type **2** *via* the zinc chloride catalyzed condensation of geraniol **5** with various alkyl-substituted hydroquinones in hot glacial acetic acid, only glasses were obtained, which were unresolvable by molecular distillation, chromatographic, or fractional crystallization techniques. Thin layer chromatograms of these glasses on silica gel were streaked, indicating the presence of many components. In the presence of acidic catalysts, geraniol (and the cis isomer, nerol) can generate linalool **6**, myrcene **7**, and a variety of monocyclic monoterpenes[8] (including α-terpineol, *dl*-limonene, terpinenes, and phellandrenes), all of which are potentially condensable with hydroquinones. Accordingly, linalool **6** and myrcene **7** were used as starting materials, since these should generate the likely reactive intermediate, carbonium ion **8**, more readily.



Condensations of various alkyl-substituted hydroquinones (Table I) gave small yields (5–31%) of products isolated by chromatography which have been assigned structures **9**, **10**, and **11** on the basis of their spectral properties. All of the compounds have nmr spectra devoid of olefinic absorption; *i.e.*, they are tricyclic.

The characteristic nmr features of type **9** and **10** compounds are the presence of a 1 H multiplet at ~2.5–2.9 and a 6 H triplet (at 60 MHz) centered at ~0.9–1.0 ppm. The triplet is transformed into a double doublet at 100 MHz and is assigned as an isopropyl group whose methyls are anisochronous by virtue of adjacent dissymmetry. Type **10** compounds have in addition a 3 H doublet at ~1.0 ppm, whereas type **9** compounds have a 3 H singlet at ~1.3 ppm. The *tert*-butyl, *tert*-octyl, and aromatic methyl absorptions appear in characteristic positions when present (see Table II).

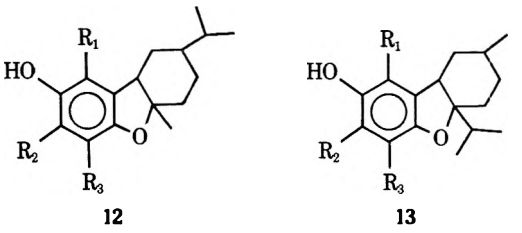
The nmr evidence led to the consideration of two possible tricyclic structures, namely, **9** and **12**, and **10** and **13**.

Distinction between the two possibilities was made on the basis of their mass spectral fragmentation (Scheme I). The loss of the fragments C_5H_8 and C_5H_{10}

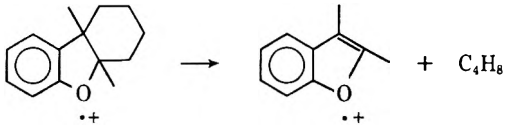
(6) T. Petrzilka, *et al.*, *Helv. Chim. Acta*, **52**, 1102 (1969).
(7) J. Salfield, *Ber.*, **73**, 376 (1940).
(8) "The Terpenes," Vol. I, J. L. Simonsen, Ed., Cambridge University Press, New York, N. Y., 1931, pp 40–43, 55, 144–147.

TABLE II
CHEMICAL SHIFTS (δ) OF TRICYCLIC COMPOUNDS

Compd	R_1	R_2	R_3	α-CH	Ang Me	*gem*-diMe	i-Pr	Ar-*t*-Bu	ArCC-*t*-Bu	$ArCMe_2$	MeCH	ArMe
9b	H	CH_3	H	2.90 (1 H)	1.30		0.92 + 1.03 (d)					2.17
9d	H	*tert*-Butyl	H	2.88 (1 H)	1.33		0.93 + 1.03 (d)	1.36				
9e	H	*tert*-Octyl	H	2.90	1.32		0.93 + 1.02 (d)		0.72	1.41		
10c	CH_3	CH_3	CH_3	2.83 (1 H)			0.99 + 1.11 (d)				0.99 (d)	2.14
10e	H	*tert*-Butyl	H	2.55 (1 H)			0.99 + 1.10 (d)		0.78	1.43	0.98 (d)	2.16
11a	H	H	H	2.69 (2 H)		0.86 + 1.04 (s)						
11c	CH_3	CH_3	CH_3	2.68 (2 H)		0.89 + 1.12 (s)						2.14
11d	H	*tert*-Butyl	H	2.62 (2 H)		0.87 + 1.06 (s)		1.36				2.16
11e	H	*tert*-Octyl	H	2.65 (2 H)		0.85 + 1.03 (s)			0.73	1.39		



for **9** and C_3H_6 and C_7H_{12} for **10**[9] follows a reasonable mechanistic path; it is hard to imagine a path whereby **12** and **13** could yield these fragments. Furthermore, **12** and **13** would be expected to fragment in a fashion similar to that found[10] for **14**; there are, however, no analogous fragment ions in the spectra of **9** and **10**.



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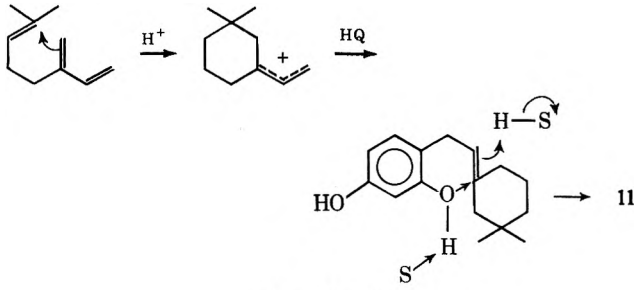
The formation of **9** and **10** are rationalized as shown in Scheme II. Reaction of the cyclized intermediate ion at the secondary carbon is reasonable from a consideration of steric factors.[11]

In products of type **11** structure, the relevant nmr data are the presence of a 2 H skewed triplet at ~2.6 ppm, whose peak separations do not change at 100 MHz, two 3 H singlets at 0.9–1.1 ppm, and the conspicuous absence of any signal for a methyl group analogous to the singlet in type **9** compounds and the doublet in type **10**. For type **11** compounds, we propose the structure given and rationalize its formation *via* the following scheme.



S = solvent

The mass spectral fragment ions of these molecules are consistent with this structure, as indicated in Scheme I and Table III.

When the condensation was carried out using *d*-limonene (**15**) and α-phellandrene (**16**) (precyclized monoterpenes, so to speak) the yield of **9** was increased substantially and the product had retained at least part of the original optical activity (Table IV). Both these results support the idea that a cyclized monoterpene is an intermediate in the reaction.

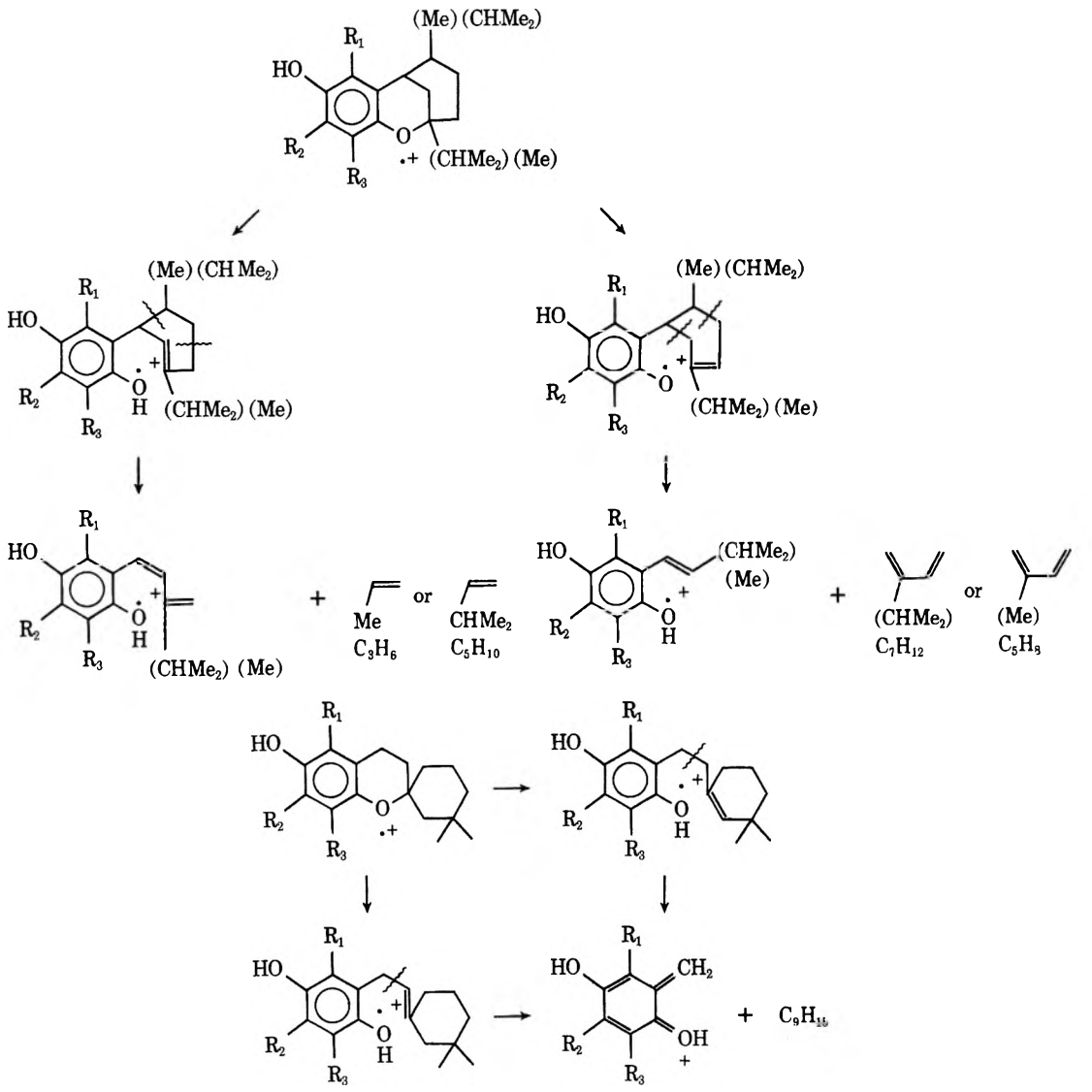
The retained optical activity argues that the carbonium ion rearrangement in Scheme II labeled step 1

(9) The loss of the appropriate fragment does not always occur from the parent ion. Prior fragmentations occur more readily when the alkyl substituents are *tert*-butyl or *tert*-octyl or when the hydroxyl is acetylated

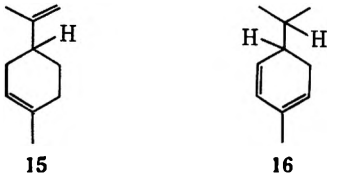
(10) S. Yamamura and Y. Hirata, *Tetrahedron*, **19**, 1485 (1963).

(11) W. S. Johnson, P. J. Neustaedter, and K. K. Schmiegel, *J. Amer. Chem. Soc.*, **87**, 5148 (1965).

SCHEME I



must be a 1,3-hydride shift (or concerted 1,2 shifts), since 1,2-stepwise shifts should lead to racemization of the intermediate and thus the product.



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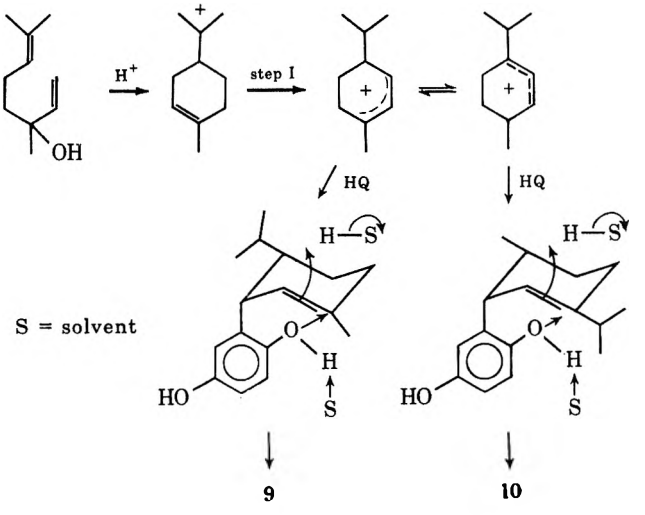
Experimental Section

Melting points (Hoover apparatus) are uncorrected. Chemical shifts are reported in parts per million downfield from tetramethylsilane in chloroform-*d* solution. Mass spectra were obtained from either a Du Pont 21-110B or Hitachi RMS 4 mass spectrometer operating at 70 eV. Uv spectra were determined in ethanol solution.

Column chromatography (hexane development) was accomplished on Doucil (sodium aluminum silicate, 60–100 mesh, Philadelphia Quartz Co.), Florisil (60–100 mesh, Floridin Co.), and MDA. The latter is our descriptive term for Merck's acid-washed alumina deactivated in the column prior to use by successive washes with equal volumes of 5% aqueous acetone and hexane. Elutions of Doucil and MDA, after hexane development, were done, respectively, with benzene, diethyl ether and 95:5 diethyl ether–ethanol.

SCHEME II



Thin layer chromatography (tlc) was effected with silica gel on glass plates and spots were detected after benzene development by spraying with aqueous rhodamine 6G solution and exposing to uv radiation.

A. Condensations with Linalool (6) in Acetic Acid Containing Zinc Chloride.—Solutions of TBHQ or TOHQ, linalool (Eastman Chemical 861), and freshly fused zinc chloride (0.1:0.13:0.14 mol) in glacial acetic acid (300 ml) were refluxed for 4–7 hr in an

TABLE III

PARTIAL MASS SPECTRA OF TRICYCLIC COMPOUNDS AND RELATIVE INTENSITY OF FRAGMENT ION RESULTING FROM THE LOSS OF R

Compd	R_1	R_2	R_3	Base peak	R: C_8H_{15}	C_3H_6	C_7H_{12}	C_5H_8	C_6H_{10}
9b	H	CH_3	H	260				43.4[a]	21.1[a]
9d	H	*tert*-Butyl	H	302				37.0	8.3
								24.6[b]	66.1[b]
9e	H	*tert*-Octyl	H	287				11.0[a,c]	4.7[c]
10c	CH_3	CH_3	CH_3	288		0	5.4[a,d]		
10e	H	*tert*-Octyl	H	287		1.7[c]	6.9[c]		
11a	H	H	H	123	100[a]				
11d	H	*tert*-Butyl	H	179	100[a]				
11e	H	*tert*-Octyl	H	287	3.9				

[a] Cleavage supported by appropriate metastable peak. [b] Cleavage takes place after loss of CH_3 from *tert*-butyl. [c] Cleavage takes place after loss of C_5H_{11} from *tert*-octyl. [d] Cleavage takes place after loss of CH_2CO from acetyl.

TABLE IV

PRODUCTS FROM CONDENSATIONS WITH CYCLIC C-10 TERPENES IN CHLOROFORM–CARBON TETRACHLORIDE–ETHER (BORON TRIFLUORIDE ETHERATE CATALYST)[a]

Crystalline product	Conditions	Yield,[b] %	Mp, °C	$E^{1\%}_{1\,cm}$ (λ_{max})	$[\alpha]^{25}D$
9d (racemic)	TBHQ, 15[c]	46.8	174–175	166 (300)	−1.32
(levo)	5°, 4 days	4.3 (20)	141–142	172 (300)	−14.9
9d (racemic)	TBHQ, 16[d]	8.1	175–176	165 (300)	+0.17
(dextro)	5°, 4 days	10.0 (17)	141–142	165 (300)	+16.1
9e (racemic)	TOHQ, 15[c]	12 (18)	139–140	156 (301)	+0.18
(levo)	20°, 4 days	11.6 (48)	136–136.5	152 (301)	−3.41

[a] Subsequent experiments demonstrated that carbon tetrachloride is unnecessary and that a 4:1 mixture of chloroform–ether is just as effective. [b] Estimated overall yields, including filtrate residues, are given in parentheses. [c] *d*-Limonene; $[\alpha]^{25}D$ +97.3°. [d] α-Phellandrene; $[\alpha]^{25}D$ −93.3°.

atmosphere of nitrogen, cooled, and poured into a mixture of ice and hexane. The organic phase was washed four times with 1 *N* sodium hydroxide and with water to neutrality and dried. After partial concentration and cooling to remove unreacted hydroquinone, the filtrate residue was distilled in a molecular still using stripped lard carrier.

Compound 10e (0.1-mol Run; from TOHQ).—The distillate paycut [11.6 g, bp 140–175° (90 μ)] with *E* (1%, 1 cm) (300 mμ) 122, gave two main spots on tlc. Crystallization from hexane gave **10e** (1.6 g), mp 141–148°, in 4.4% yield. Recrystallization from acetonitrile gave white platelets: mp 154–155°; *E* (1%, 1 cm) (301 mμ) 146; ir (Nujol) 2.93 (OH) and 8.4 μ (CO); M^+ *m/e* 358.

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.8; mol wt, 358. Found: C, 80.1; H, 10.8; mol wt, 347.

Chromatography of the filtrate residues on Doucil followed by crystallization of the hexane filtrate fraction gave additional **10e** (0.5% yield).

Compound 9d (0.2-mol Run; from TBHQ).—Two distillate paycuts were obtained [16 g, bp 113° (3 μ), and 13 g, bp 150° (4 μ)] having *E* (1%, 1 cm) (296–297 mμ) values of 141 and 117, respectively, and similar infrared spectra. Chromatography of the higher boiling fraction (five spots on tlc) on Doucil (300 g) and crystallization of the resulting filtrate fraction (8.1 g) from petroleum ether (bp 30–60°) at −20° gave **9d**: mp 172–173° (3% yield); ir (Nujol) 2.95 (OH) and 8.37, 8.42 μ (CO); M^+ *m/e* 302. Recrystallization from acetonitrile raised the melting point to 174–175°.

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 9.99; mol wt, 302. Found: C, 79.0; H, 10.0; mol wt, 275.

Chromatography of the filtrate residue from **9d** on Brockmann neutral alumina (175 g) and then elution of the top zone with ether gave mixed chromanol-like products, *E* (1%, 1 cm) (300 mμ) 152, with nmr different from nmr of both **9** and **11**.

B. Condensations with Myrcene (7) in Acetic Acid–Zinc Chloride.—Myrcene (0.22 mol, Aldrich) in acetic acid (20 ml) was added, with stirring, to a heated (50–60°) solution of the substituted hydroquinone (0.2 mol) and zinc chloride (0.3 g) in acetic acid (64 ml). After stirring at 50–55° for 3.5 hr, the crude product was isolated as described above.

Compounds 9d and 11d (from TBHQ).—Chromatography of the glass (56.8 g) obtained from myrcene and TBHQ on MDA (1.2 kg) gave three column-held fractions eluted separately with 95:5 ether–ethanol. Crystallization (from hexane) of the fraction from the bottom zone gave **9d** (2.2 g), mp 173–174°, *E* (1%, 1 cm) (300 mμ) 170, in 3.6% overall yield.

Similar crystallization of the middle-zone fractions gave spiran **11d** (4.8 g), mp 127–136°, *E* (1%, 1 cm) (298 mμ) 153, in 8% yield. Recrystallization from acetonitrile gave platelets (2.5 g, mp 145–147°) having the same uv spectrum, ir (Nujol) 2.98 (OH) and 8.35, 8.5 μ (CO); M^+ *m/e* 302.

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 9.99; mol wt, 302. Found: C, 79.1; H, 10.0; mol wt, 304.

Compound 11e (from TOHQ).—The viscous oil was separated from excess TOHQ (12 g) by crystallization from hexane at 5° and then chromatographed on MDA (2 kg). Elution of the column-held material gave a glass (40.9 g) that crystallized (hexane) to give the spiran **11e** (5.1 g), mp 141–150°, in 7% yield (recrystallization from acetonitrile raised the melting point to 151–153°): ir (Nujol) 2.95 (OH) and 8.5 μ (CO); M^+ *m/e* 358.

Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68; mol wt, 358. Found: C, 80.2; H, 10.3; mol wt, 301.

Compound 11a (from Hydroquinone).—The reaction mixture was cooled, diluted with ethyl ether, and washed successively with 0.52 *M* KOH solution and water. After the extract had been dried and the solvent evaporated, the residue (19 g) was purified by solvent distribution (Skellysolve F–80% ethanol). The alcohol-soluble fraction (10 g) was crystallized from Skellysolve F–ether (5:1) at −20° to give a crop of crystals (2.1 g) of **11a**, mp 110–113° (recrystallization raised the melting point to 113–115°), *E* (1%, 1 cm) (298 mμ) 141. An additional 1.3 g of crystals was recovered from the filtrates.

C. Condensations (Neat) with Myrcene and Boron Fluoride Etherate.—Compounds **9b**, **11a**, and **11c** were prepared by condensing myrcene with the appropriate hydroquinone in a slurry containing a catalytic quantity of boron trifluoride etherate. The reactions were highly exothermic. Purification was accomplished by solvent distribution (Skellysolve F–83% ethanol), an additional reductive cyclization step (zinc–alcoholic sulfuric acid), chromatography on Florisil, and finally *via* formation of crystalline piperazine complexes.

Compound 9b (from Monomethylhydroquinone).—The chromatographed product (8.1 g) from a 0.16-mol run was dissolved in ether and mixed with a solution of piperazine (1.6 g) in acetone (40 ml). After evaporation, the residue was dissolved in Skellysolve F (65 ml), filtered, and cooled to −20° to give 1.4 g of solid

piperazine complex, mp 127–135°. A sample (1.2 g) of this complex in ether was washed successively with dilute sulfuric acid and water to regenerate the tricyclic compound **9b** (0.99 g), which was crystallized from Skellysolve F, mp 154–156°, *E* (1%, 1 cm) (298 mμ) 182.

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.5; H, 9.25. Found: C, 78.7; H, 9.5.

Compound 11c (from Trimethylhydroquinone).—The chromatographed product (14 g) from an 0.08-mol run was treated with piperazine (2.6 g) as above to give a solid complex (7.7 g), mp 123–133°. A sample (2 g) of the complex gave 1.8 g of the regenerated compound **11c**, which crystallized from Skellysolve F, mp 100–102°, *E* (1%, 1 cm) (292 mμ) 110.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.2; H, 9.7. Found: C, 79.3; H, 10.0.

D. Compound 10c from Trimethylhydroquinone and Myrcene–HCl Adduct.—A solution of trimethylhydroquinone (15.2 g, 0.1 mol) and $SnCl_2 \cdot 2H_2O$ (22.5 g) in 200 ml of glacial acetic acid was stirred at reflux (N_2 atmosphere) while the myrcene–HCl adduct (21.4 g, 87% estimated purity of mixed neryl geranyl chlorides) was added over 3 hr. After 90 min of additional reflux, the product mixture was cooled and filtered and the filtrate was diluted with water. The pentane extract was washed with water, dried, and chromatographed on Florisil. The middle fraction (22 g, 75% purity, 50% estimated yield) was acetylated (pyridine–acetic anhydride) and the actate was crystallized from hexane at −30°, mp 80–81°, mol wt 330, *E* (1%, 1 cm) (284 nm) 72. This was then saponified to give **10c**.

E. Condensations with *d*-Limonene and α-Phellandrene in Chloroform–Carbon Tetrachloride–Ether Containing Boron Fluoride Etherate.—Solutions of the appropriate hydroquinone and cyclic terpene (0.1-mol runs) in a 4:2:1 mixture of $CHCl_3$:CCl_4:ether were cooled to 5–10°, treated with 4 ml (0.032 mol) of boron fluoride etherate, and stored at 5 or 20°. The products were isolated from the organic layer after washes with ice water, 1 *N* sodium hydroxide, and water.

Compound 9e (from TOHQ and *d*-Limonene, 4 Days, 20°).—The glassy product (tlc showed mainly one component other than unreacted TOHQ) was crystallized from acetonitrile to give 4.15 g of **9e** (6.4 g, 18% weight yield): mp 139–140°; *E* (1%, 1 cm) (301 mμ) 156; $[\alpha]^{25}D$ +0.18°; ir (Nujol) 2.98 (OH) and 8.42 μ (CO); M^+ *m/e* 358.

Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.60; mol wt, 358. Found: C, 80.5; H, 10.7; mol wt, 323.

A second portion of the original filtrate residue was chromatographed on MDA (700 g) using 1:1 benzene–hexane for development. Evaporation of the filtrate gave material (17.4 g, 48.5% crude yield, one component by tlc) that crystallized from acetonitrile in 11.6% overall yield to give an optical isomer of **9e** (4.15 g), mp 135–136°, with $[\alpha]^{25}D$ −3.41. Recrystallization raised the melting point only slightly to 136–136.5°; the mixture melting point with **9e** was 136.5–138°. Its ir and uv absorption spectra were identical with those of **9e**.

Compound 9d (from TBHQ and *d*-Limonene, 4 Days, 20°).—Trituration of the glassy product with hexane gave 11.6 g of solids, mp 174–175°, *E* (1%, 1 cm) (300 mμ) 166, with nmr and mass spectra identical with those of **9d** prepared from linalool or myrcene. Two more crops of crystalline **9d** were obtained from the hexane mother liquor, giving a total 46.8% yield, $[\alpha]^{25}D$ −1.32°.

The filtrate residue, *E* (1%, 1 cm) (296 mμ) 138, was chromatographed on MDA (300 g). Elution of the bottom 50% of the column with ether containing 5% ethanol, followed by recrystallization of the eluate residue from hexane at 5°, gave 1.3 g (4.3% yield) of a lower melting (mp 141–142°) optical isomer having $[\alpha]^{25}D$ −14.9°; its nmr, infrared, and uv spectra were identical with those of **9d**. An overall 20% yield of the lower melting isomer was estimated on the basis of tlc analyses of the filtrate residue.

Compounds 9d (from TBHQ and α-Phellandrene, 7 Days, 5°).—The glassy product crystallized after several days from hexane to give solids (6.75 g), mp 113–117°, and mother liquor (A). A benzene solution of the solid was chromatographed on MDA and the nonadsorbed fraction was crystallized to give crude **9d** (2.5 g), mp 167–170°, in 8.1% yield. Recrystallization from hexane gave purified **9d** (1.48 g), mp 175°, *E* (1%, 1 cm) (300 mμ) 165, having only slight optical activity ($[\alpha]^{25}D$ +0.17°).

Chromatography of the filtrate residue from mother liquor (A) on MDA (400 g) followed by elution of the lower 60% of the column gave a glass (7.3 g) that crystallized from hexane. The product (3 g, 10% yield), mp 141–142°, *E* (1%, 1 cm) (300 mμ) 165, $[\alpha]^{25}D$ +16.1°, proved identical by nmr with the levorotatory isomer isolated from TBHQ and *d*-limonene, but gave a mixture melting point of 141–175°.

Registry No.—**6**, 78-70-6; **7**, 123-35-3; **9b**, 38359-57-8; **9b** (piperazine complex), 38359-63-6; **9d**, 38359-58-9; **9e**, 39050-42-5; **10c**, 38359-59-0; **10e**, 39050-43-6; **11a**, 31130-21-9; **11c**, 38359-61-4; **11c** (piperazine complex), 38359-64-7; **11d**, 38359-62-5; **11e**, 39050-44-7; **15**, 5989-27-5; **16**, 99-83-2; TOHQ, 719-03-9; TBHQ, 1948-33-0; methyl HQ, 95-71-6; trimethyl HQ, 700-13-0; hydroquinone, 123-31-9.

Acknowledgments.—The authors wish to thank Drs. G. J. Lestina and I. F. Salminen, of the Kodak Research Laboratories, for helpful suggestions and Mr. D. Nelan of the Tennessee Eastman Research Laboratories for his preparation of compound **10c**.

Inversions of Both Adjacent Centers in the Formolysis of a 2,2,6-Trialkylcyclohexyl Tosylate. Formation of a 13α-D-Homo Steroid[1]

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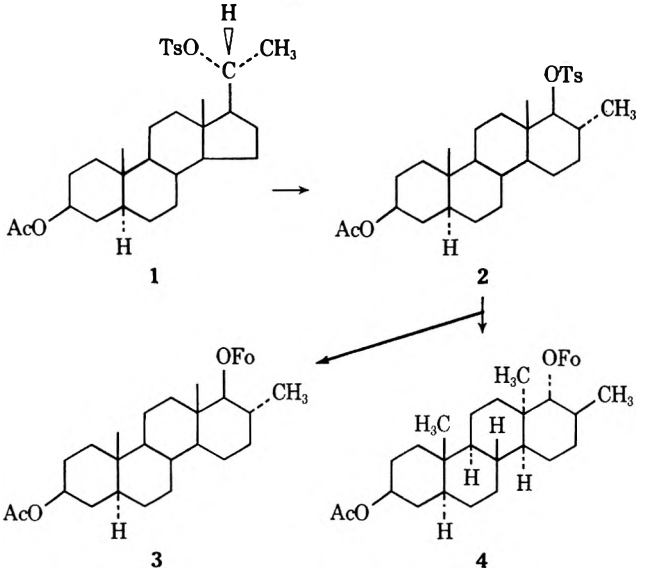
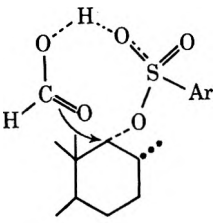
A side product (4) obtained from the formolysis of 3β-acetoxy-5α-pregnan-20β-yl tosylate (1) or of 3β-acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl tosylate (2) has been identified by partial synthesis and nmr spectroscopy as 3β-acetoxy-17β-methyl-*D*-homo-5α,13α-androstan-17aα-yl formate. The parent diol of 4 was prepared from 3β-acetoxy-5α,13α-androstan-17-one by a series of steps which included cleavage of the D ring, elongation of the longer chain by two carbon atoms, recyclization, and hydrogenolysis. Conceivable mechanisms for the extraordinary inversions at C-13 and C-17 during the formolysis of 2 are discussed. These would also account for the unusual course of the main reaction which converts 2 to the 17a-formate 3 with retention of configuration and preservation of the carbon skeleton.

The conversion of a 20β-tosyloxypregnane (1) to a 17aβ-formoxy-17α-methyl-*D*-homoandrostane (3) upon reaction with formic acid occurs in two stages.[2] The first is the rapid formation of the corresponding 17aβ-tosyloxy-17α-methyl-*D*-homoandrostane (2), which slowly gives the final product (3). The second



step was unexpected, as it represented a substitution reaction without change of the configuration or of the carbon skeleton. Retention of configuration seemed explicable if the approach of solvent from the α side were unduly restricted. There was no evidence[2] that this was the case, and more recent demonstrations of inversions of 17aβ derivatives in displacement reactions[3,4] cast further doubt on the validity of such an explanation. Moreover, a 17a carbocation would be adjacent to a carbon with four alkyl substituents and therefore be prone to a Wagner–Meerwein rearrangement. Alternatives to an ionization yielding a C-17a cation, therefore, had to be considered. An attack on the S–O instead of the C-17a–O bond of the tosylate could be disproved for the acetolysis and an alcoholysis[2] and is, therefore, most improbable for the formolysis. Leboeuf, *et al.*,[4] have more recently proposed an SNi process with a cyclic transition state (5), which we consider an equally implausible mechanism.[5] Another explanation would be the formation of a carbocation other than the open C-17a cation. In our earlier report[2] we mentioned two bridged ions (23, 24) as possible intermediates, either of which would account for the retention by a double inversion. As the structure of the ionic intermediate might be revealed by those of the side products of the formolysis, we have sought to identify a compound previously characterized by its ir and nmr spectra as another acetate formate (4).[2] It was obtained by formolysis of either 3β-acetoxy-5α-pregnan-20β-yl tosylate (1)[2] or of 3β-acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl tosylate (2) in comparable yield (2%). We have now established its rather unusual structure, which is that of 3β-acetoxy-17β-methyl-*D*-homo-5α,13α-androstan-17aα-yl formate (4).



5

The most revealing feature of its nmr spectrum (Table I) was the signal of the proton linked to the carbon atom to which the formoxy group is attached. This signal was observed as a doublet at 5.09 ppm with a

(1) Supported by U. S. Public Health Service Grants AM 9105 and K6-AM-14367.

(2) H. Hirschmann, F. B. Hirschmann, and A. P. Zala, *J. Org. Chem.*, **31**, 375 (1966).

(3) R. T. Li and Y. Sato, *ibid.*, **33**, 3635 (1968).

(4) M. Leboeuf, A. Cavé, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 2100 (1969).

(5) As the stabilization provided by a hydrogen bond is not very large and as an eight-membered cyclic transition state on the β facet of C-17a would encounter and cause major steric compressions and distortions, it seems dubious whether **5** can be significantly more favorable than the transition state of an SN2 process with retention for which no example appears to be known [N. L. Allinger, J. C. Tai, and F. T. Wu, *J. Amer. Chem. Soc.*, **92**, 579 (1970)]. Although some regard the conversion of a chloro sulfite to a chloride of the same configuration as the intramolecular analog of this process, doubts have been expressed in this postulate of a nonionic mechanism. [Streitwieser ("Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 158) has reviewed the evidence indicative of an ionization yielding pairs of the carbocation first with the chloro sulfite and then with the chloride ion.] Similar objections must be raised in the present case. Although precise measurements are lacking, it is evident that the solvolysis of a 17aβ tosylate in methanol[4] or acetic acid[2] is slow compared to that in formic acid.[2] Relative to equatorial *trans*-4-*tert*-butylcyclohexyl tosylate [S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955)], which on acetolysis yields practically no 4-*tert*-butylcyclohexyl acetate of retained configuration [N. C. G. Campbell, D. M. Muir, R. R Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc. B*, 355 (1968)], the 17aβ tosylate reacts somewhat faster in formic acid (25°)[2] and somewhat slower in acetic acid (100°)[2]. There is no indication, therefore, that in going from the cyclohexyl tosylate to the steroid the role of formic acid changes from a solvating agent for developing ions to one that acts primarily as a nucleophile, as would be expected if **5** represented the transition state.

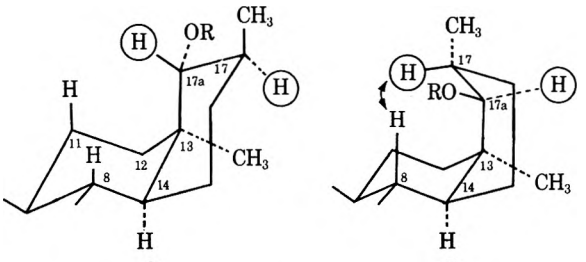
Table I

Nmr Signals of 3β-Acetoxy-17-methyl-D-homo-5α-androstan-17a-yl Esters[a]

Configuration at C-13	α	α	β	β	
Substituent at C-17a					
FoO (4)	AcO (19b)	FoO (3)	AcO		Assignment
1.00	0.98	0.87	0.85		18-H
0.85	0.85	0.79	0.79		19-H
0.87 (d, 6)	0.84 (d, 6.3)	b	0.79 (d, 6)		17-Me
2.01	2.01	2.00	2.00		3-Ac
	2.05		2.05		17a-Ac
5.09 (d, 10)	4.97 (d, 10.7)	4.42 (d, 11)	4.33 (d, 10)		17a-H
8.18		8.18			Fo

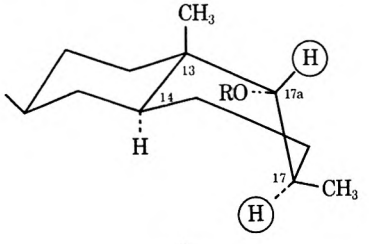
[a] All compounds have equatorial orientations of their substituents at C-17 and C-17a (*i.e.*, 17β,17aα in the 13α and 17α,17aβ in the 13β series). All signals listed are singlets except those marked d. Chemical shifts are in parts per million from TMS; the coupling constants of the doublets (in cycles per second) are given in parentheses. [b] Not resolved.

coupling constant of 10 cps. This indicated the partial structure $C_3CCH(OCHO)CHC_2$ with a dihedral angle of about 180° between the two vicinal C–H bonds. Like the main reaction product **3**, the compound contained two tertiary methyl groups (with singlets at 0.85 and 1.00 ppm) and a secondary methyl giving rise to a doublet at 0.87 ppm. As such a structure had to be derived from **2**, it probably represented a stereoisomer of uranediol acetate formate (**3**). If it had an all-chair conformation and if the configurational changes were confined to the vicinity of the reaction site, **4** had to be isomeric at both C-13 and C-17 in order to accommodate the coupling constant of the doublet at 5.09 ppm (**6**).

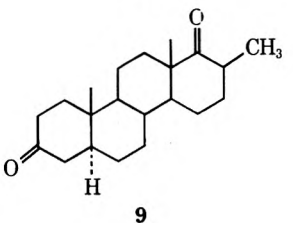


6

7



8



9

R=H or HCOO

Only if we make the rather unlikely assumption that a 1,3-diaxial interaction between two methyl groups could be strong enough to force the D or the C ring into a boat, would inversion at either C-13 (**7**)[6] or C-17 (**8**) also be consistent with the coupling phenomenon. The trans relationship of the coupled protons further requires that an inversion at C-17 be accompanied by one at C-17a. Therefore, **7** is a 17aβ formate like **3** whereas **6** and **8** have the 17aα configuration. Structure **8** was readily excluded because conversion of the isolated acetate formate to the diketone gave a product distinct from a sample of 17-epiuranedione (**9**) prepared by the method of Fukushima, *et al.*[7] As the two remaining structures under consideration were both 13α-D-homo steroids, we set out to prepare such compounds to identify, if possible, the solvolysis product by comparison with a 13α compound of proven structure.

The irradiation of 17-oxo steroids affords ready access to their 13 epimers.[8] As these have been found to be less reactive or unreactive in several addition reactions to their 17-keto group,[8] it was not too surprising that we had no success in converting 3β-acetoxy-5α,13α-androstan-17-one (**10**)[9] to its cyanohydrin, which was required for applying the Goldberg procedure for D-homoannulation.[10] We were also unable to enlarge the D ring by treating **10** with diazomethane[11] in the presence of boron trifluoride and abandoned these trials in favor of the scheme that is outlined in Chart I.

The D ring of **10** was cleaved by a procedure which we had used previously with 3β-hydroxy-5α-androstan-17-one.[12] Oxidation of the purified or crude acetoxybenzylidene compound **11b** with chromic acid in acetic acid gave two degradation products in comparable amounts. Of these, the desired 16,17-dioic acid was recovered partly and its lower homolog predominantly as the anhydride (**12** and **13**, respectively) from the neutral fraction of the reaction mixture.[12a] These compounds were readily differentiated by their ir spectra, which showed the characteristic twin peaks of anhydrides in the carbonyl region at frequencies typical of six- and five-membered rings.[13a] The homologs were separated by chromatography after the essentially complete conversion of the reaction products to anhydrides. Compound **12** yielded the dimethyl ester **14**[14] on hydrolysis, treatment of the dioic acid with diazomethane, and reacetylation. Hydrolysis with

(6) This structure is particularly improbable because the bow–stern interaction which is between a methine carbon (C-8) and a hydrogen is larger than usual. If instead ring C were a boat (not shown), a comparable interaction would exist between C-18 and 9α-H.

(7) D. K. Fukushima, S. Dobriner, and R. S. Rosenfeld, *J. Org. Chem.*, **26**, 5025 (1961).

(8) A. Butenandt, A. Wolff, and P. Karlson, *Chem. Ber.*, **74**, 1308 (1941); A. Butenandt and L. Poschmann, *ibid.*, **77**, 394 (1944).

(9) (a) J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, **34**, 2053 (1951); (b) M. Fétizon and J. C. Gramain, *Bull. Soc. Chim. Fr.*, 3444 (1966); 1003 (1967); (c) T. Nambara, H. Hosoda, and M. Usui, *Chem. Pharm. Bull.*, **17**, 1687 (1969).

(10) M. W. Goldberg and R. Monnier, *Helv. Chim. Acta*, **23**, 376 (1940).

(11) C. D. Gutsche, *Org. React.*, **8**, 364 (1954); H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Amer. Chem. Soc.*, **82**, 4099 (1960).

(12) H. Hirschmann, *J. Biol. Chem.*, **150**, 363 (1943).

(12a) Note Added in Proof.—The formation of a lower homolog which we had not observed in 13β series may be due to the tendency of 16,17 diketones to enolize if there is a cis junction of the C and D rings [L. J. Chinn, *J. Org. Chem.*, **29**, 3304 (1964)].

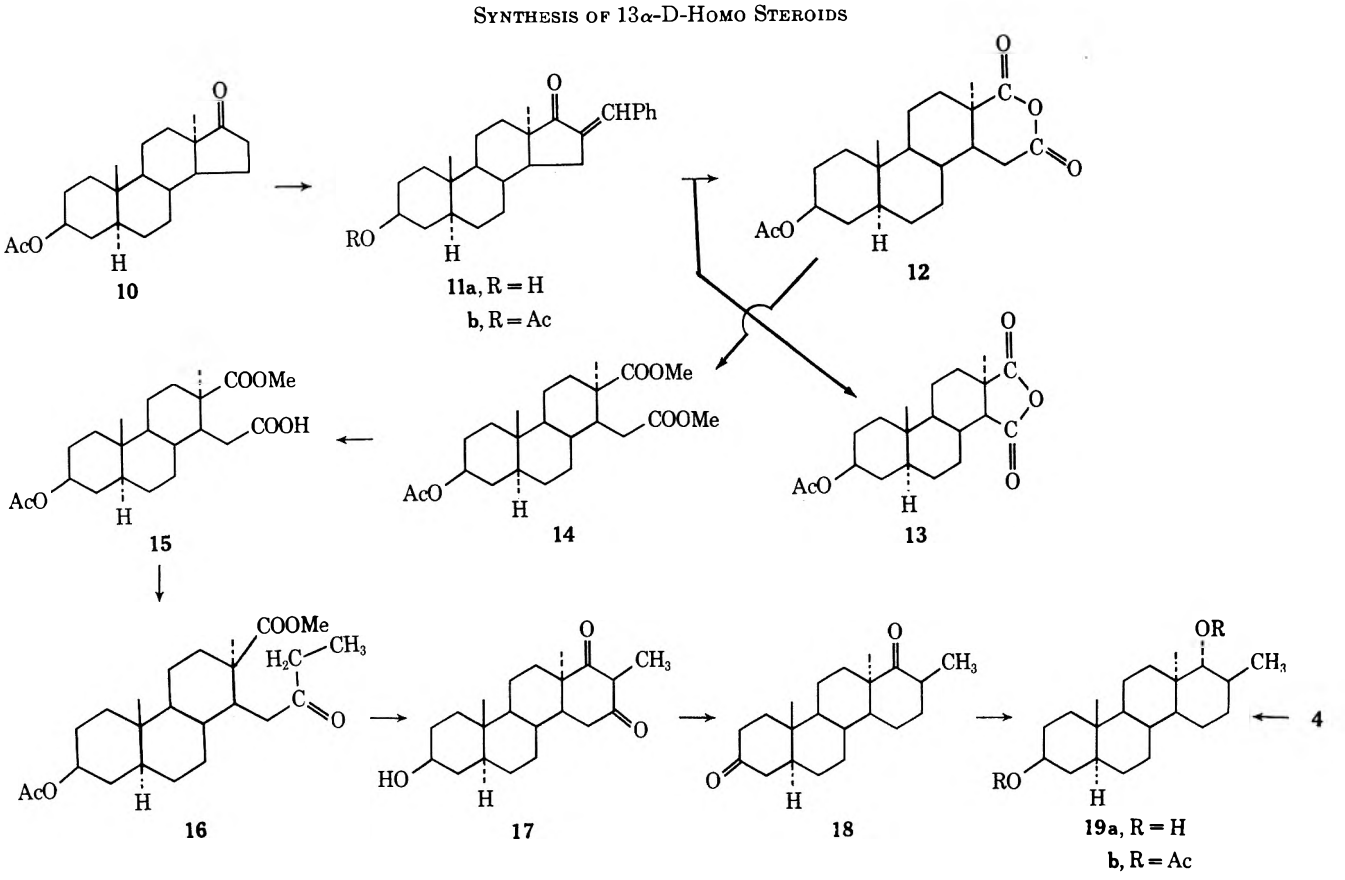
(13) L. J. Bellamy "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954: (a) p 110; (b) p 123.

(14) Attention should be directed to the unexpectedly high frequency of a conspicuous band which was observed at 3018 cm^{-1} in **14**. It was also seen (3016–3018 cm^{-1}) in other saturated methyl esters (**15**, **16**, and two independent preparations[15] of methyl 3β-hydroxy-5α-etianate and of methyl 3β-acetoxy-5α-etianate) but was absent from the curves of the anhydrides **12** and **13**.

(15) F. B. Hirschmann, D. M. Kautz, S. S. Deshmane, and H. Hirschmann, *Tetrahedron*, **27**, 2041 (1971).

CHART I

SYNTHESIS OF 13α-D-HOMO STEROIDS



sodium carbonate[16] followed by reacetylation gave the 17-monomethyl ester **15**. It was converted to its acid chloride,[17] which afforded the ethyl ketone **16** on reaction with diethylcadmium. Cyclization of **16** with sodium hydride in benzene gave poor and erratic results, but high yields of **17** were obtained consistently when the solvent was changed to dimethyl sulfoxide.[18] The product had the characteristics of an enolizable β diketone. It could be extracted from ether with aqueous sodium carbonate. In ethanol the enolic tautomer or tautomers predominate, as shown by an intense peak at 266 nm.[19] The final crystals, when examined in the ir, had only the peaks characteristic of enolic forms (2684 and 1599 cm^{-1}).[13b,20] The ir curves of other preparations, however, indicated the presence also of the dioxo form, which may be presumed to have the more stable β configuration at C-17.

The unwanted oxygen at C-16 could be removed by hydrogenolysis on platinum, but this process was accompanied by hydrogenation. The latter became evident on oxidation of the mixture of neutral reaction products, as this step regenerated some enolic material. The products which remained insoluble in carbonate were fractionated by chromatography. The main crystalline component (**18**) showed two well-resolved peaks in the carbonyl region of the ir. The complete spectrum matched the one we had obtained for the oxidation product of the diol derived from formate **4** (see above). If we consider the partial structure deduced for **4** from the nmr signal at 5.09 ppm, it follows that hydrogenolysis had removed the oxygen function at C-16 and not at C-17a. Conversely it follows from the synthesis of **18** from **10** that **4** is a 13α-D-homo steroid. The spectrum of the synthetic 3,17a diketone remained unchanged upon treatment with alkali under conditions that caused the inversion at C-17 in an analog of **9**.[7] We conclude that the 17-methyl group of **18** has the stable (equatorial) β orientation and we can make the same assignment for **4** unless an inversion to the more stable configuration occurred during the oxidation. This unusual event (*cf.* footnote 18 of ref 2) can be excluded if it is possible to prepare the parent diol of **4** by reduction of **18**.

To obtain **19a** from **18**, the hydrogen which has to be added to the 17a-carbonyl is axial and in syn-axial interaction with both C-11 and C-8 (**6**). The steric hindrance of the axial approach could, therefore, be expected to be comparable to that encountered in the reduction of an 11 ketone to the 11α-ol. As the only effective procedure for this conversion is reduction by a metal–proton donor combination, we treated **18** with sodium in propanol after a trial experiment with 5α-cholestan-3-one had shown that the reduction of its 3-

(16) (a) E. B. Hershberg, E. Schwenk, and E. Stahl, *Arch. Biochem.*, **19**, 300 (1948); (b) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and R. Robinson, *J. Chem. Soc.*, 361 (1953).

(17) Procedure of A. L. Wilds and C. H. Shunk, *J. Amer. Chem. Soc.*, **70**, 2427 (1948).

(18) J. J. Bloomfield, *J. Org. Chem.*, **27**, 2742 (1962).

(19) This is close to the expected wavelength. The peak observed for 1,3-dioxo-5β steroids is 256–257 nm in alcohol [data by C. Tamm quoted by J. J. Schneider, P. Crabbé, and N. S. Bhacca, *ibid.*, **33**, 3118 (1968)]; the increment expected for methyl substitution on the α carbon of similar β diketones was estimated by E. G. Meek, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 2891 (1953), to be about 8–9 nm.

(20) As such uv and ir bands have been attributed to conjugated chelation [R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Amer. Chem. Soc.*, **71**, 1068 (1949)], it should be noted that the cyclic dimeric structure which has been postulated for derivatives of 1,3-cyclohexanedione by Rasmussen, *et al.*, appears to be sterically impossible in our case. However, a larger cycle, such as a tetramer, can be constructed without excessively long hydrogen bonds or unduly close distances between nonbonded atoms.

keto group under these conditions gives a very high preponderance of the equatorial alcohol. The reduction of **18** afforded **19a** in good yield. It was identical with the hydrolysis product of **4**,[21] as was shown by comparisons of the melting points and ir spectra of the diols and their diacetates. These identities show that the compound we have isolated from the formolysis products of **1** and **2** has a structure that conforms in all particulars to the one depicted in formula **4**.

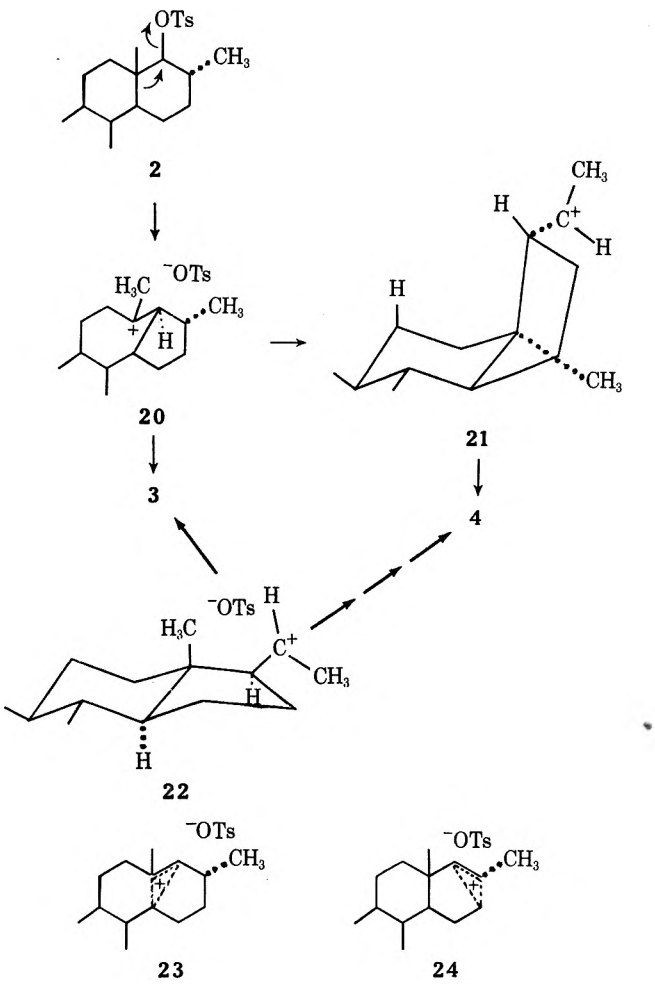
Comparison of the nmr spectra of **4**[2] and **19b** with those of the corresponding 17a formate (**3**) and 17a-acetate of uranediol 3 acetate[2] suggests the assignment of signals given in Table I. The attribution of the peak near 1 ppm to the 18- rather than to the 19-methyl of **4** and **19b** seems to fit better with observations on the effect of inversion at either C-10 or C-13 of 5α-androstane. These inversions caused a downfield shift (0.23 or 0.17) in the signal of the inverted methyl and a smaller upfield change (0.005 or 0.08 ppm) for the methyl that retained its orientation.[9b] The tabulated results further show that the only large difference between the two stereoisomeric series of D-homo steroids is the shift in the signal of the 17a-H.

Discussion

Formate **4** differs from the starting compound **2** or from its main formolysis product **3** in the configurations of three centers, C-13, C-17a, and C-17. To account for this unusual reaction one can envisage two basically different processes. The first would involve migration of the methyl groups. As there appears to be no precedent for the crossing of the plane of a ring when a methyl group is transferred to an adjacent carbon atom, inversion by methyl migration would seem to be possible only if there is an exchange of the methyl groups at C-13 and at C-17. This in turn appears to require a 1,3 shift of one of these groups. Although such a step cannot be dismissed *a priori*, it seems justified to give preference, at least initially, to mechanisms that involve only the much more common 1,2 migrations. Accordingly, we shall limit this discussion to pathways in which the methyl groups remain stationary.

To allow for the inversion of C-13 in such a scheme, this center must assume a planar configuration at some intermediate stage. A suitable structure is shown in **20** (Chart II). It is attractive to picture its formation from **2** as a concerted process, as this would place the reaction in close analogy to the ionization of an equatorial mesylate group at C-12.[22] The completion of the inversion process requires the restoration of the bond between C-13 and C-14. This step may be thought to be facilitated if a new bond forms at the site of the developing charge (C-17a). This would be demanded by the principle of microscopic reversibility if there is an internal return to **2** and if the forward reaction has been correctly formulated as a concerted process. It, therefore, seems a plausible mechanism also for the conversion of **20** to **3**. In contrast a concerted process analogous to **20** → **2** but leading to a 17a tosylate with the 13α configuration is not a likely event.

Chart II



Unless the C ring has a particularly unfavorable boat conformation,[6] an entry of the tosylate ion, antiparallel to the displaced C-14–C-17a bond of **20**, is possible only if the product were the 13α,17aα isomer of **2**. Its formation from **20**, however, would require a change in the orientation of the 17a-hydrogen from α to β across the path of the incoming tosylate ion. The net result would constitute a retention of configuration and, therefore, ought not occur in a single step. In contrast an attack of the 16–17 bond on C-17a to yield **21** would represent an inversion.[23] This 13α,17α-pregnan-20-yl ion is shown in **21** in its favored conformation with the methyl group above the hydrogen. A reversal of the latter bond shift with equatorial entry of the solvent would lead to the isolated product (**4** ≡ **6**).

We have also considered a similar scheme which would start rather than end with the inversion of C-17 of **2**. Although a precedent seems to exist for the shift of the 16–17 bond toward C-17a in certain rearrangements of 17,17a-D-homo ketols,[24] we regard a sequence beginning

(21) Any conceivable doubts about the 3β configuration of **19a** are dispelled by this identity and by a second synthesis from the 3 acetate of **17**, in which no oxidation occurred at C-3.

(22) R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey, and N. L. Wendler, *J. Amer. Chem. Soc.*, **76**, 4013 (1954).

(23) As the geometry is not too favorable, it seems uncertain whether both bond shifts would occur simultaneously, or in rapid succession to relieve the syn-axial interaction of methyl groups of an intermediate 17α-methyl-D-homo-13α-androstan-17a-yl cation. The preferential formation of the 17α isomer (**21**) can be expected by either mechanism because as judged from models and from studies of 13α-pregnan-20-ones [T. Nambara and J. Goto, *Chem. Pharm. Bull.*, **19**, 1937 (1971)] the α isomer at C-17 is more stable than the β.

(24) N. L. Wendler, D. Taub, and R. W. Walker, *Tetrahedron*, **11**, 163 (1960).

with the ion pair **22** as a less likely pathway toward formate **4**.[25]

The formolyses of **2** and of its 17a epimer[2] were shown to take wholly different courses. The scheme presented for the formation of **3** and **4** is consistent with this high degree of steric control and would account for the formation of these two products by a common first step. These suggestions would avoid the problems mentioned in the introduction, as the formation of **3** from **2** would represent two successive inversions if it proceeds *via* **20** or **22**. Although this would be equally true if the initially formed ion had the nonclassical structure **23** or **24**,[2] these would be expected to retain their configuration at C-13 and C-17 in an attack on C-17a and, therefore, would fail to explain the formation of **4**. The elucidation of its structure and the hypothesis that there is a common cause of the unusual aspects of the conversion of **2** to **3** and **4**, therefore, would limit the choice of pathways to the main product and suggest new tests for the mode of its formation.

Experimental Section

General Procedures.—Melting points reported are corrected. Rotations were measured on solutions in $CHCl_3$ in a 1-dm tube on a Perkin-Elmer polarimeter (Model 141). Ir spectra were recorded on solutions in CS_2 except for **17** and **19a**, which were examined as KBr pressings. Except when noted otherwise, these were obtained by adding a solution of the steroid in a small volume of methanol to the ground KBr. This mixture was dried *in vacuo*, ground, and pressed. The instrument was a Perkin-Elmer grating photometer, Model 421. The peaks listed are those characteristic of functional groups and other prominent bands. Uv spectra were measured on a Beckman spectrophotometer with a photomultiplier. Nmr spectra were recorded for solutions in $CDCl_3$ containing TMS on a Model HA-100 of Varian. Data are given as shifts in parts per million downfield from TMS.

Neutral steroids were usually isolated from the diluted reaction mixture by extraction with ether or benzene. These extracts were washed (when appropriate) with dilute hydrochloric acid, sodium carbonate, and water and were taken to dryness *in vacuo*. Chromatography was usually done on 2:1 mixtures of silica gel (Merck-Darmstadt, finer than 200 mesh) and Celite, washed as described.[15]

3β-Hydroxy-16-benzyliden-5α,13α-androstan-17-one (11a).—3β-Acetoxy-5α,13α-androstan-17-one (**10**)[9] [mp 135.5–137°; $[\alpha]^{29}$ −97° (589 nm), −115 (546), −205 (436), −361 (365); nmr 0.67 (19-H), 0.97 ppm (18-H)] was prepared essentially as described.[9a] To its solution in methanol (827 mg in 30 ml) were added 5.5 ml of sodium methoxide in methanol (from 266 mg of sodium) and 0.55 ml of freshly distilled benzaldehyde (in two portions). The mixture was heated under reflux for 2 hr. The neutral product (1.12 g) was isolated by ether extraction and repeatedly recrystallized from dilute acetone: mp 109–113.5°; ν_{max} 3609, 1715, 1630, 1128, 1035, 689 cm^{-1}. The mother liquors were chromatographed and recrystallized to similar melting point, yield 748 mg.

Anal. Calcd for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05. Found: C, 81.81; H, 9.22.

3β-Acetoxy-16-benzyliden-5α,13α-androstan-17-one (11b).—A solution of 203 mg of **11a** in 2 ml of pyridine and 1 ml of acetic anhydride was kept at room temperature for 16 hr. The excess of anhydride was hydrolyzed by slowly adding water to the chilled solution. The product was isolated by ether extraction and the neutral material (228 mg) was recrystallized from 95% ethanol. The melting point (67–77°) of **11b** (which retained solvent when dried at room temperature) could not be sharpened by continued recrystallization: ir 1736, 1716, 1631, 1239, 1129, 1029, 689 cm^{-1}.

Anal. Calcd for $C_{28}H_{36}O_3$: C, 79.96; H, 8.63. Found: C, 79.13; H, 8.78.

3β-Acetoxy-16,17-seco-5α,13α-androstane-16,17-dioic Acid Anhydride (12).—A solution of the acetoxybenzylidene compound **11b** (1.8 g, obtained from 1.32 g of **10** by the steps described but without purifying either **11a** or **11b**) in 295 ml of acetic acid was heated to 73° and maintained at this temperature for 30 min after a solution of CrO_3 (3.77 g) in 52 ml of 90% acetic acid (73°) had been added. The cooled solution was treated with 25 ml of methanol. After 1 hr most of the solvents was removed *in vacuo* and the residue was distributed between dilute hydrochloric acid and ether. The ether phase was washed with water and taken to dryness. The residue (1.79 g) was kept in 5 ml of pyridine and 2.5 ml of acetic anhydride overnight. The solution was distributed between ether and water. The phases were shaken repeatedly and separated after 2 hr. The material in ether was partitioned into an acidic (0.41 g) and neutral fraction (1.14 g). The latter was dissolved in benzene and chromatographed on 114 g of silica gel–Celite. Elution with benzene containing 1% ether gave first 3β-acetoxy-16,17-seco-16-nor-5α,13α-androstane-15,17-dioic acid anhydride (**13**) (25%), then **12** (25%), and elution with methanol gave the remainder as free acids. These were converted to their anhydrides, which on chromatography afforded 9% of **13** and 26% of **12**.

The anhydride fractions with peaks at 1860 and 1791 cm^{-1} (**13**) were recrystallized from acetone–petroleum ether (bp 60–70°): mp 141.5–142.5°; ester peaks at 1736, 1239, and 1030 cm^{-1}.

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 69.13; H, 8.10.

The anhydride fractions with peaks at 1805 and 1765 cm^{-1} (**12**) were recrystallized from acetone: mp 219–221.5°; ester peaks at 1736, 1239, and 1032 cm^{-1}.

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.78; H, 8.22.

Separations of the anhydrides with far less hydrolysis were obtained initially with an old batch of silica gel (Davison) but these results could not be duplicated with their present product. The ratio **12**:**13** was slightly lower when the oxidation was conducted at lower temperature (70°, 30 min; 65°, 120 min) and markedly lower when acid (H_2SO_4) or base ($NaHCO_3$) were added to the medium.

Dimethyl 3β-Acetoxy-16,17-seco-5α,13α-androstane-16,17-dioate (14).—A solution of 221 mg of the acetoxy anhydride **12** in 48 ml of 90% methanol containing 2% of KOH was kept at room temperature for 2 hr and partitioned into a neutral (0.8 mg) and acidic fraction (226 mg). The latter in 1.5 ml of methanol was treated with an excess of diazomethane in 10 ml of ether. The residue on distribution between ether and sodium carbonate gave 235 mg of neutral and 0.3 mg of acidic products. The neutral fraction was acetylated and the product (253 mg) was recrystallized from petroleum ether. The dimethyl ester (**14**) had mp 99–100°; the carbonyl peak (1736 cm^{-1}) was not resolved; acetate bands at 1241, 1030 cm^{-1}.

Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.86; H, 8.95.

The same procedure was carried out with the mother liquors of the anhydride. Thus from 282 mg of chromatographically purified **12**, 279 mg of **14** were obtained.

Methyl 3β-Acetoxy-16-ethyl-16-oxo-16,17-seco-5α,13α-androstan-17-oate (16).—A mixture of 267 mg of dimethyl ester **14** in 35 ml of methanol and 2 g of potassium carbonate in 7.8 ml of water was heated under reflux for 12.5 hr and kept at room temperature overnight. The product, after the removal of methanol *in vacuo*, was separated into a neutral (3 mg) and acidic (228 mg) fraction. The latter was acetylated at room temperature with 4 ml of pyridine and 2 ml of acetic anhydride. The product **15**, which was free (ir) of mixed anhydrides,[16b] failed to crystallize. It was neutralized in methanol with aqueous sodium hydroxide. The dry sodium salt (272 mg) was suspended in 15 ml of dry benzene containing 7 drops of pyridine. Oxalyl chloride (2.5 ml) was added to the chilled mixture, which was kept at 0° for 8 min and at 15° for 15 min. Solvents were removed *in vacuo* (bath temperature <15°) and again after the addition of dry benzene. The residue in 7.5 ml of benzene[26] was added dropwise to a stirred solution of diethylcadmium (prepared from ethyl bromide according to the directions of Guenthard, *et al.*[27]) in 15 ml of ether and maintained throughout in an atmosphere of nitrogen. The mixture was heated under reflux for 1 hr and cooled. Water was

(25) Tentative assessment based on the results with the 20α tosylate.[15] We hope to obtain a more definitive basis for evaluating this alternative route by studying the formolysis of the 17 epimer of **2**.

(26) J. Cason, *J. Amer. Chem. Soc.*, **68**, 2078 (1946).

(27) H. H. Guenthard, E. Beriger, C. R. Engel, and H. Heusser, *Helv. Chim. Acta*, **35**, 2437 (1952).

added until the evolution of gas ceased. The neutral reaction product (286 mg) was recrystallized from dilute methanol: mp 120–121.5°; ν_{max} 1735, 1732 (main), 1241, 1028 cm^{-1}. Presence of a keto group, indicated by a shoulder at 1718 cm^{-1}, was confirmed by λ_{max} 273 nm (ε 27, 95% ethanol).

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.89; H, 9.44.

The mother liquors on chromatography on silica gel–Celite and elution with benzene containing 2% ether gave additional amounts of **16**. Total yield from **14** was 66%.

3β-Hydroxy-17-methyl-*D*-homo-5α,13α-androstane-16,17a-dione (**17**).—The reaction was conducted in a stream of dry nitrogen passing through a three-neck flask equipped with magnetic stirrer and a reflux condenser. A dispersion (210 mg) of 57% sodium hydride in mineral oil was freed of the latter by repeated rinsings with petroleum ether. A solution of 150 mg of methyl 3β-acetoxy-16-ethyl-16-oxo-16,17-seco-5α,13α-androstan-17-oate (**16**) in 10 ml of freshly distilled dimethyl sulfoxide was added to the dry powder. The mixture was maintained at 75–78° for 165 min, cooled, and distributed between ether–benzene and hydrochloric acid. The organic phase was extracted with sodium carbonate, which gave on acidification and extraction 123.7 mg of **17**. Recrystallization of the product from methanol and of the material in the mother liquors furnished 114.4 mg (93%) of **17**, mp 222–225°. Continued recrystallization raised the melting point to 225–227°. These crystals had ν_{max} ~3250, ~2684, ~1599 (no other peak in this region),[28] 1379, 1100, 1064, 1045 cm^{-1}; λ_{max} 266 nm [ε 13,420 in 95% ethanol containing 0.1% 1 *N* HCl; in ordinary alcohol there was a second peak at 295 nm (enolate)[30]].

Anal. Calcd for $C_{21}H_{32}O_3$; C, 75.86; H, 9.70. Found: C, 74.66, 74.78; H, 9.84, 9.90.[31]

17β-Methyl-*D*-homo-5α,13α-androstane-3,17a-dione (**18**).—A solution of freshly prepared compound **17** (59 mg) in 15 ml of acetic acid was shaken with platinum (from 51 mg of Adams dioxide, previously hydrogenated in acetic acid for 3 min) in an atmosphere of hydrogen for 5.5 hr. The product, after removal of the catalyst, was separated into an acidic (7 mg) and neutral (48 mg) fraction. The former (**17**) was reused for further hydrogenations. The neutral fractions from two such experiments (73 mg) in 3.5 ml of acetone were maintained at 10° while 0.25 ml of CrO_3–H_2SO_4 reagent[33] was added. After 4 min the steroids were extracted and separated into an acidic (17 mg) and neutral (47 mg) fraction. (According to its spectrum the former contained enolic 3,16,17a triketone. It gave additional neutral material with platinum and hydrogen.) The neutral oxidation product was chromatographed on 4.7 g of silica gel–Celite. A small crystalline fraction (1.8 mg) was eluted with petroleum ether–benzene (6:4). This had mp 145–147.5° after recrystallization from methanol and ν_{max} 1703, 1128, 996, 968, 842 cm^{-1}. It probably represents **17β-methyl-*D*-homo-5α,13α-androstan-17a-one**. Further elution of the column with benzene containing 2% ether gave 26 mg of eluate, which was recrystallized from methanol to give the 3,17a dione **18**: mp 147–149° and 150.5–152.5° on reheating of the solidified melt; $[\alpha]^{31}$ +63° (589 nm), +80 (546), +189 (436), and +511 (365 nm); ν_{max} 1712 (3-keto), 1704 (17a-keto), 1226, 1127, 963, and 843 cm^{-1}.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.62; H, 10.18.

A solution of 1.6 mg of **18** in 2 ml of 2.5% methanolic potassium hydroxide was heated under reflux for 2 hr. The ir spectrum of the recovered material was virtually not altered by this treatment.

17β-Methyl-*D*-homo-5α,13α-androstane-3β,17aα-diol (**19a**).—Sodium (280 mg) was added in portions to a boiling solution of 21 mg of **18** in 4 ml of 1-propanol. The product was isolated after 85 min and had after recrystallization from methanol a double melting point (144 and 153–154°); ν_{max} ~3390, 1046 (probably C-3–O), 1007, 986, 953, 844 cm^{-1}; yield 17.2 mg.

An identical preparation was obtained by acetylation of **17**, partial hydrolysis of the product at 18° with 1 equiv of KOH in methanol (1 m*M*) for 40 hr to the 3-acetate of **17**, hydrogenolysis and oxidation as described for the preparation of **18**, and reduction with sodium in propanol. This route is not recommended, as the 3-acetate of **17** proved to be even more unstable than **17**.

The diacetate (**19b**), prepared with pyridine and acetic anhydride at room temperature (18 hr), had mp 132.5–134°; $[\alpha]^{26}$ −2° (589 nm), −1 (436), +4 (365 nm); ν_{max} 1731, 1242, 1032, 1022 (main), 975, 971, 955, 931, 894, 604 cm^{-1}; nmr δ 4.68 ppm (m, 3α-H) and those listed in Table I.

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.28; H, 10.08.

Isolation and Identification of Compound 4.—3β-Acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl tosylate (**2**) was prepared from **1** with formic acid as described[2] and recrystallized three times from acetone. The ir spectra of the final crystals and of the third mother liquor agreed with the spectrum of a preparation obtained from **3** by partial hydrolysis and tosylation.[2] A solution of 250 mg of **2** in 10 ml of benzene and 15 ml of acetone was diluted with 225 ml of formic acid and kept at 23° for 24 hr. **3** (150 mg, mp 216–219°) was isolated as described for the formolysis of **1**.[2] The mother liquors (38 mg) were chromatographed from silica gel (old preparation of Davison)–Celite. The eluates (4 mg) just ahead of **3** gave **4**, identified by comparison of its melting point (179–180.5°) and ir spectrum with the sample obtained from **1** which has been characterized previously.[2]

A solution of 5.3 mg of **4** (derived from both **1** and **2**) in 2 ml of 2% methanolic potassium hydroxide was kept at room temperature for 20 hr. The product was recrystallized from methanol. The melting point (142 and 153–155°) was not depressed by admixture with **19a**. The ir spectra (KBr) also agreed. The diol was acetylated to give diacetate with mp 131–134° which was not depressed by admixture with **19b**. The ir spectra agreed. Another aliquot of the diol (2.1 mg) obtained from **4** by reaction with lithium aluminum hydride in ether was oxidized in acetone with 5 μl of CrO_3–H_2SO_4[33] for 5 min at 15°. The ir spectrum of the product was distinct from those of uranedione and of its 17 epimer (**9**), but agreed with that of **18**.

Registry No.—**1**, 38456-46-1; **2**, 5611-68-7; **4**, 38456-48-3; **10**, 13383-12-5; **11a**, 38456-50-7; **11b**, 38456-51-8; **12**, 38456-52-9; **13**, 38456-52-1; **14**, 38456-53-0; **16**, 38456-54-1; **17**, 38456-55-2; **18**, 38456-56-3; **19a**, 38456-57-4; **19b**, 38456-58-5; 17β-methyl-*D*-homo-5α,13α-androstan-17a-one, 38456-59-6.

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(28) This spectrum was observed on a pellet prepared by grinding the crystals of **17** with KBr. Other cruder preparations of **17** which had been incorporated into KBr by adding their solutions in methanol showed in addition to the enol peak near 1600, bands near 1700 and 1720 cm^{-1} (the latter usually as a shoulder) which are presumably due to the 16,17a-dione tautomer.[29] The intensity ratio of these keto and enol bands varied widely.

(29) (a) C. Tamm and R. Albrecht, *ibid.*, **43**, 768 (1960); (b) H. Muehle and C. Tamm, *ibid.*, **45**, 1475 (1962).

(30) For similar observations see B. Eistert and W. Reiss, *Chem. Ber.*, **87**, 108 (1954), and E. R. Blout, V. W. Eager, and D. C. Silberman, *J. Amer. Chem. Soc.*, **68**, 566 (1946).

(31) This analysis was not repeated, as the compound, like other α-alkyl substituted β diketones,[29b,32] decomposed. Broadening of the melting point and increased coloration of the melt were noticeable within 2 days of preparation.

(32) R. B. Woodward and E. R. Blout, *J. Amer. Chem. Soc.*, **65**, 562 (1943).

(33) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

Intramolecular Catalysis. VI. Selectivity in 7α,12α-Dihydroxy Steroids and Enhancement of 12α-Hydroxyl Reactivity by Substituents at Carbon 3[1]

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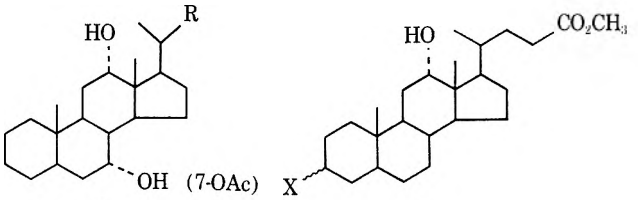
A series of 7α,12α-dihydroxy steroids (**1a, 1b, 1e, 1f, 1g, 1h**) was synthesized and compared regarding their reactivity with acetic anhydride and pyridine. All were acetylated selectively at the 7-hydroxyl and in comparable yields, indicating that the type of terminus of the side chain is immaterial with respect to preferential acetylation of the 7-hydroxyl. A series of 3-substituted 12α-hydroxy steroids was synthesized and similarly compared. Several 3 substituents enhance 12α-hydroxyl reactivity, notably oxo, chloro, and tosyloxy.

The preferential acetylation of methyl 3α-acetoxy-7α,12α-dihydroxy-5β-cholanate to the 3,7-diacetate in spite of the inherently greater reactivity of the 12-hydroxyl has been partially explained in terms of deactivation of the 12-hydroxyl by the side chain and activation of the 7-hydroxyl by both the 3α-acetoxy group and the 12-hydroxyl group.[2] A comparable explanation (except for reference to the 3-OAc group) would apply to the selective acetylation of methyl 7α,12α-dihydroxy-5β-cholanate (**1a**).[2] Without detailed knowledge of the mechanisms of these effects, it seemed possible that with other side chains the selectivity observed with **1a** might disappear or be reversed.

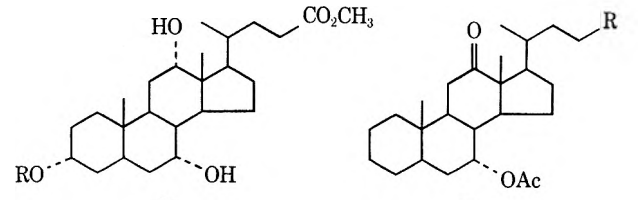


R

1a, $CH_2CH_2CO_2CH_3$ (**2a**)
b, $CH_2CH_2C(CH_3)_2OH$ (**2b**)
c, $CH_2CH_2CH_2OH$
d, $CH_2CH_2CH_2O_3SCH_3$
e, $CH_2CH_2CH_2Cl$ (**2e**)
f, $CH_2CH_2CH_2N(C_2H_5)_2$ (**2f**)
g, $CH_2CH_2CH_3$ (**2g**)
h, $CH_2CH_2CO_2H$ (**2h**)

X

5a, O
b, $(CH_3)_2NN$
c, α-$(CH_3)_2N$
d, α-HO
e, α-AcO
f, α-BzO
g, α-CH_3OCO_2
h, α-N_3CO_2
i, α-TsO
j, β-N_3
k, β-NH_2
l, β-$(CH_3)_2N$
m, β-Cl
n, H



R

3a. H
b. CH_3SO_2

R

4a. $C(CH_3)_2OH$
b. CH_2Cl
c. CH_3

We have synthesized a series of 7α,12α-dihydroxy steroids which differ in the structure of the side chain, and examined their acetylation behavior in order to determine (a) if the 7α-hydroxyl is preferentially acetylated, and (b) if the yield of 7-acetate is influenced appreciably by the side chain.

24,24-Dimethyl-5β-cholane-7α,12α,24-triol (**1b**, Table I) was synthesized by a Grignard reaction on methyl 7α,12α-dihydroxy-5β-cholanate (**1a**).[2] Reduction of **1a** with lithium aluminum hydride[3] gave 5β-cholane-7α,12α,24-triol (**1c**), which was also prepared in a more direct fashion from methyl cholate (**3a**) by selective mesylation (methanesulfonyl chloride and triethylamine in tetrahydrofuran at 0°) and, without isolating the intermediate 3-monomesylate (**3b**), reduction with lithium aluminum hydride. The triol **1c** was selectively mesylated to give 24-mesyloxy-5β-cholane-7α,12α-diol (**1d**), the intermediate for the synthesis of three more compounds in the series. The 24-mesylate **1d** reacted with pyridinium chloride in pyridine to give 24-chloro-5β-cholane-7α,12α-diol (**1e**), and with diethylamine to give 24-diethylamino-5β-cholane-7α,12α-diol (**1f**). Reduction of the mesylate **1d** with lithium aluminum hydride gave 5β-cholane-7α,12α-diol (**1g**).

As some of these compounds were only slightly soluble in the benzene medium used previously for acetylation comparisons,[2] the acetylations were carried out in pyridine (24 hr at 25°). The yields, based on weight of product isolated by column chromatography, are given in Table II. Three of the monoacetates were shown to be 7-acetates by oxidation to the corresponding 12-ketones **4**, which exhibited positive Cotton effect curves (the acid **2h** was converted to the methyl ester **2a**, identical with that previously described[2]).

The compounds in this series were chosen to include a range of electron-withdrawing groups [CO_2CH_3, Cl, and $N(C_2H_5)_2$] and electron-releasing groups (CH_3 and CO_2^-). The significant finding is that all compounds in the series acetylate selectively at the 7-hydroxyl to a nearly equal extent. Thus, deactivation of 12α-hydroxyl reactivity by the side chain is most likely a steric phenomenon, the exact nature of which is unlikely to depend on any particular kind of association between the terminal group and the hydroxyl. Deactivation has been discussed in terms of shielding,[4] which was not defined. Shielding by these types of

(1) Intramolecular Catalysis. (a) III: R. T. Blickenstaff, K. Atkinson, D. Breaux, E. Foster, Y. Kim, and G. C. Wolf, *J. Org. Chem.*, **36**, 1271 (1971). (b) IV: A. Sattar and R. T. Blickenstaff, *Steroids*, **17**, 357 (1971). (c) V: R. T. Blickenstaff and K. Sophasan, *Tetrahedron*, **28**, 1945 (1972). (d) Unpublished results from this laboratory.

(2) R. T. Blickenstaff and B. Orwig, *J. Org. Chem.*, **34**, 1377 (1969).

(3) R. T. Blickenstaff and F. C. Chang, *J. Amer. Chem. Soc.*, **80**, 2726 (1958).

(4) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 222.

TABLE I

12α-HYDROXY AND 7α,12α-DIHYDROXY STEROIDS[f]

No.	Compd	Preparation	Yield, %	Mp, °C	Ir, μ
1b	24 24-Dimethyl-5β-cholane-7α,12α,24-triol	Grignard reaction with CH_3I and 1a	66	153–154[a]	2.90–3.00
2b	7-Acetate of 1b			158–160[b]	2.78, 5.82
1d	24-Mesyloxy-5β-cholane-7α,12α-diol	CH_3SO_3Cl, 1c and $(C_2H_5)_3N$ in THF	54	169–170[b]	2.95–3.05, 7.42, 8.52
1e	24-Chloro-5β-cholane-7α,12α-diol	1d and pyridinium chloride in pyridine	48	173–175[b]	2.9–3.0
2e	7-Acetate of 1e			131–133[b]	2.77, 5.82
1f	24-Diethylamino-5β-cholane-7α,12α-diol	1d in refluxing $(C_2H_5)_2NH$ for 24 hr	81	149.5–150[b]	2.9–3.0
1g	5β-Cholane-7α,12α-diol	Reduction of 1d with $LiAlH_4$ in THF	78	204–205[b]	2.88–2.98
2g	7-Acetate of 1g			134–135[b]	2.77, 5.85
1h	7α 12α-Dihydroxy-5β-cholanic acid	Hydrolysis of 1a		206–207[b]	(lit.[g] 206)
4a	7α-Acetoxy-24,24-dimethyl-24-hydroxy-5β-cholan-12-one	Oxidation of 2b with $Na_2Cr_2O_7$ in AcOH	93	156–157[b]	2.95, 5.78, 5.88
4b	7α-Acetoxy-24-chloro-5β-cholan-12-one	Oxidation of 2e with $Na_2Cr_2O_7$ in AcOH	54	200–201[b]	5.78, 5.89
4c	7α-Acetoxy-5β-cholan-12-one	Oxidation of 2d with $Na_2Cr_2O_7$ in AcOH	65	183–184[b]	5.76, 5.89
5a	Methyl 12α-hydroxy-3-oxo-5β-cholanate	Oppenauer oxidation of methyl deoxycholate		138–140[b]	(lit.[h] 140–142)
5b	Methyl 3-(*N*,*N*-dimethylhydrazino)-12α-hydroxy-5β-cholanate	5a and $(CH_3)_2NNH_2$ in EtOH and pyridine	69.3	164–164.5[c]	3.08, 5.82, 6.18
5c	Methyl 3α-dimethylamino-12α-hydroxy-5β-cholanate	5a in refluxing DMF and HCO_2H	84.4	138–141[d]	2.9–3.05, 5.8
5f	Methyl3α-benzoyloxy-12α-hydroxy-5β-cholanate	Benzoyl chloride in pyridine		102–102.5	(lit.[i] 90–95)
5g	Methyl 3α-carbomethoxyoxy-12α-hydroxy-5β-cholanate	Methyl chloroformate in benzene and pyridine	58	180–182[b]	
5i	Methyl 3α-tosyloxy-12α-hydroxy-5β-cholanate	Tosyl chloride in pyridine		147	(lit.[j] 149–150)
5j	Methyl 3β-azido-12α-hydroxy-5β-cholanate	5j and NaN_3 in DMSO	67.4	124[b]	2.8, 4.77, 5.8
5k	Methyl 3β-amino-12α-hydroxy-5β-cholanate	Reduction of 5k with H_2 and Raney Ni	52	150–152[e]	3.17, 6.32
5m	Methyl 3β-chloro-12α-hydroxy-5β-cholanate	5j and pyridinium chloride	66	135	(lit.[j] 129–130)

[a] Analytical samples were recrystallized from toluene–hexane. [b] From methanol–H_2O. [c] From acetone. [d] From acetone–H_2O. [e] From benzene–petroleum ether. [f] Satisfactory analytical data (±0.3% for C, H, N, S, Cl) were reported for all new compounds listed in the table. [g] S. Kuwada and S. Morimoto, *Bull. Chem. Soc. Jap.*, **17**, 147 (1942). [h] A. S. Jones, *et al.*, *J. Chem. Soc.*, 2164 (1949); C. Djerassi, *Bull. Soc. Chim. Fr.*, 741 (1957); V. Burckhardt, *Helv. Chim. Acta*, **25**, 821 (1942). [i] B. F. MacKenzie, *J. Biol. Chem.*, **162**, 555 (1946). [j] F. C. Chang, *et al.*, *J. Amer. Chem. Soc.*, **79**, 2164 (1957).

TABLE II

ACETYLATION OF HYDROXY STEROIDS WITH ACETIC ANHYDRIDE AND PYRIDINE

Compd no.	Name	Yield of 7-acetate,[c] %
1a	Methyl 7α,12α-dihydroxy-5β-cholanate	66–73
1b	24,24-Dimethyl-5β-cholane-7α,12α,24-triol	68
1e	24-Chloro-5β-cholane-7α,12α-diol	64–69
1f	24-Diethylamino-5β-cholane-7α,12α-diol	61[b]
1g	5β-Cholane-7α,12α-diol	66–73
1h	7α,12-Dihydroxy-5β-cholanic acid	60–63

[c] Steroid (0.50 mmol) and Ac_2O (1.44 mmol) in pyridine (2.0 ml total volume), room temperature, 24 hr, yield determined by column chromatography. [b] Yield determined by glc (see Experimental Section).

side chains that are branched at C-20 recently has been ascribed to the steric effect of the C-21 methyl group,[1d] a finding consistent with the results in this communication.

Previous work has shown that the 12α-hydroxyl, though deactivated by the bile acid side chain, can be enhanced in reactivity by a 3α substituent. Thus, methyl deoxycholate 3-acetate (**5e**) gave a higher yield on acetylation of the 12-hydroxyl than methyl 12α-hydroxy-5β-cholanate (**5n**).[2] Similarly, 3α-acetoxy and 3α-tosyloxy groups were shown to enhance the yield of 12α-hydroxyl acetylation in a 5β-pregnan-20-one series.[1a] In order to determine what other substituents at C-3 might influence the 12α-hydroxyl, the series **5a–n** has now been synthesized and acetylated.

Methyl 12α-hydroxy-3-oxo-5β-cholanate (**5a**) was treated with 1,1-dimethylhydrazine to give the corresponding hydrazone **5b**, and with formic acid in DMF (Lekart reaction[5]) to give methyl 3α-dimethylamino-12α-hydroxy-5β-cholanate (**5c**). The 3α configuration for **5c** was shown by its comparison with the 3β epimer **5l**, to be described later. The acetate (**5e**), benzoate (**5f**), and tosylate (**5i**) were prepared by standard methods, as was the carbomethoxyoxy derivative (**5g**). The action of phosgene on methyl deoxycholate (**5d**) gave a chloroformate intermediate that reacted with sodium azide to give methyl 3α-azidoformoxy-12α-hydroxy-5β-cholanate (**5h**). The action of sodium azide on the tosylate (**5i**) gave methyl 3β-azido-12α-hydroxy-5β-cholanate (**5j**), reduction of which gave the corresponding amine **5k**. Reductive alkylation of **5k** with formaldehyde and hydrogen gave methyl 3β-dimethylamino-12α-hydroxy-5β-cholanate (**5l**). It did not crystallize, but was shown to differ from the isomer **5c** by ir and melting point compar-

(5) R. R. Savers, *J. Amer. Chem. Soc.*, **80**, 4721 (1958).

isons of their respective hydrochlorides (see Experimental Section). Methyl 3β-chloro-12α-hydroxy-5β-cholanate (**5m**) was prepared from the tosylate (**5i**) and pyridinium chloride.[6]

The compounds were acetylated as described previously,[2] except that in many cases it was more convenient to analyze the reaction mixture by thin layer chromatography (tlc) or by gas chromatography (glpc), rather than by miniature column chromatography (see Experimental Section for details). The results, shown in Table III, indicate that tlc and glpc gave

TABLE III

ACETYLATION OF 3-SUBSTITUTED METHYL 12α-HYDROXYCHOLANATES WITH ACETIC ANHYDRIDE AND PYRIDINE IN BENZENE

Compd no.	Name	Yield of acetate formed in 24 hr, %: Column[a]	tlc[a]	glc[a]
5a	Methyl 12α-hydroxy-3-oxo-5β-cholanate	19		
5b	Methyl 3-dimethylhydrazino-12α-hydroxy-5β-cholanate		11	11–12
5c	Methyl 3α-dimethylamino-12α-hydroxy-5β-cholanate			15–16
5e	Methyl 3α-acetoxy-12α-hydroxy-5β-cholanate	11–13	16	15
5f	Methyl 3α-benzoyloxy-12α-hydroxy-5β-cholanate		16–17	
5g	Methyl 3α-carbomethoxyoxy-12α-hydroxy-5β-cholanate		16–20	
5h	Methyl 3α-azidoformoxy-12α-hydroxy-5β-cholanate		11–13	
5i	Methyl 12α-hydroxy-3α-tosyloxy-5β-cholanate		26–29	
5j	Methyl 3β-azido-12α-hydroxy-5β-cholanate		13	
5l	Methyl 3β-dimethylamino-12α-hydroxy-5β-cholanate			13
5m	Methyl 3β-chloro-12α-hydroxy-5β-cholanate	16		
5n	Methyl 12α-hydroxy-5β-cholanate	5–8	11	10

[a] Values labeled "Column" represent yield of product isolated by column chromatography.[2] Values labeled tlc and glc were obtained by thin layer chromatography and gas–liquid chromatography, respectively, as described in the Experimental Section. All compounds except **5a**, **5c**, **5l**, and **5n** were run in duplicate or triplicate.

comparable values, while column chromatography gave slightly lower values. The yields for the dimethylhydrazino (**5b**) and α-azidoformoxy (**5h**) derivatives, while numerically greater than that of the unsubstituted compound **5n**, are not significantly different. The α-dimethylamino (**5c**) and β-dimethylamino (**5l**), as well as the β-azido (**5j**) derivatives, are borderline, while the α-acetoxy group (**5e**) is confirmed as weakly enhancing. The strongest groups that enhance 12-hydroxyl acetylation are α-benzoyloxy (**5f**), α-carbomethoxyoxy (**5g**), β-chloro (**5m**), oxo (**5a**), and α-tosyloxy (**5e**). We are currently examining the effects of some of these groups on the rate of acetylation of the 7α-hydroxyl group.

(6) F. C. Chang, *et al.*, *J. Amer. Chem. Soc.*, **79**, 2164 (1957).

Experimental Section[7]

5β-Cholane-7α,12α,24-triol (**1c**).—This compound was prepared by two different routes. In the first, methyl 7α,12α-dihydroxy-5β-cholanate (**1a**, 12.198 g, 0.030 mol) was dissolved in 300 ml of THF (dried over molecular sieves). This solution was then slowly added to $LiAlH_4$ (4.554 g, 0.120 mol) suspended in 400 ml of THF. Then the final solution was refluxed for 16 hr and hydrolyzed with 5 *N* NaOH. When the excess $LiAlH_4$ was destroyed, the mixture was acidified with concentrated HCl. The solution was filtered into 2500 ml of water, whereupon the product readily precipitated. This solid was collected and recrystallized from methanol–water to give 10.039 g (89%) of the expected triol, mp 197–198°.

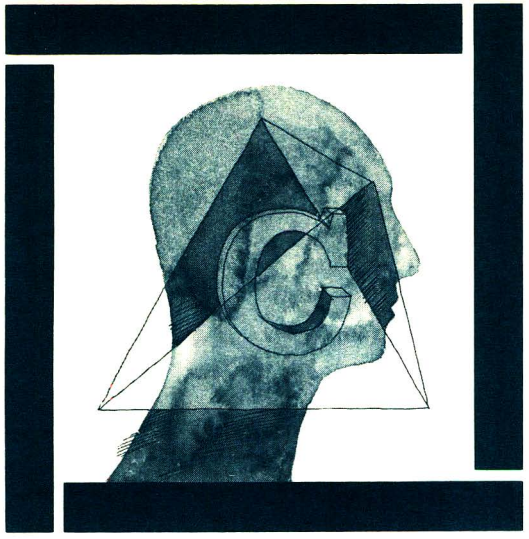
Although the above procedure worked quite well to give a good yield of reduced product, the starting ester could be prepared much less readily. In our hands the removal of the 3α-hydroxy group from methyl cholate was achieved in only a 30% yield (*via* Oppenauer oxidation and Wolff–Kishner reduction) and required an appreciable amount of time. In an effort to circumvent these difficulties an alternate approach to **2a** was sought. To this end, methyl cholate (13.640 g, 0.030 mol) was dissolved in 100 ml of dry THF and to this was added triethylamine (3.137 g, 0.031 mol). This homogeneous solution was cooled to 0° and subsequently methanesulfonyl chloride (3.551 g, 0.031 mol) in 50 ml of THF was added dropwise over a 45-min period. The mixture was left to warm to room temperature for 1 hr while a second solution containing $LiAlH_4$ (11.386 g, 0.300 mol) in 150 ml of THF at 0° was prepared. The first solution was then filtered directly into the second over 1 hr. The final mixture was allowed to stir overnight at 45–50°. The excess hydride was hydrolyzed with water and the mixture was acidified with HCl. It was then poured into 1500 ml of water and extracted with two 500-ml portions of $CHCl_3$. Combining the organic extracts, drying, and evaporating the solvent left a solid residue, which was recrystallized from methanol–water to give 7.809 g (69%) of white needles, mp 194–196°, ir 2.98 μ.

Anal. Calcd for $C_{24}H_{42}O_3$: C, 76.14; H, 11.18. Found: C, 75.99; H, 11.23.

Acetylation Procedure.—The acetylations of the 7,12-diol series (**1**) were carried out using 2.0 ml of a pyridine solution which was 0.25 *M* in steroid and 0.72 *M* in acetic anhydride. This solution was kept at 25° for 24 hr and then transferred to a separatory funnel with *ca.* 10 ml of ether. Subsequently it was washed three times with 10-ml portions of water [in the case of 7α,12α-dihydroxycholanic acid (**1h**), the organic solution was first washed with enough 5 *N* HCl to ensure that the free acid was present and not the carboxylate anion; the reaction mixture of **1f** was analogously washed with 5 *N* NaOH] and the organic layer was separated, dried briefly over Na_2SO_4, and filtered. The solvent was allowed to evaporate and the residue was chromatographed on 20 g of 30–60 mesh Florisil using 0.5–3% methanol in benzene as the eluent. The progress of the separations was followed by tlc (silica gel G developed in 3–10% methanol in benzene and subsequently sprayed with 50% H_2SO_4 and heated). In most instances separation was quite good and appropriate fractions (20 ml) were combined, the solvent was removed, and the weight of residue was recorded; both product and starting material were isolated. The acetates were identified (in the cases where they were unknown) by synthesizing them on a larger scale, recording their ir spectra, and obtaining analyses. A few per cent of a second product (possibly 7,12-diacetate) was usually observed; total recovery was 95% or better.

In the acetylation of the amine **1f**, all attempts to separate the product acetate from the starting material *via* column chromatography were unsuccessful. Consequently, a glpc analysis of the reaction mixture was carried out using a 5-ft column packed with OV 17 on Chromosorb G and at a column temperature of 273°. Three components were noted with retention times of 14.7, 16.5, and 18.2 min in a ratio of 2:61:37. The retention time of the last peak was exactly the same as that of the starting material (**1f**); the second peak was ascribed to the 7α-acetate; the first was probably due to either the 12α-acetate or the 7α,12α-diacetate.

(7) Compounds not listed in Table I are described in this section. Melting points were taken on a Unimelt apparatus and are uncorrected; the ir spectra were recorded on a Perkin-Elmer Infracord as Nujol mulls. The ORD and CD spectra were determined on a Cary Model 60 spectropolarimeter at Eli Lilly and Co., Indianapolis, Ind. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.



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The same problem of separation arose in the acetylation of **1h**; in this case, the crude residue was dissolved in 30 ml of methanol and 1 ml of concentrated HCl and refluxed for 2 hr to esterify the acid side chain. [We have found 5β-cholane-7α,12α-diol 7-acetate (**2g**) to be completely stable to these conditions.] The solvent was then removed and the methyl esters were separated on Florisil.

Methyl 3α-Azidoformoxy-12α-hydroxy-5β-cholanate (5h).—Methyl deoxycholate in cold toluene was treated with phosgene for 3 hr to give methyl 3α-chloroformoxy-12α-hydroxy-5β-cholanate. The solvent was evaporated under a stream of hot air and the residue was recrystallized from acetone–petroleum ether (bp 30–60°), mp 135°. Methyl 3α-chloroformoxy-12α-hydroxy-5β-cholanate (900 mg) and 1.8 g of sodium azide were dissolved in DMSO and heated at 75° for 3 hr. After standing at room temperature overnight, the mixture was diluted with water and extracted with chloroform to give 990 mg of crude material. This material was chromatographed on 22 g of Florisil; the product (751 mg) was eluted by 4:1 benzene–ether. Recrystallization from acetone–water gave 238 mg, mp 164–165° (analytical sample), and 400 mg, mp 161–162°, ir 4.58, 4.70 (N_3), 5.77, 5.84 μ (C=O).

Anal. Calcd for $C_{26}H_{41}N_3O_5$: C, 65.66; H, 8.69; N, 8.83. Found: C, 65.67; H, 8.64; N, 8.70.

Methyl 3β-Dimethylamino-12α-hydroxy-5β-cholanate (5l).—Methyl 3β-amino-12α-hydroxy-5β-cholanate (**5k**, **1g**) was dissolved in 45 ml of methanol and 25 ml of 37% CH_2O, 205 mg of 5% Pd/C was added, and the mixture was hydrogenated under a hydrogen pressure of 36 psi for 3 days. The mixture was then filtered and the solvent was removed under reduced pressure. The residue was taken up in chloroform, the chloroform solution was washed with water and dried over sodium sulfate and the solvent was evaporated to give 946 mg of crude product. This material was dissolved in acetone and cooled. The acetone solution was then saturated with HCl followed by the addition of ether to give 570 mg of solid material, mp 254–256°. Approximately 70 mg of this material was treated with aqueous methanol–sodium carbonate to give the free amine, which we were unable to crystallize. The amine was purified by means of thin layer chromatography and isolated as an oil.

Anal. Calcd for $C_{27}H_{47}NO_3$: C, 74.78; H, 10.92; N, 3.23. Found: C, 74.72; H, 11.89; N, 3.15.

The infrared spectrum of methyl 3β-dimethylamino-12α-hydroxy-5β-cholanate hydrochloride showed absorptions at 3.78 and 4.07 (tertiary $^+$NH) and 5.82 μ (C=O) [lit.[8] 3.88 and 4.1 μ (tertiary $^+$NH)]. The α epimer showed absorptions at 3.74 and 3.97 (tertiary $^+$NH) and 5.76 μ (C=O) [lit.[11] 3.7 and 4.02 μ (tertiary $^+$NH)]. The hydrochloride salts of methyl 3β-dimethylamino-12α-hydroxy-5β-cholanate and its 3α epimer were prepared by treating a solution of the free amines in acetone with HCl (g) and precipitating the salts by addition of ether. The hydrochloride of the α derivative had a melting point of 252–253° and the β-epimer, mp 253–255°, mmp 234–238°.

Acetylation and Yield Determination By Thin Layer Chromatography and Gas Chromatography.—The steroid (0.37 mmol) was dissolved in 0.1 ml of pyridine, some benzene was added, and 0.1 ml of acetic anhydride was added, followed by enough benzene to make the total volume 1 ml. The reactions were carried out at room temperature (25 ± 1°) over a period of 24 hr and quenched with methanol to stop the reaction. The solvent was allowed to evaporate and 15–35 mg of the steroidal material was streaked on a silica gel G thin layer plate and developed in a suitable solvent system. Various solvent mixtures of benzene–ether and benzene–methanol were used. Thin layer chromatography plates were sprayed at one end with sulfuric acid to locate the bands. Once the bands were located, the two fractions were recovered separately and weighed.

From reaction mixtures that had evaporated to dryness, approximately 4 mg of the residue was redissolved in 1 ml or more of acetone or chloroform for chromatography in a Micro Tek 220 equipped with a flame ionization detector and a Disc integrator. Two to three separate injections of 1 μl each were averaged. Samples to be analyzed were chromatographed on either a 6-ft 1% OV-17 on Chrom G column (methyl 3α-acetoxy-12α-hydroxy-5β-cholanate, methyl 3-dimethylhydrazino-12α-hydroxy-5β-cholanate, methyl 3α- and 3β-dimethylamino-12α-hydroxy-5β-cholanate) or a 4-ft 3% polysulfone on Chrom Q column (methyl 12α-hydroxy-5β-cholanate). Column temperature ranged from 275 to 290° and a carrier gas (N_2) flow rate of 55 ml/min was used.

Registry No.—**1a**, 3701-54-0; **1b**, 38379-63-4; **1c**, 32624-95-6; **1d**, 38431-60-6; **1e**, 38431-61-7; **1f**, 38431-62-8; **1g**, 17041-50-8; **2b**, 38431-63-9; **2d**, 38379-65-6; **2e**, 38379-66-7; **2g**, 38379-67-8; **4a**, 38379-68-9; **4b**, 38379-69-0; **4c**, 38379-70-3; **5a**, 10538-58-6; **5b**, 38379-72-5; **5c**, 38379-73-6; **5c** HCl, 38379-74-7; **5g**, 38359-35-2; **5h**, 38359-36-3; **5j**, 38359-37-4; **5k**, 38359-38-5; **5l**, 38359-39-6; **5l** HCl, 38359-40-9; methyl 3α-chloroformoxy-12α-hydroxy-5β-cholanate, 38359-41-0.

Acknowledgment.—We wish to express our sincere gratitude to Mr. Frank Beasley of the Eli Lilly Company for recording the ORD and CD spectra. We gladly acknowledge the expert technical assistance of Mr. Dominique Breaux.

(8) R. Glasser and E. J. Gabbay, *J. Org. Chem.*, **35**, 2907 (1970).

Transformations of Steroidal Neopentyl Systems. VII. Mechanism of the Transformation of (19*R*)-Hydroxy-19a-methyl-(5α)-3-ones to 19-Keto-19a-methyl-(5α)-3α-hydroxy Analogs[1]

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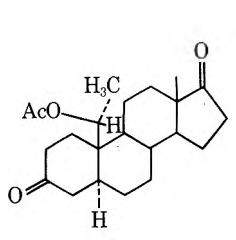
The synthesis of *19-d*-(19*R*)-19-hydroxy-19a-methyl-5α-androstane-3,17-dione is described. The product on treatment with base rearranged to *3β-d*-3α-hydroxy-19a-methyl-5α-androstane-17,19-dione without loss of deuterium. The results are in agreement with the hypothesis that the rearrangement involves an intramolecular hydride ion transfer. A mechanism for the rearrangement is proposed.

We have previously reported two cases[3,4] of the rearrangement of (19*R*)-hydroxy-19a-methyl-3 ketones to 3α-oxygenated 19a-methyl-19 ketones. This rearrangement was first noted when (19*R*)-acetoxy-19-methyl-5α-androstane-3,17-dione (**1**) was treated with ethylene glycol and *p*-toluenesulfonic acid in boiling benzene.[3] In addition to the expected 3,17 diketal, the 17,17-bisethylenedioxy-3α-(2-hydroxyethoxy)-19-methyl-5α-androstan-19-one (**2**) was obtained. Similarly, exposure of (19*R*)-hydroxy-19a-methyl-5α-androstane-3,17-dione (**3a**) to ethanolic potassium hydroxide[4] resulted in several compounds, among them 3α-hydroxy-19a-methyl-5α-androstane-17,19-dione (**4a**). On the basis of stereochemical considerations we have proposed a mechanism involving an intramolecular hydride ion transfer from C-19 to C-3β for this rearrangement.



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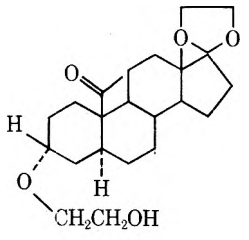

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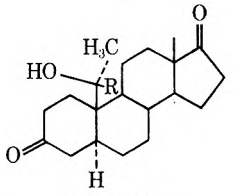

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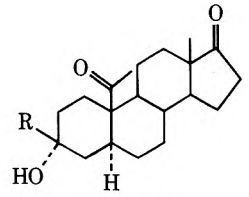
b, R = D



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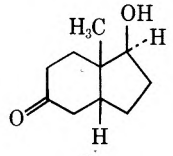

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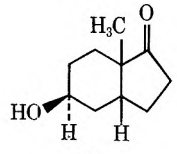

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Several cases of similar rearrangements were previously reported. Acklin and Prelog[5] observed the transformation of hydrindanone (**5**) to product **6** on an alumina column. Dvornik and Edwards[6] treated the hydoxy ketone **7** with alcoholic potassium hydroxide and obtained **8**. Without providing experimental proof, these authors also assumed that the rearrangements involved an intramolecular hydride ion transfer.

It may be noted that the rearrangements observed by us and by others occurred in compounds in which the spatial orientation of the participating functions was essentially similar. Presumably relief from the steric compression is the driving force for the process. Since this appears to be a rather general reaction for the systems under consideration, we undertook to define the mechanism of the reaction.

We chose to study the rearrangement using *19-d*-(19*R*)-19-hydroxy-19-methyl-5α-androstane-3,17-dione **3b** as a model. From the loss or retention of deuterium in the derived 19 ketone **4** the mechanism of the reaction could then be deduced. With this in mind, the synthesis of the 19-deuterated alcohol **3b** was undertaken.

The 3β,17β-diacetoxyandrost-5-en-19-ol was treated with chromic acid in pyridine[7] and the resulting aldehyde **9a** was oxidized with potassium permanganate in pyridine[8] to yield the diacetoxy carboxylic acid[9] **9b**. Saponification of **9b** provided the dihydroxy acid[9] **9c**. The dihydroxy acid **9c** was treated with diazomethane and the obtained ester **9d** on exposure to dihydropyran and *p*-toluenesulfonic acid gave methyl 3β,17β-bis(2-tetrahydropyranyloxy)androst-5-en-10-carboxylic acid ester **9e**.

The bis-THP ether **9e** was reduced with $LiAlH_4$ to yield the alcohol **9f**, which was oxidized with chromium trioxide in pyridine[7] to the aldehyde **9g**. An analogous reduction of **9e** with $LiAlD_4$ gave *19-d*$_2$ alcohol **9h**, which was subsequently oxidized to the *19-d* aldehyde **9i**. The mass spectrum of the alcohol **9h** was devoid of a peak of *m/e* 474 but had a peak at *m/e* 476 indicating the presence of *two* atoms of deuterium at C-19. The mass spectrum of the aldehyde **9i** did not have a peak at *m/e* 472 and had a peak at *m/e*

(1) This work was supported by Grants CA 07137 and K3-16614 from the National Institutes of Health.

(2) Postdoctoral Fellow (1964–1966) on leave of absence from The Warsaw University, Warsaw, Poland.

(3) J. Wicha and E. Caspi, *J. Chem. Soc. C*, 1740 (1968).

(4) J. Wicha and E. Caspi, *Tetrahedron*, **25**, 3961 (1969).

(5) W. Acklin and V. Prelog, *Helv. Chim. Acta*, **42**, 1239 (1959).

(6) D. Dvornik and J. O. E. Edwards, *Proc. Chem. Soc.*, 280 (1958).

(7) G. I. Poos, G. E. Arth, E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

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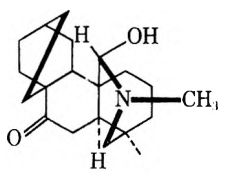

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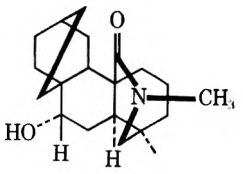

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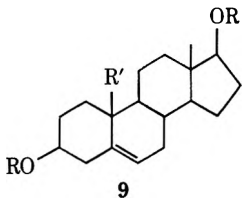

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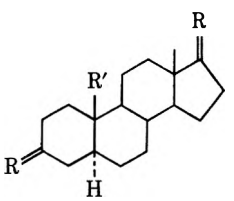


10

9a, R = Ac; R′ = CHO
b, R = Ac; R′ = COOH
c, R = H; R′ COOH
d, R = H; R′ = $COOCH_3$
e, R = THP; R′ = $COOCH_3$
f, R = THP; R′ = CH_2OH
g, R = THP; R′ = CHO
h, R = THP; R′ = CD_2OH
i, R = THP; R′ = CDO
j, R = THP; R′ = $CD(OH)CH_3$
k, R = THP; R′ = $CD(OAc)CH_3$
l, R = H; R′ = $CD(OAc)CH_3$

10a, R = β-OH, H; R′ = $CD(OAc)CH_3$
b, R = O; R′ = $CD(OAc)CH_3$
c, R =  ; R′ = $CD(OAc)CH_3$
d, R =  ; R′ = $CD(OH)CH_3$

473 as expected for monodeuterated product. Supporting evidence for the assigned structure of the d_2 alcohol **9h** and *d* aldehyde **9i** was provided by ir and nmr spectroscopy (see Experimental Section).

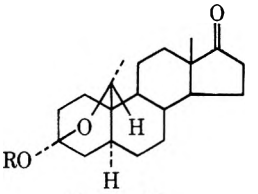
The *d* aldehyde **9i** was treated with methyllithium to yield the *19-d*-(19*R*)-hydroxy-19a-methylbis-THP ether[1] **9j**. The arguments for assigning the 19*R* configuration to the alcohol have been previously presented.[3,10] The crude **9j** was converted to the 19 acetate **9k**, which was not characterized and was hydrolyzed to yield *19-d*-(19*R*)-acetoxy-19a-methylandrost-5-ene-3β,17β-diol (**9l**). The mass spectrum of **9l** had a peak at *m/e* 363, but was lacking a peak at *m/e* 362, indicating the retention of a *whole atom* of deuterium at C-19. As could be expected, the **9l** nmr spectrum showed a singlet at τ 8.7 for the 19a-methyl.

Hydrogenation of **9l** over a 10% palladium on carbon catalyst provided the 5α-(H)-3,17-diol **10a**. We have previously proven that the hydrogenation product has indeed the critically important 5α configuration.[5] The diol **10a** was oxidized with Jones regent[11] to the 19-acetoxy-3,17-dione **10b**, which was converted in the conventional manner to the diketal acetate **10c**, *m/e* 449. The crude **10c** was first treated with $LiAlH_4$ and the resulting 19-hydroxy diketal **10d** was hydrolyzed to yield the required *19-d*-(19*R*)-19-hydroxy-19a-methyl-5α-androstane-3,17-dione (**3b**). The structure **3b** was confirmed by ir and nmr spectroscopy and its mass spectrum (*m/e* 319) confirmed the presence of a *whole atom* of deuterium at C-19.

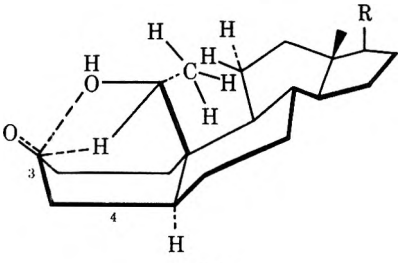
The obtained *19-d*-(19*R*)-19-hydroxy-19a-methyl-5α-androstane-3,17-dione (**3b**) was treated with aqueous methanolic potassium hydroxide. The resulting reaction mixture was fractionated by preparative thin layer chromatography on alumina. The less mobile product proved to be unchanged **3b**. The more mobile material had an R_f idendical with that of authentic (nondeuterated) **4a**. The nmr spectrum of **4b** had a signal at τ 7.80 for the 10-acetyl. The chemical shifts for the 10-acetyl and for the C-13 methyl in **4a** and **4b** were the same. Significantly, the narrow multiplet at τ 5.93 for the C-3 equatorial proton, present in **4a**, was absent in the deuterated **4b**. Finally, the mass spectrum of **4b** had a peak at *m/e* 319 for M^+ but was devoid of a peak at *m/e* 318.

It is evident that the transformation of **3b** to **4b** proceeded with complete retention of deuterium, which is consistent with intramolecular hydride ion transfer.

The observed reactions of 5α-steroidal (19*R*)-19-hydroxy-19a-methyl-3 ketones require comment. *A priori* it may be accepted that the reaction will occur when ring A assumes a boat form. It is feasible that the boat form could be stabilized by transannular interaction of the oxygen atom of the C-19 hydroxyl with the carbon of the C-3 carbonyl. Under acidic conditions both the C-19 to C-3 hydride ion transfer (*e.g.*, **2**, **4**) and 3β,19-oxide formation (*e.g.*, **11**) take



11a, R = H
b, R = CH_3



12

place,[3] while under alkaline conditions the β-face hydride ion transfer predominates.[4,10] For an intramolecular hydride ion transfer to occur, the C-19 hydrogen must approach and, in a sense, "bridge," the C-3 of the carbonyl. Similarly, a C-3,19 oxide formation is possible when the 19-hydroxyl is located in the proximity of the C-3 carbon. Hence the rearrangement can be viewed as occurring when either the 19-H or the 19-OH comes close to the C-3 electrophilic receptor.

An alternative interpretation based on the hypothesis of simultaneous positioning of the participating C-19 oxygen atom and 19-hydrogen atom in the proximity of C-3 of the carbonyl seems less plausible. In this instance the rearrangement would proceed through a four-centered transition state shown in **12**. The four-centered transition state **12** encompasses C-19, the 19-oxygen, 19-hydrogen, and C-3. Formation of the transition state requires rotation around the 10–19 bond and this could occur by flattening of ring C, which would minimize the interference of the 11β-hydrogen with the 19α-methyl. The high energy of the four-centered transition state would greatly favor either one of the observed reactions, as both would provide relief from the strain.

(10) J. Wicha and E. Caspi, *J. Chem. Soc. C*, 947 (1969).
(11) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

However, it should be noticed that a four-centered transition state cannot be formed in the case of **7** which is transformed to **8**. Also, we have previously indicated that, in the 19-hydroxy-19a-methyl steroids, the rotation around the C-10,19 bond is rather restricted.[3,10] Confirmation of this view is provided by the fact that, while the 19*R* alcohol **3a** readily gave the 3α-methoxy 3β,19-oxide **11b**, the 19*S* alcohol under similar conditions resisted oxide formation, and only starting material was recovered.[10] Thus the four-centered transition like **12** could possibly function only when products of both types **4** and **11** are formed.

Experimental Section

Melting points were taken on a micro hot stage and are corrected. Infrared spectra were recorded on solids incorporated in KBr wafers. Ultraviolet spectra were taken on methanol solutions. Unless otherwise stated, deuteriochloroform was used for nmr spectra which were recorded at 60 MHz on a Varian HA-60 instrument, and are given in the τ scale. The mass spectra were taken on a Varian M66 instrument. Analyses were performed by I. Beetz, Kronach, Germany.

3β,17β-Acetoxyandrost-5-ene-10β-carboxylic Acid (9b).—To a stirred and cooled (in an ice–salt bath) solution of the aldehyde **9a** (10 g) in anhydrous pyridine (70 ml), a suspension of powdered potassium permanganate (10 g) in pyridine (100 ml) was added in several portions. The mixture was then stirred for 4 hr at ambient temperature and filtered, and the filtrate was diluted with ether (1 l.). The ether solution was washed sequentially with ice, cold 5% sulfuric acid, water, and a saline solution, dried over magnesium sulfate, and concentrated to a residue under reduced pressure. The residue was crystallized from a mixture of chloroform–ether to yield **9b** (8.5 g). The analytical specimen showed mp 211–214° (reported[9] mp 213–215°), ν_{max} (KBr) 1740, 1700, and 1250 cm^{-1}.

3β,17β-Dihydroxyandrost-5-ene-10β-carboxylic Acid (9c).—A mixture of the diacetate **9b** (8 g), methanol (500 ml), potassium hydroxide (10 g), and water (10 ml) was kept at room temperature for 16 hr. After the addition of water (100 ml), the solution was acidified with hydrochloric acid. The resulting crystalline acid **9c** was filtered, washed with aqueous methanol, and dried (6 g). A sample was sublimed at 190–200° (0.1 Torr), mp 320–322°, ν_{max} (KBr) 3400, 3180, and 1710 cm^{-1}. The physical constants agree with those previously reported.[9]

Methyl 3β,17β-Dihydroxyandrost-5-ene-10β-carboxylate (9d).—A suspension of the acid **9c** (6 g) in methanol (200 ml) was treated with an excess of an ethereal solution of diazomethane. Removal of the solvents and crystallization of the residue from acetone gave the ester **9d** (5.7 g), mp 172–174°. The analytical specimen showed mp 173–175°; ν_{max} (KBr) 3450, 1720, 1170 cm^{-1}; nmr ($CDCl_3$) τ 4.47 (1 H, 6-H), 6.3 (s, 3 H, 19-OCH_3), 9.3 (s, 3 H, 13-CH_3).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.0. Found: C, 72.10; H, 9.12.

Methyl 3β,17β-Bis(2-tetrahydropyranyloxy)androst-5-ene-10β-carboxylate (9e).—A mixture of **9d** (5 g), dihydropyran (3.2 g), *p*-toluenesulfonic acid (50 mg), and anhydrous chloroform (80 ml) was stored for 16 hr at ambient temperature. The reaction was terminated by the addition of powdered sodium hydrogen carbonate, and, after stirring for 10 min, the contents were poured into a saturated solution of sodium hydrogen carbonate. The chloroform phase was separated, washed, dried, and concentrated to a residue under reduced pressure. The crude bis-THP ether (7.4 g) was crystallized several times to yield plates, mp 108–113°, ν_{max} (KBr) 1720 and 1170 cm^{-1}.

Anal. Calcd for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22. Found: C, 71.52; H, 9.13.

Reduction of 9e and Introduction of Deuterium at C-19. A.—A mixture of the ester **9e** (200 mg) and $LiAlH_4$ (200 mg) in dry ether (30 ml) was refluxed for 16 hr. The reaction was terminated by the addition of a saturated solution of sodium sulfate (cooling). The obtained solid was collected by filtration and washed with ether, and the combined filtrate was washed with water. Removal of the ether gave the crystalline **9f** (165 mg). A sample was crystallized several times: mp 161–167°; ν_{max} (KBr) 3430 cm^{-1}; nmr τ 4.42 (1 H, C-6 H), 6.07 (d), and 6.67 (d, 2 H, J = 19 Hz, C-19 H_2), 9.2 (s, 3 H, C-13 CH_3); *m/e* 474 (M^+).

Anal. Calcd for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found: C, 73.31; H, 9.59.

B.—A similar reduction of ester **9e** (5 g) with $LiAlD_4$ (4 g) in dry ether (600 ml) gave *19-d_2* alcohol **9h** (4.2 g): mp 159–167°; ν_{max} (KBr) 3430 cm^{-1}; nmr τ 6.07 (s) and 6.67 (s); *m/e* 476 (M^+), 444 (M − 32), 426 (444 − 18), 392 (476 − 84), 374 (392 − 18), 360 (392 − 32).

***19-d*-3β,17β-Bis(2-tetrahydropyranyloxy)androst-5-en-19-al (9i).**—The deuterated alcohol *19-d_2*-**9h** (4 g) in pyridine (2 ml) was treated with a suspension of chromic acid (4 g) in pyridine (4 ml). After 6 hr at room temperature the mixture was diluted with ethyl acetate (300 ml) and the solid was removed by filtration. The filtrate was processed in the conventional manner and the obtained residue was crystallized from acetone to yield the aldehyde **9i**: ν_{max} (KBr) 1720 cm^{-1}; nmr ($CDCl_3$) τ 4.38 (1 H, C-6 H), 9.12 (s, 3 H, C-13 CH_3); *m/e* 473 (M^+), 455 (M − 18), 454 (M − 19), 389 (473 − 84, C_5H_8O), 371, 361, 359.

A nondeuterated sample (**9g**) was obtained by oxidation of 19 alcohol **9f** (100 mg) with chromic acid (100 mg) in pyridine (0.4 ml). The recovered aldehyde was crystallized several times from acetone: mp 115–116°; ν_{max} (KBr) 1720 cm^{-1}; nmr ($CDCl_3$) τ 0.3 (s, 1 H, C-19 H), 4.38 (1 H, C-6 H), 9.12 (s, 3 H, C-13 CH_3).

Anal. Calcd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.40; H, 9.21.

***19-d*-(19*R*)-19-Acetoxy-19a-methylandrost-5-ene-3β,17β-diol (9l).**—To a solution of the aldehyde **9i** (3.3 g) in anhydrous ether (70 ml), a 1.6 *M* solution of methyllithium (10 ml) was added during 10 min. The mixture was refluxed for 30 min, then cooled, and the excess reagent was decomposed with water. The product **9j** was recovered with ether, washed with water, dried, and concentrated to a residue. The obtained **9j** (3.4 g) was dissolved in a mixture of acetic anhydride–pyridine (1:1, 40 ml) and the solution was stored for 20 hr at room temperature. The reaction mixture was poured on ice and HCl, and after 2 hr the product was recovered with ether. The ether extract was washed with 5% aqueous HCl, water, a saturated solution of sodium bicarbonate, and again with water, then dried and evaporated. Crystallization from ether gave the dihydroxy-19-monoacetate **9l** (1.1 g): mp 80–82°; ν_{max} (KBr) 3550, 1740, and 1245 cm^{-1}; nmr τ 4.53 (1 H, C-6 H), 8.0 (s, 3 H, 19-OAc), 8.70 (s, 3 H, 19a-CH_3), 9.18 (s, 3 H, C-13 CH_3); *m/e* 363 (M^+, less than 1%), 303 (M − 60, CH_3COOH, 90%), 285 (303 − H_2O, 42%), 275 (M − 88, CH_3-CDOAc, 100%).

***19-d*-(19*R*)-19-Acetoxy-19a-methyl-5α-androstane-3β,17β-diol (10a).**—A mixture of **9l** (520 mg), a 10% palladium on carbon catalyst (300 mg), and methanol (100 ml) was agitated under normal pressure in an atmosphere of hydrogen for 8 hr. The uptake of hydrogen was 32 ml. The catalyst was removed by filtration and the filtrate was concentrated to a residue. The saturated diol **10a** (490 mg) showed mp 92–97°; a mixture melting point of the deuterated material with an authentic ^{1}H sample[3] was not depressed; ν_{max} (KBr) 3550, 1730, and 1245 cm^{-1}; nmr τ 8.00 (s, 3 H, 19-OAc), 8.65 (s, 3 H, 19a-CH_3), 9.18 (s, 3 H, C-13 CH_3); *m/e* 365 (M^+, small), 305 (M^+ − 60), 287 (305 − 18), 277 (M − 88, CH_3CDOAc), 261, 259, 241.

***19-d*-(19*R*)-19-Acetoxy-19a-methyl-5α-androstane-3,17-dione (10b).**—The diol **10a** was dissolved in acetone (70 ml) and treated with Jones reagent.[9] After the usual processing of the reaction mixture, the diketone **10b** (350 mg) was obtained: mp and mmp with authentic unlabeled product 145–150°; ν_{max} (KBr) 1740, 1710, and 1220 cm^{-1}; nmr τ 7.93 (s, 3 H, 19-OAc), 8.60 (s, 3 H, 19a-CH_3), 9.05 (s, 3 H, C-13 CH_3); *m/e* 361 (M^+, 90%), 301 (M − 60, 100%), 318 (M − 43, CH_3CO), 273 (M − 88, CH_3·CD-OAc, 98%).

***19-d*-(19*R*)-19-Hydroxy-19a-methyl-5α-androstane-3,17-dione (3b).**—A mixture of the diketone **10b** (340 mg), ethylene glycol (10 ml), and *p*-toluenesulfonic acid (5 mg) was distilled at 0.05 Torr in an atmosphere of nitrogen. The distillation was continued for 2 hr at 80°, during which time 5 ml of distillate was collected.

The mixture was cooled, pyridine (0.4 ml) was added, and the product was recovered with ether in the usual manner. The diketal **10c** (280 mg) showed mp 97–100°; *m/e* 449 (M^+), 405 (M − 44), 390 (405 − 15), 377 (405 − 28), 361 (M − 88), 125, 112, 99.

The crude diketal **10c** was dissolved in anhydrous ether (50 ml), $LiAlH_4$ (400 mg) was added, and the mixture was refluxed for 16 hr. After work-up the hydroxy diketal **10d** (220 mg) was obtained as a colorless syrup, *m/e* 407 (M^+).

To a solution of the above diketal **10d** in dioxane (10 ml), 2 *N* hydrochloric acid (1 ml) was added and the mixture was stored for 20 hr at the ambient temperature. The hydroxy diketone **3b** (110 mg) was recovered with ether. The product **3b** showed mp 167–170°. A mixture melting point with authentic[1] unlabeled material (**3a**) was not depressed; ν_{max} (KBr) 3400, 1740, 1712 cm^{-1}; *m/e* 319 (M^+), 304 (M − 15), 274 (M − 45, $CH_3 \cdot CDO$), 256 (274 − 18).

Rearrangement of *19-d*-(19*R*)-19-Hydroxy-19a-methyl-5α-androstane-3,17-dione (3b) to *3β-d*-3α-Hydroxy-19a-methyl-5α-androstane-17,19-dione (4b).—A solution of the deuterated **3b** (100 mg) in methanol (50 ml) containing potassium hydroxide (100 mg) and water (0.5 ml) was refluxed for 3 hr in an atmosphere of nitrogen. The mixture was cooled, diluted with water, and neutralized with acetic acid. The product was recovered with ethyl acetate in the usual manner. The obtained residue (103 mg) was fractionated by thin layer chromatography on neutral alumina (purchased from Woelm A.G.). The plates were developed with ethyl acetate. The two major products were recovered with ethyl acetate and were identified as starting material **3b** (12 mg) and the deuterated alcohol **4b** (46 mg).

The 3α-hydroxy-*3β-d* product (**4b**), mp 170–171°, showed ν_{max} (KBr) 3550, 1730, and 1680 cm^{-1}; nmr ($CDCl_3$) τ 7.8 (s, 3 H, 19a-CH_3), 9.21 (s, 3 H, 13-CH_3); *m/e* 319 (M^+), 301 (M − 18), 276 (M − 43), 258 (276 − 18), 240 (258 − 18).

Registry No.—**3b**, 38308-99-5; **4b**, 38309-00-1; **9a**, 2951-52-2; **9b**, 14413-29-7; **9c**, 14413-27-5; **9d**, 38431-64-0; **9e**, 38309-04-5; **9f**, 38309-05-6; **9g**, 38309-06-7; **9h**, 38309-07-8; **9i**, 38309-08-9; **9j**, 38309-09-0; **9l**, 38309-10-3; **10a**, 38309-11-4; **10b**, 38312-19-5; **10c**, 38312-20-8; **10d**, 38312-21-9.

Introduction of a 2′,3′ Double Bond into 1-(5′-*O*-Benzoyl-β-D-lyxofuranosyl)uracil by Selective Elimination Reactions. A Facile Synthesis of 5′-*O*-Benzoyl-3′-deoxy-2′-ketouridine

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For the purpose of synthesizing 2′,3′-didehydrouracil nucleosides from 1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**1**) by base-induced elimination reactions, **1** was monotosylated to 1-(5′-*O*-benzoyl-2′-*O*-tosyl-β-D-lyxofuranosyl)-uracil (**2**) and 1-(5′-*O*-benzoyl-3′-*O*-tosyl-β-D-lyxofuranosyl)uracil (**3**). Mesylation of **2** and **3** gave isomers **4** and **7**, respectively. Dimesylation of **1** gave 2′,3′-di-*O*-mesyl analog **9**. Elimination reactions on **4**, **7**, and **9** gave 5′-*O*-benzoyl-3′-deoxy-2′-ketouridine (**6**). The intermediary 2′-*O*-tosyl-2′,3′-didehydro nucleoside (**5**) was isolated and characterized. Action of alcoholic ammonia on **4** gave 1-(2′-*O*-tosyl-β-D-lyxofuranosyl)uracil (**10**) *via* debenzoylation and demesylation.

In a previous paper,[1] the results of some base-catalyzed elimination reactions on 2′,3′-di- and 2′,3′,5′-tri-*O*-mesyl derivatives of 3-benzyluridine were described. One of the important features of these results was the selective 2′-hydrogen abstraction in the trans-elimination reactions regardless of the size of the 5′-*O* substituent. However, there was a known drawback in that the 3-benzyl group in the uracil skeleton cannot be removed by hydrogenolysis.[2,3]

This report describes the results of similar elimination reactions on 2′,3′-di-*O*-mesyl, 3′-*O*-mesyl-2′-*O*-tosyl, and 2′-*O*-mesyl-3′-*O*-tosyl derivatives of 1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**1**),[4] in which both the leaving groups are syn with respect to the base moiety, thus precluding cyclonucleoside formation. Further interesting situations foreseen for this series of compounds are that the sugar protons $H_{1'}$–$H_{4'}$, are all in β and trans relation to one of the leaving groups, suggesting various possible directions in β elimination, and that basic catalysts must attack, advantageously, from the less hindered bottom side of the nucleoside derivatives.

1-(5′-*O*-Benzoyl-β-D-lyxofuranosyl)uracil (**1**) was treated with 2 molar equiv of tosyl chloride to give the monotosylated compounds, 1-(5′-*O*-benzoyl-2′-*O*-tosyl-β-D-lyxofuranosyl)uracil (**2**) and 1-(5′-*O*-benzoyl-3′-*O*-tosyl-β-D-lyxofuranosyl)uracil (**3**) in 41 and 6% yield, respectively, presumably for steric reasons. Compounds **2** and **3** were crystals which included one molecule of methanol and acetone, respectively. In the nmr spectrum of **2** free of solvent, the signal of the anomeric proton appeared at δ 6.25 as a doublet with $J_{1',2'}$ = 6.8 Hz, while the resonance of $H_{2'}$ occurred at δ 5.3 as a doublet of doublets with $J_{1',2'}$ = 6.8 Hz and $J_{2',3'}$ = 4.7 Hz. The assignment of $H_{2'}$ was self-evident on the basis of a strong deshielding effect by the tosyl group, but was also confirmed by spin decoupling, since irradiation at δ 6.25 collapsed the signal at δ 5.3 to a doublet with a splitting of 4.7 Hz. Thus, the structure of **2** and therefore that of **3** was established.

The monotosylation of **1** is useful for elucidating the structure of the elimination products when another different leaving group is introduced into **2** or **3**. Hence, **2** was converted to 1-(5′-*O*-benzoyl-3′-*O*-mesyl-2′-*O*-tosyl-β-D-lyxofuranosyl)uracil (**4**) using the less bulky mesyl chloride. On treatment with excess sodium benzoate under relatively mild reaction conditions **4** gave the expected 1-(5′-*O*-benzoyl-3′-deoxy-2′-*O*-tosyl-β-D-*glycero*-pent-2′-enofuranosyl)uracil (**5**) as the sole product in 20% yield, 43% of the starting material being recovered. Some degree of resinification was also observed. The nmr spectrum of **5** is shown in Figure 1. The resonance pattern is quite similar to that of 1-(3′-deoxy-2′,5′-di-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil.[1] The

(1) T. Sasaki, K. Minamoto, and H. Suzuki, *J. Org. Chem.*, **38**, 598 (1973).
(2) N. Imura, T. Tsuruo, and T. Ukita, *Chem. Pharm. Bull.*, **16**, 1105 (1968).
(3) T. Kunieda and B. Witkop, *J. Amer. Chem. Soc.*, **93**, 3478 (1971).
(4) R. Fecher, J. F. Codington, and J. J. Fox, *ibid.*, **83**, 1889 (1961).

presence of a tosyl and not of a mesyl group in this compound and also the presence of the $H_{1'}$ signal in the nmr spectrum precluded a structure with a 1′,2′ double bond, while the presence of the $H_{4'}$ signal at an expected position of 5.15 ppm precluded a 3′,4′-didehydro structure. Reasons for the assignments of these signals are as described in detail in the previous paper.[1] Thus, the structure of **5** was unequivocally established.

Another elimination reaction of **4** was carried out using the same catalyst under relatively drastic conditions (3 hr at 120°) until the starting material disappeared, when 5′-*O*-benzoyl-3′-deoxy-2′-ketouridine (**6**) was obtained in 11% yield. The intervention of compound **5** was evidenced by thin layer chromatography as described in the Experimental Section. The ir spectrum of **6** showed the characteristic absorption at 1750 cm^{-1} for the sugar ketone.[5,6] On the other hand, 1-(5′-*O*-benzoyl-2′-*O*-mesyl-3′-*O*-tosyl-β-D-lyxofuranosyl)uracil (**7**) obtained from **3** reacted with sodium benzoate extremely rapidly to give **6** in 18% yield. In this case, the starting material **7** was almost completely consumed in 20 min at 100°. Although 2′,3′-didehydro nucleoside **8** must have intervened in this reaction, its detection by tlc was impossible.

This observation spurred us to examine a similar reaction on 1-(5′-*O*-benzoyl-2′,3′-di-*O*-mesyl-β-D-lyxofuranosyl)uracil (**9**). Compound **9** obtained from **1** reacted with sodium benzoate merely to give **6** in 21% yield. This reaction was also as rapid as in the case of **7** and did not premit detection of any intervening **8**. The unusual ease with which **5** or **8** can be converted to the keto nucleoside **6** is in contrast with the previous observations[1] on the elimination products from 2′,3′-di-*O*-mesyl-3-benzyluridine and its 5′-substituted analogs and suggests the presence of anchimeric assistance by the ionized base moiety.[7]

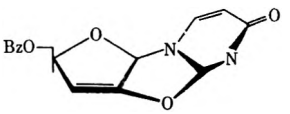
In the previous report,[1] the ammonia-catalyzed elimination reaction of 5′-*O*-benzoyl-2′,3′-di-*O*-mesyl-3-benzyluridine to 1-(3′-deoxy-2′-*O*-mesyl-β-D-*glycero*-pent-2′-enofuranosyl)-3-benzyluracil was described. With a view to converting **4** directly to the 5′-O-unsubstituted analog of **5** or **6**, compound **4** was heated with excess alcoholic ammonia to give, unexpectedly, 1-(2′-*O*-tosyl-β-D-lyxofuranosyl)uracil (**10**) as the sole product, which seems to have formed by simple debenzoylation and demesylation. The structural assignment is essentialy based on its nmr spectrum, in which the anomeric proton gave a doublet at δ 6.15 with $J_{1',2'}$ = 6.8 Hz, while the signal of $H_{2'}$, appeared at δ 5.25 as a doublet of doublets with $J_{1',2'}$ = 6.8 and $J_{2',3'}$ = 4.7 Hz. These coupling constants are identical with those for $H_{1'}$ and $H_{2'}$ in compound **2**.

Thus, a tendency for 2′-hydrogen abstraction was again proved in the β-elimination reactions of 1-β-D-lyxofuranosyluracil derivatives.[9] The facile formation of **6** is quite interesting, since this series of chemical modifications is reminiscent of the observation that 3′-deoxyadenosine (cordycepin) is formed from adenosine in cultures of *Cordyceps militaris*.[10] For this biological process, a 2′,3′-en-2′-ol formed *via* a trans elimination of a molecule of water from adenosine was proposed as an intermediate.[10]

(5) A. F. Cook and J. G. Moffatt, *J. Amer. Chem. Soc.*, **89**, 2697 (1967).

(6) U. Brodbeck and J. G. Moffatt, *J. Org. Chem.*, **35**, 3552 (1970).

(7) The reaction conditions used by us are more or less comparable with those under which 2,2,-anhydrouracil nucleosides were synthesized.[8] The transient formation of a 2,2′-anhydro-2′,3′-didehydro nucleoside (a) followed



a

by hydrolytic cleavage to give **6** might also be considered as far as a molecular model study is concerned. However, as one of the referees suggested, the nucleophilic substitution at an unsaturated 2′ carbon by uracil-2-carbonyl is unlikely. An interspacial repercussion between the ionized uracil-2-carbonyl and the electron-rich sulfonyl group seems to be the more probable reason for the formation of **6**.

(8) For examples, see (a) J. F. Codington, R. Fecher, and J. J. Fox, *J. Amer. Chem. Soc.*, **82**, 2794 (1960); (b) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964); (c) N. C. Yung and J. J. Fox, *J. Amer. Chem. Soc.*, **83**, 3060 (1961).

Experimental Section

All melting points are uncorrected. Electronic spectra were measured on a JASCO Model ORD/UV-5 spectrophotometer, TMS being used as an internal standard. In the case of hy-

(9) The generally low yields of **5** and **6** can be explained by the concomitant formation of resinous products, which stayed immobile at the start lines of tlc plates. It might be noted that we could not detect any other noticeable side products which were movable on the tlc plates.

(10) J. N. Davidson and W. E. Cohn, *Progr. Nucl. Acid Res. Mol. Biol.*, **5**, 298 (1967).

droxyl-containing substances, measurements after D_2O addition were also carried out. Mass spectra were measured by a Hitachi RMU-D double-focusing spectrometer operating at an ionization potential of 80 eV. Solid samples were ionized by electron bombardment after sublimation directly into the electron beam at 200°. Wakogel B-5 silica gel, supplied by the Wako Pure Chemical Industries, was used for thin layer chromatography.

1-(5′-O-Benzoyl-2′-O-tosyl-β-D-lyxofuranosyl)uracil (2) and 1-(5′-O-Benzoyl-3′-O-tosyl-β-D-lyxofuranosyl)uracil (3).—To a stirred, ice-cold solution of 1-(5′-O-benzoyl-β-D-lyxofuranosyl)-uracil (1) (1.28 g, 3.7 mmol) in anhydrous pyridine (12 ml) was added tosyl chloride (1.54 g, 9.1 mmol) in several portions. After standing overnight at room temperature, the mixture was poured into ice–water (150 ml) and the semisolid precipitate was filtered, dried on a porous plate, and crystallized from methanol to give 0.7 g of colorless needles of **2**. Thin layer chromatography on the filtrate indicated the presence of two substances in comparable amounts, one of which proved to be **2**. The filtrate was evaporated to a foam and triturated with acetone to give another crystalline substance, **3** (70 mg). The filtrate separated from **3** was submitted to preparative thin layer chromatography with the use of silica gel and a solvent mixture, chloroform–ethyl acetate (1:1), to give second crops of **2** and **3**. The combined crops of **2** were recrystallized from methanol to give 0.8 g (41%) of needles, which melted at 195–197° after effervescence at 125–130°, λ_{max}^{EtOH} 227 nm (ε 29,000) and 259 (11,100).

Anal. Calcd for $C_{23}H_{22}N_2O_9S \cdot CH_3OH$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.91; H, 4.70; N, 5.18.

A portion of the methanolate **2** was dissolved in hot acetone and the solvent was evaporated. This procedure was repeated three times to give a colorless powder, mp 195°, which was used for nmr measurement after drying in a desiccator under high vacuum: nmr (DMSO-d_6) δ 2.42 (3 H, s, methyl in the tosyl group), 4.2–4.7 (4 H, m, 2 $H_{5'}$ + $H_{4'}$ + $H_{3'}$), 5.3 (1 H, dd, $J_{1',2'}$ = 6.8, $J_{2',3'}$ = 4.7 Hz, $H_{2'}$), 5.6 (1 H, dd, $J_{5,6}$ = 8, $J_{5,NH}$ = 2.25 Hz, H_5), 6.25 (1 H, d, $J_{1',2'}$ = 6.8 Hz, $H_{1'}$), 6.30 (1 H, br s, OH, lost on D_2O addition), and 7.35–8.1 (10 H, m, H_6 and aromatic protons).

On the other hand, the combined crops of **3** were recrystallized from acetone to give 0.12 g (6%) of needles (acetonate of **3**), mp 168–170°, λ_{max}^{EtOH} 225 nm (ε 31,100) and 260 (12,400).

Anal. Calcd for $C_{23}H_{22}N_2O_9S \cdot CH_3COCH_3$: C, 55.71; H, 5.04; N, 5.00. Found: C, 55.60; H, 4.92; N, 4.91.

A portion of the acetonate was repeatedly evaporated with hot chloroform to give acetone-free compound **3** as a foam, which was used for nmr measurement after drying: nmr (DMSO-d_6) δ 2.38 (3 H, s, methyl in the tosyl group), 4.45 (4 H, m, 2 $H_{5'}$ + $H_{2'}$ + $H_{4'}$), 5.35 (1 H, m, $H_{3'}$, partially merged with H_5 signal), 5.51 (1 H, dd, $J_{5,6}$ = 8, $J_{5,NH}$ = 2.25 Hz, H_5), 6.1 (1 H, d, OH, lost on D_2O addition), 6.15 (1 H, d, $J_{1',2'}$ = 6 Hz, $H_{1'}$), and 7.3–8.2 (10 H, m, aromatic protons containing H_6).

1-(5′-O-Benzoyl-3′-O-mesyl-2′-O-tosyl-β-D-lyxofuranosyl)uracil (4).—To a suspension of acetone-free **2** (502 mg, 1.02 mmol) in dry pyridine (2 ml) was added mesyl chloride (0.1 ml, 1.28 mmol) and the mixture was stirred at room temperature overnight. It was then poured into ice–water (100 ml) to give a precipitate which was filtered, dried on a porous plate, and recrystallized from methanol to give colorless needles (**4**) which gradually melted between 131 and 138° dec: yield 430 mg (72%); λ_{max}^{EtOH} 227 nm (ε 27,900) and 259 (9960); nmr ($CDCl_3$) δ 2.37 (3 H, s, methyl in the tosyl group), 3.12 (3 H, s, mesyl), 4.59 (3 H, br s, 2 $H_{5'}$ + $H_{4'}$), 5.55 (2 H, m, $H_{2'}$ and $H_{3'}$), 5.65 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 6.28 (1 H, d, $J_{1',2'}$ = 4.5 Hz, $H_{1'}$), and 7.1–8.1 (10 H, m, aromatic protons containing H_6).

Anal. Calcd for $C_{24}H_{24}N_2O_{11}S_2$: C, 49.66; H, 4.17; N, 4.83. Found: C, 49.78; H, 4.26; N, 4.91.

1-(5′-O-Benzoyl-3′-deoxy-2′-O-tosyl-β-D-*glycero*-pent-2′-enofuranosyl)uracil (5).—A mixture of 1-(5′-O-benzoyl-3′-O-mesyl-2′-O-tosyl-β-D-lyxofuranosyl)uracil (**4**) (0.3 g, 0.518 mmol) and sodium benzoate (0.3 g, 2.1 mmol) in dry DMF (5 ml) was heated at 90° for 30 min under stirring and poured into ice–water (100 ml). The precipitate was filtered, dried on a porous plate, and recrystallized from methanol to give pale-yellow needles, which were collected by filtration (0.13 g, 43%, mp 120–135°) and identified with **4** by ir and uv spectroscopy. The filtrate was concentrated and submitted to preparative thin layer chromatography with the use of a silica gel plate and a solvent mixture, chloroform–ethyl acetate (2:1), to give 50 mg (20%) of **5**: mp 149–151° (methanol); λ_{max}^{EtOH} 227 nm (ε 26,300) and 258 (8900);

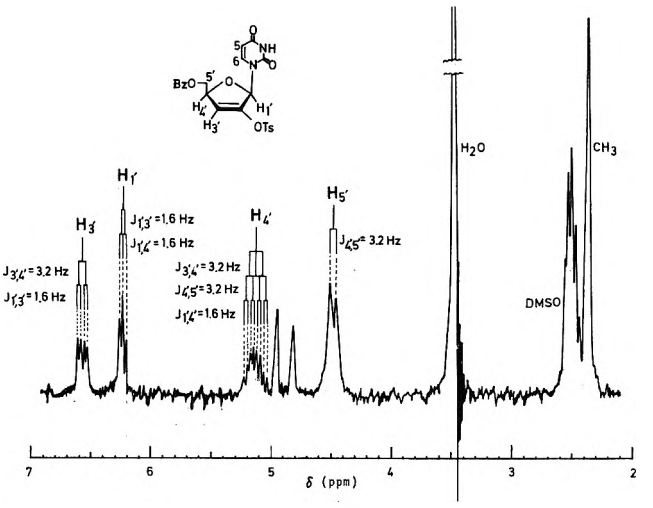


Figure 1.—Nuclear magnetic resonance spectrum of 1-(5′-O-benzoyl-3′-deoxy-2′-O-tosyl-β-D-*glycero*-pent-2′-enofuranosyl)-uracil in DMSO-d_6 + D_2O at 60 MHz.

nmr (DMSO-d_6) δ 2.4 (3 H, s, methyl in the tosyl group), 4.50 (2 H, d, $J_{4',5'}$ = 3.2 Hz, 5′-CH_2), 4.90 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 5.15 (1 H, octet, $J_{1',4'}$ = 1.6 Hz, $J_{3',4'}$ = $J_{4',5'}$ = 3.2 Hz, $H_{4'}$), 6.25 (1 H, t, $J_{1',3'}$ = $J_{1',4'}$ = 1.6 Hz, $H_{1'}$), 6.58 (1 H, dd, $J_{1',3'}$ = 1.6, $J_{3',4'}$ = 3.2 Hz, $H_{3'}$), and 7.8–8.0 (10 H, m, aromatic protons); mass spectrum *m/e* 373 (M − base), 362 (M − BzOH), 349, 251, and 207.

Anal. Calcd for $C_{23}H_{20}N_2O_8S$: C, 57.02; H, 4.16; N, 5.78. Found: C, 56.77; H, 4.25; N, 5.93.

5′-O-Benzoyl-3′-deoxy-2′-ketouridine (6).—A mixture of 1-(5′-O-benzoyl-3′-O-mesyl-2′-O-tosyl-β-D-lyxofuranosyl)uracil (**4**) (1.14 g, 1.95 mmol) and sodium benzoate (1.3 g, 9.1 mmol) in DMF (25 ml) was stirred at 120°. An aliquot of the reaction mixture was taken every 20 min and examined by tlc with the use of silica gel and a solvent mixture, chloroform–ethyl acetate (2:1). The appearance of **5** as the single product was indicated during the first 20 min, following which **5** gradually disappeared with the appearance of a new product which moved on the tlc plates slightly slower than the former. Concomitant increase in resinous products was also indicated by the deep coloration of the mixture. After 1 hr no spot for **5** was observed on tlc. After 3 hr, during which most of the starting material was consumed, the black mixture was evaporated *in vacuo* to give a tarry residue, which was triturated with water (30 ml) and extracted with ethyl acetate (200 ml). The extract obtained after evaporation of the solvent was left at room temperature with a small amount of ethanol to give a crystalline substance, which was collected by filtration. Preparative thin layer chromatography on the filtrate gave a small amount of second crop. The combined product was crystallized from methanol to give 70 mg (11%) of colorless granules: mp 195°; ir (KBr) $\nu_{C=O}$ 1680, 1705, and 1750 cm^{-1}; λ_{max}^{EtOH} 228 nm (ε 16,500) and 258 (11,400); nmr (DMSO-d_6) δ 2.8 (2 H, t, J = 8 Hz, 5′-CH_2), 4.5 (2 H, q, J = 7.8 and 4 Hz, 3′-CH_2), 5.0 (1 H, complex multiplet, $H_{4'}$), 5.6 (1 H, s, $H_{1'}$), 5.65 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), and 7.2–8.1 (10 H, aromatic protons containing H_6); mass spectrum *m/e* 330 (M^+), 219 (M − base), 195 (M − $BzOCH_2$), and 208 (M − BzOH).

Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.26; H, 4.41; N, 8.48.

1-(5′-O-Benzoyl-2′-O-mesyl-3′-O-tosyl-β-D-lyxofuranosyl)uracil (7).—To a stirred ice-cold solution of the acetonate of **3** (0.35 g, 0.69 mmol) in anhydrous pyridine (3 ml) was added mesyl chloride (0.08 ml, 1 mmol) and the mixture was left at 0° overnight. The brown-colored solution was mixed with ethanol (1 ml), left at room temperature for 1 hr, and evaporated *in vacuo*. The residual paste was extracted with ethyl acetate (2 × 50 ml) in the presence of water (10 ml). The combined ethyl acetate solution was then washed with 5% sodium bicarbonate (10 ml) and water, and dried with sodium sulfate. Evaporation of the solvent gave 360 mg (90%) of a homogeneous foam (**7**). A portion of this material was further purified for elemental analysis by thin layer chromatography using silica gel and chloroform–ethyl acetate (1:1).

Anal. Calcd for $C_{24}H_{24}N_2O_{11}S_2$: C, 49.66; H, 4.17; N, 4.83. Found: C, 49.91; H, 4.33; N, 5.11.

Reaction of 1-(5′-*O*-Benzoyl-2′-*O*-mesyl-3′-*O*-tosyl-β-D-lyxofuranosyl)uracil (7) with Sodium Benzoate.—A mixture of 7 (360 mg, 0.62 mmol) and sodium benzoate (270 mg, 1.86 mmol) in DMF (4 ml) was stirred at 100° for 20 min. Thin layer chromatography with an aliquot of the reaction mixture indicated one main product and essentially no starting material. The mixture was poured into ice–water (50 ml) and extracted with ethyl acetate (2 × 50 ml). The ethyl acetate solution was dried with sodium sulfate and evaporated to a foam, which was submitted to preparative thin layer chromatography using silicic acid and chloroform–ethyl acetate (1:1) to give 37 mg (18%) of a crystalline substance, mp 192–194°. Its identity with 6 was confirmed by ir and uv spectroscopy.

1-(5′-*O*-Benzoyl-2′,3′-di-*O*-mesyl-β-D-lyxofuranosyl)uracil (9).—A solution of 1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (1) (0.32 g, 0.92 mmol) in dry pyridine (3 ml) was treated with mesyl chloride (0.17 ml, 2.2 mmol) at 0° overnight and the mixture was worked up as in the case of compound 7. The finally obtained pasty product contained trace amounts of impurities as indicated by tlc. Preparative thin layer chromatography with the use of silica gel and ethyl acetate as developer gave 0.36 g (78%) of a homogeneous foam, which was used as such for the next elimination reaction, nmr ($CDCl_3$) δ 3.15 (6 H, d, two mesyl).

Reaction of 1-(5′-*O*-Benzoyl-2′,3′-di-*O*-mesyl-β-D-lyxofuranosyl)uracil (9) with Sodium Benzoate.—A mixture of 9 (0.36 g, 0.72 mmol) and sodium benzoate (270 mg, 3.6 molar equiv) in DMF (5 ml) was stirred at 110°. Thin layer chromatography with the use of an aliquot of the reaction mixture indicated that over 50% of the starting material was converted to another faster moving substance after 15 min of reaction. After 35 min, the rest of the starting material was remarkably reduced with the appearance of a slight amount of a new product and with increase in resinous substances. It took totally 2 hr of stirring for the complete disappearance of the starting material. The mixture was now evaporated *in vacuo* as far as possible and the residue was extracted with ethyl acetate (4 × 30 ml) in the presence of water (15 ml). The ethyl acetate solution was dried with sodium sulfate and evaporated to a paste, which was submitted to preparative thin layer chromatography with the use of silica gel and ethyl acetate. Elution of the main band with ethyl acetate gave a crystalline substance, mp 192–193° (50 mg, 21%), whose identity with an authentic sample of 6 was confirmed by ir spectra and the mixture melting point determination.

1-(2′-*O*-Tosyl-β-D-lyxofuranosyl)uracil (10).—Compound 4 (0.3 g, 0.517 mmol) was combined with saturated ethanolic ammonia (16 ml) in a pressure tube, which was heated in an oil bath at 100–105° for 16 hr. After cooling, the solvent and excess ammonia were evaporated and the solid residue was crystallized from methanol to give 94 mg (45%) of colorless needles of **10**: mp 259–261°; λ_{max}^{EtOH} 225 nm (ε 14,000) and 260 (9100); nmr (DMSO-d_6) δ 2.43 (3 H, s, methyl in the tosyl group), 3.6 (3 H, br m, 2 $H_{5'}$ + $H_{4'}$), 4.15 (1 H, dd, $J_{2',3'}$ = 4.7, $J_{3',4'}$ = 3.7 Hz, $H_{3'}$), 5.25 (1 H, dd, $J_{1',2'}$ = 6.8, $J_{2',3'}$ = 4.7 Hz, $H_{2'}$), 5.6 (1 H, d, $J_{5,6}$ = 8 Hz, H_5), 6.15 (1 H, d, $J_{1',2'}$ = 6.8 Hz, $H_{1'}$), and 7.2–7.8 (5 H, m, aromatic protons containing H_6).

Registry No.—**1**, 38359-50-1; **2**, 38359-51-2; **3**, 38359-52-3; **4**, 38359-53-4; **5**, 38359-54-5; **6**, 38359-55-6; **7**, 38431-66-2; **9**, 38431-65-1; **10**, 38359-56-7.

The Use of Papain in Resolving Racemic *N*-(Alkoxycarbonyl)glycines and *N*-(Alkoxycarbonyl)alanines That Contain Small Alkoxy Groups[1]

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Papain promoted very rapid reactions at pH 4.5 between small molecular weight *N*-(alkoxycarbonyl)amino acids and *m*- or *p*-anisidine. Hindrance toward reactions was evident when ortho-substituted anilines were used. For *N*-(*tert*-butoxycarbonyl)- and *N*-(*tert*-pentyloxycarbonyl)-DL-alanines, resolution amounted to ~95 to 100%. A few *N*-(alkoxycarbonyl)glycines were used in which the asymmetric center was placed in the alkoxycarbonyl group. These groups included (*R,S*)-*N*-(*sec*-butoxycarbonyl), (*R,S*)-*N*-(1-methylbutoxycarbonyl), (*R,S*)-*N*-(2-methylbutoxycarbonyl), and (*S*)-*N*-(2-methylbutoxycarbonyl). A preference for one enantiomer was shown for each racemic mixture investigated. Anisidides formed from (*R,S*)-*N*-(2-methylbutoxycarbonyl)glycine displayed a preponderance of the *S* enantiomer to the extent of ~56% after an early period of incubation. This conclusively demonstrated the ability of papain to exert a modest stereochemical control, even though the asymmetric center is removed four or five atoms away from its usual position in *N*-acyl-DL-amino acids.

N-(*tert*-Butoxycarbonyl)- and *N*-(*tert*-pentyloxycarbonyl)amino acids have been used in solid-phase peptide syntheses of bradykinin,[2] ferredoxin,[3] ribonuclease,[4] and human growth hormone.[5] Although papain has been used to catalyze the synthesis of anilides of many *N*-acylamino acids,[6] anilides of low molecular weight *N*-(alkoxycarbonyl)amino acids have not been prepared in this manner. It was the purpose of the present research to explore the use of papain as a catalyst for reactions between a few substituted anilines and such *N*-acylamino acids, which contain only four or five carbons in the alkoxy group. By placing an asymmetric center in the alkoxy group of *N*-(alkoxycarbonyl)glycines, the zone of stereochemical control exerted by papain would be substantially altered and a considerably different perspective would therefore be achieved.

Four principal objectives were attained through this research. First, the use of *N*-*tert*-alkoxycarbonyl derivatives of glycine, DL-alanine, and L-alanine permitted a comparison to be made of their relative rates of reactions with known rates of more familiar *N*-acyl derivatives of these same amino acids. Second, by careful selection of ortho-, meta-, and para-substituted anilines, the effect of position and kind of substituent on the ability of this type of base to participate in such reactions was disclosed. Third, the extent of resolution of racemic *N*-(alkoxycarbonyl)amino acids was revealed through comparison of specific rotations of their reaction products with specific rotations of corresponding products from single enantiomers of the given *N*-acyl-

(1) Presented before the Pacific Conference on Chemistry and Spectroscopy, Tenth Pacific Meeting, Seventh Western Regional Meeting, Anaheim, Calif., Oct 19, 1971.

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(5) (a) C. H. Li and D. Chung, *Int. J. Protein Res.*, **3**, 73 (1971); (b) W. Danho and C. H. Li, *ibid.*, **3**, 81, 99 (1971); (c) K. Kovacs, Y. Kovacs-Petres, and C. H. Li, *ibid.*, **3**, 93 (1971).

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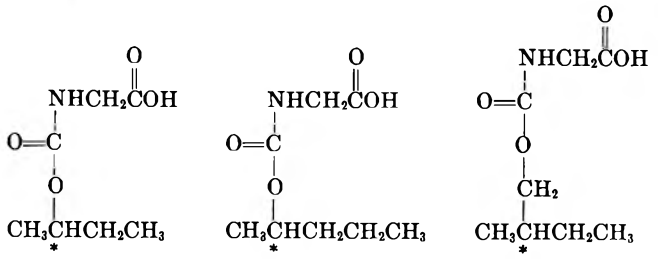
amino acids. Fourth, the most significant feature of this investigation was to subject (*R,S*)-*N*-(*sec*-butoxycarbonyl)glycine (I), (*R,S*)-*N*-(1-methylbutoxycarbonyl)glycine (II), and (*R,S*)-*N*-(2-methylbutoxycarbonyl)glycine (III) to papain-catalyzed reactions with



I II III

m- and *p*-anisidines. The asymmetric center (*) was removed either four or five atoms away from the customary position next to the carboxyl group.

Results and Discussion

An interpretation of the results of these and other experiments has been made easier because many obscure points concerning papain have been cleared up. In other instances, the obscurity has increased and requires clarification by further research. Numerous experiments have progressively exposed the nature of papain's catalytic activity and the types of reactions that papain can foster. Its chirality and conformation provide features for unique stereochemical control. It is known that the mercapto group, –SH, of cysteine residue 25, counted from the amino terminal, can form thio esters, –SCOR,[7,8] on exposure to appropriate substrates. These include *N*-acylamino acids,[9] esters,[10] amides,[11] polypeptides,[12] or proteins.[13] A dilobal, spheroidal conformation[14] has emerged from an elucidation of the complete primary structure of the 212 amino acid residues of papain, combined with a rigorous X-ray analysis. This has afforded a more sophisticated basis for probing into many of the intimate details of its activity.

Kinetic experiments[7,8] have shown that the enzyme–substrate, thio ester, complex is formed in essentially two phases. Actually, the dynamic, atomic interactions would obviously be much more intricate, owing to the variety of hydrophobic, ionic, and hydrogen-bonding regions available. The initial phase involves noncovalent binding (ES) of a substrate (S) to the enzyme (E). During this phase, the chief stereochemical preference is exhibited, often toward a choice of positions of attack within diastereoisomeric reactants, or else toward one isomer of a mixture of stereoisomers.[6,12,15] After the enzyme exerts this control, the main complexities of catalytic action of the second phase occur in two steps that require breakage and formation of covalent bonds in each step. The first step produces the thio ester (ES′) at the mercapto group of the enzyme,[7,8] while the second step[9] yields the principal reaction product (BS′). The acyl portion of the original substrate is thereby transferred to the enzyme and then to the reaction product. The progress of events can be expressed in the following abbreviated form[7,8,16] where B is the Lewis base.

$$E + S \rightleftharpoons ES \longrightarrow ES' \xrightarrow{B} E + BS'$$

The substrate (S) must penetrate a crevice between the two lobes of the enzyme, where the mercapto group resides. The Lewis base can be water, during hydrolytic reactions,[12] an alcohol,[17] or an amino base such as aniline or substituted anilines,[6] which were employed in the current research. A generalized, tentative mechanism[18] is given in Scheme I.

Papain readily resolved *N*-(*tert*-alkoxycarbonyl)-DL-alanines. The percentage of L enantiomer in the product varied from ~95 to 100%, as listed in Table I.

TABLE I
PER CENT OF L ENANTIOMER IN THE PRODUCTS FORMED FROM SUBSTITUTED ANILINES AND *N*-(ALKOXYCARBONYL)-DL-ALANINES

Product	L Enantiomer, %
N-(*tert*-Butoxycarbonyl)alanine *p*-anisidide	95.3
N-(*tert*-Pentyloxycarbonyl)alanine *m*-anisidide	100.0
N-(*tert*-Pentyloxycarbonyl)alanine *p*-anisidide	99.3
N-(*tert*-Pentyloxycarbonyl)alanine *o*-fluoroanilide	99.7

Other details of these reactions are summarized in Table II. Space filled models[15b] have been used in conjunction with X-ray analysis of a bound, iodinated, competitive inhibitor, namely *N*-(*tert*-butoxycarbonyl)-L-*p*-iodophenylalanyl-L-leucine, as an excellent means for exposure of stereochemical control. Since the position of the iodine can be located, and since the carboxyl of this substrate must form a thio ester with the –SH of the enzyme, other features were easily inferred from the models. These included antiparallel, pleated sheet or β-structure types of interactions through peptide hydrogen bonding between the enzyme and this substrate. For racemic *N*-acylalanines, an L configuration is decidedly preferred by the enzyme because the α-CH of the substrate normally contacts the β-CH_2– of cysteine residue 25 of the enzyme. A concurrent proper disposition of the substrate carboxyl toward the –SH of cysteine residue 25 of papain and simultaneous hydrogen bonding at that carboxyl by the protonated imidazole ring of histidine residue 159 are necessary, as formulated in Scheme I. The α-CCH_3 of the D enantiomer largely inhibits such simultaneous contacts with the enzyme, thus explaining the stereochemical control exerted by the enzyme during resolutions of such substrates. From these well-chosen

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(15) (a) A. Berger and I. Schechter, *Phil. Trans. Roy. Soc. London*, **B257**, 249 (1970); (b) A. Berger, I. Schechter, H. Benderly, and N. Kurn, *Proc. Eur. Symp. Peptide, 10th*, 290 (1971).
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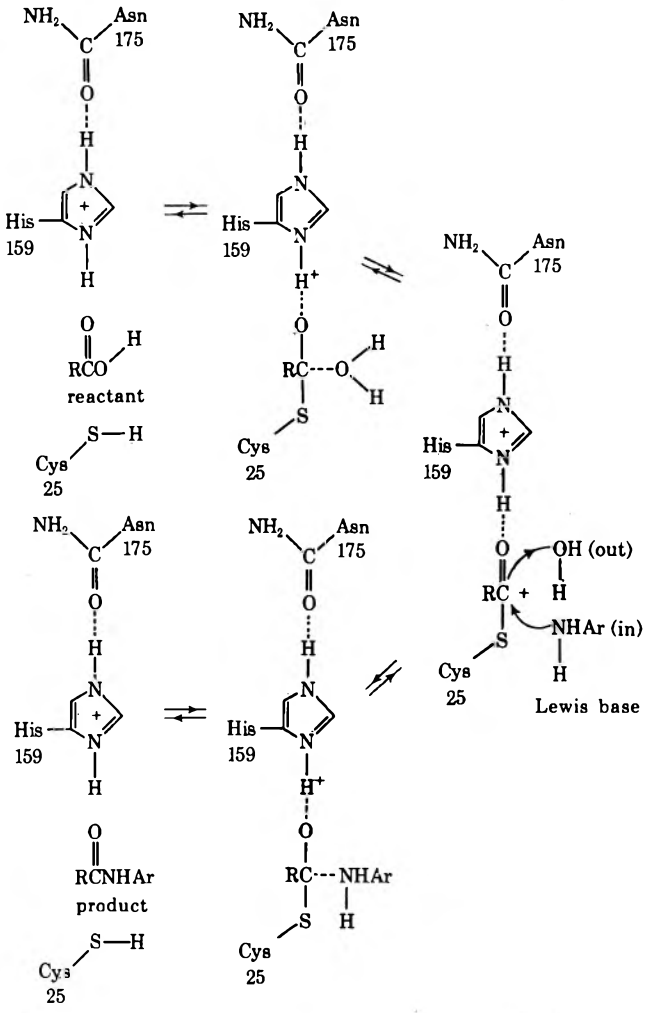
(17) A. N. Glazer, *J. Biol. Chem.*, **241**, 3811 (1966).
(18) J. N. Drenth, J. N. Jansonius, R. Koekoek, L. A. A. Sluyterman, and B. G. Wolthers, *Phil. Trans. Roy. Soc. London*, **B257**, 231 (1970).

SCHEME I[a]

MECHANISM FOR PAPAIN CATALYSIS OF THE FORMATION OF ANILIDES OF *N*-ACYLAMINO ACIDS

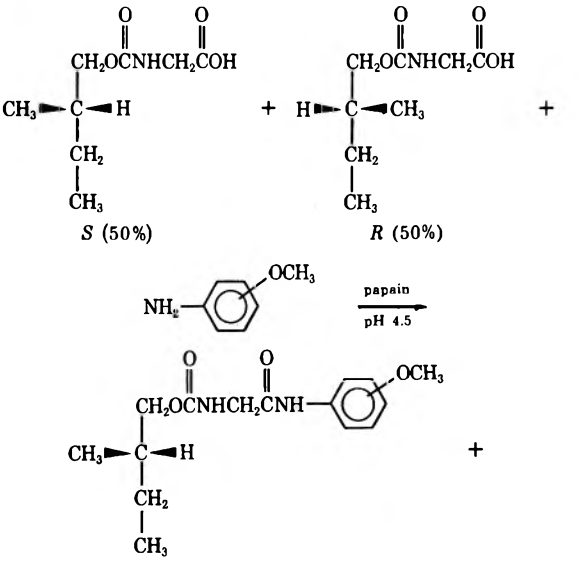


[a] More generalized terms: (a) in carbonyl-containing reactant, RC(=O)X, X can be –OH, –OR′, –NH_2, –NHR″ (a peptide or protein). (b) Lewis base, :B, can be :$\ddot{O}H_2$, :$\ddot{O}$HR, :NH_2Ar, :NH_2NHAr, :NH_2NHCOAr, :NH_2N$\ddot{H}SO_2$Ar.

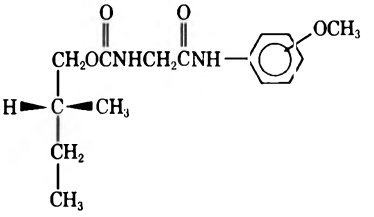
experiments, much delineation of details has been possible. However, more intimate analyses of complex systems such as enzymes could certainly benefit through development of more revealing cybernetic approaches.

o-Anisidine and *o*-aminophenol did not give a reaction product, while *o*-fluoroaniline reacted very slowly. It would appear that an ortho substituent is sterically unfavorable. Reduction in the basicity of the amino group ordinarily decreases the reaction velocity of the substituted aniline owing to distortion of the nonbonding orbital in a manner that makes the electron pair less available for reaction. The same factors that increase the basicity of the amine, and therefore its reactivity in the unprotonated form, also decrease the concentration of the unprotonated amine added to the solution. Therefore the potential reaction velocity is reduced by formation of the conjugate acid at the acidic pH used for these experiments. The importance of this factor can readily be seen by inspection of the pK_a values for aniline, *o*-, *m*-, and *p*-anisidines, *o*-fluoroaniline, and *o*-aminophenol, which are respectively 4.6, 4.6, 4.2, 5.3, 3.2, and 4.8.[19] The concentration of unprotonated *o*-fluoroaniline would be more than 2 times as great as that of the unprotonated form of *o*-anisidine under comparable conditions of concentration of total base added at the same pH of 4.5.

In all instances, when (*R*,*S*)-*N*-(alkoxycarbonyl)-glycines were used as the reactants, at least moderate resolution was observed during the formation of the *m*-anisidides and *p*-anisidides. For (*R*,*S*)-*N*-(2-methylbutoxycarbonyl)glycine, the extent of resolution, as shown by specific rotation of the product in pyridine after a 3-hr incubation period, could be determined by replacement of the racemic reactant with (*S*)-*N*-(2-methylbutoxycarbonyl)glycine and then determination of the specific rotation of the *S* enantiomeric product. The percentage composition of the nonracemic products was calculated by the method previously reported.[20]



(*S*)-*N*-(2-methylbutoxycarbonyl)glycine
m-anisidide (55.8%)
p-anisidide (54.6%)



(*R*)-*N*-(2-methylbutoxycarbonyl)glycine
m-anisidide (44.2%)
p-anisidide (45.4%)

Papain is not able to distinguish as readily between enantiomers of these *N*-acylglycines when the asymmetric center is located in the *N*-alkoxycarbonyl group. Better recognition occurs when the asymmetric carbon is closer to the carboxyl group, as displayed by the experimental results. When the center is removed farther from the carboxyl, the control is probably chiefly through hydrophobic contact of the *N*-alkoxycarbonyl group with a hydrophobic region of the enzyme. Increased hydrolysis rates for esters of *N*-(benzyloxycarbonyl)amino acids, as compared with *N*-acetyl

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(20) J. L. Abernethy, E. Albano, and J. Comyns, *J. Org. Chem.*, **36**, 1580 (1971).

TABLE II

PRODUCTS FROM N-(*tert*-ALKOXYCARBONYL)AMINO ACIDS AND SUBSTITUTED ANILINES FORMED BY PAPAIN-CATALYZED REACTIONS

Registry no.	Compd	Mp, °C	$[\alpha]^{23}D$ in Pyridine	N, %
34917-97-0	*N*-(*tert*-Butoxycarbonyl)glycine *m*-anisidide *t*-BOC-gly *m*-A[a]	109–110	Symmetric	Calcd: 9.99 Found: 9.65
34885-75-1	*N*-(*tert*-Butoxycarbonyl)glycine *p*-anisidide *t*-BOC-gly *p*-A	146–147	Symmetric	Calcd: 9.99 Found: 10.12
34885-76-2	*N*-(*tert*-Pentyloxycarbonyl)glycine *m*-anisidide *t*-POC-gly *m*-A	122–123	Symmetric	Calcd: 9.51 Found: 9.51
34885-77-3	*N*-(*tert*-Pentyloxycarbonyl)glycine *p*-anisidide *t*-POC-gly *p*-A	82–83	Symmetric	Calcd: 9.51 Found: 9.68
34885-78-4	*N*-(*tert*-Butoxycarbonyl)-L-alanine *m*-anisidide *t*-BOC-L-ala *m*-A	145–146	−67.9	Calcd: 9.51 Found: 9.38
	N-(*tert*-Butoxycarbonyl)alanine[b] *m*-anisidide *t*-BOC-ala *m*-A	144–146	−61.5	Mixture mp, no depression
34885-79-5	*N*-(*tert*-Pentyloxycarbonyl)-L-alanine *m*-anisidide *t*-POC-L-ala *m*-A	133–134	−63.5	Calcd: 9.08 Found: 8.90
	N-(*tert*-Pentyloxycarbonyl)alanine[b] *m*-anisidide *t*-POC-ala *m*-A	130–132	−63.5	Mixture mp, no depression
34885-80-8	*N*-(*tert*-Pentyloxycarbonyl)-L-alanine *p*-anisidide *t*-POC-L-ala *p*-A	102–104	−61.9	Calcd: 9.08 Found: 9.19
	N-(*tert*-Pentyloxycarbonyl)alanine[b] *p*-anisidide *t*-POC-ala *p*-A	102–103	−61.0	Calcd: 9.08 Found: 9.18
34885-81-9	*N*-(*tert*-Pentyloxycarbonyl)-L-alanine *o*-fluoroanilide *t*-POC-L-ala *o*-F	128–129	−68.4	Calcd: 9.45 Found: 9.66
	N-(*tert*-Pentyloxycarbonyl)alanine[b] *o*-fluoroanilide *t*-POC-ala *o*-F	125–126	−68.0	Mixture mp 125–126°

[a] Abbreviations used in the Experimental Section. [b] Products from *N*-acyl-DL-alanine often contain a small amount of the D enanticmer.

derivatives,[21] have been attributed to better hydrophobic bonding. Intimate details of hydrophobic bonding have been possible, by use of a molecular model, in connection with the previously mentioned iodinated inhibitor.[15b] For example, the α-CR side chain of the L-leucine residue, the iodinated phenyl group of the *p*-iodo-L-phenylalanyl residue, and the *N*-*tert*-butoxycarbonyl radical contact specific, but different, hydrophobic regions of the enzyme. Furthermore, insertion of an L-phenylalanyl residue into special polypeptides has shown that the phenyl group exerts powerful hydrophobic bonding with the enzyme, in such a manner that the enzyme attacks the polypeptide[15] at the carbonyl of a residue next to that phenylalanyl residue to form the thio ester intermediate, -SCOR, during hydrolysis. The R contains the remainder of the residue next to the phenylalanyl residue, and then the phenylalanyl residue in sequence.

The rigorous X-ray analysis of papain[14] immediately recognized the histidine residue 159 to be in juxtaposition across the dilobal region from the -SH group. The catalytic activity of the serine enzyme, α-chymotrypsin,[22] had been explained by a coordinated action between the serine residue -OH, which was acylated, and the imidazole ring of the histidine residue. There was hesitancy in the instance of papain to incorporate the protonated imidazole ring of histidine residue 159 because a nonenzymic imidazole ring of histidine did not have an appropriate pK_a value. When related to various other factors of the total primary structure and conformation of papain, the difficulty could be at least partially removed.[14] The present research has therefore been related to current information concerning papain. It has been conclusively demonstrated that the chirality of papain can bring about resolutions of racemic *N*-acylamino acids, even though the asymmetric center is at a considerable distance from the carboxyl group.

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(22) R. E. Dickerson and I. Geis, "The Structure and Action of Proteins," Harper and Row, New York, N. Y., 1969, p 83.

Experimental Section

Activation of Papain.—Papaya latex, imported from the Congo region of Africa, was extracted, activated, and dried as described previously,[20] with the exception that 400 ml of distilled water was used for each 100-g sample, rather than 100 ml.

***N*-Acylamino Acids.**—Many of the compounds are available from the Protein Research Foundation of Osaka University, Osaka, Japan. Dr. Shumpei Sakakibara, Director of this Foundation, cooperated in the preparation of *N*-(*tert*-pentyloxycarbonyl)-DL-alanine. Synthesis of this compound follows the general procedure which employs *tert*-pentyl chloroformate, formed from phosgene and *tert*-pentyl alcohol.[23] The ethyl ester was treated with *tert*-pentyl chloroformate in the presence of pyridine, followed by saponification[24] to the *N*-acylamino acid. *N*-(*tert*-Butoxycarbonyl)-DL-alanine was prepared[25] by the Fox Chemical Co. of Los Angeles. These data are pertinent. *N*-(*tert*-Pentyloxycarbonyl)-DL-alanine had mp 105–106°. *Anal.* Calcd: N, 6.89. Found: N, 6.86. *N*-(*tert*-Butoxycarbonyl-DL-alanine had mp 111–112°. *Anal.* Calcd: N, 7.40. Found: N, 7.50.

The four *N*-(alkoxycarbonyl)glycines were synthesized in cooperation with Dr. Shumpei Sakakibara, starting with (*R,S*)-2-butanol, (*R,S*)-2-pentanol, (*R,S*)-2-methyl-1-butanol, and (*S*)-2-methyl-1-butanol, $[\alpha]^{20}D$ −4.5° (neat). The alkyl chloroformates of these alcohols,[26–29] were prepared with excess liquid

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(24) S. Sakakibara, M. Shin, M. Fujino, Y. Shinonishi, S. Inoye, and N. Inuka, *Bull. Chem. Soc. Jap.*, **38**, 1522 (1965).

(25) (a) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis," W. H. Freeman, San Francisco, Calif., 1969; (b) A. Marglin and R. B. Merrifield, *J. Amer. Chem. Soc.*, **88**, 5051 (1966).

(26) K. H. Meyer and Y. Go., *Helv. Chim. Acta*, **17**, 1488 (1934).

(27) F. C. McKay and N. F. Albertson, *J. Amer. Chem. Soc.*, **79**, 4686 (1957).

(28) A. C. Chibnal and P. F. Spahr, *Biochem. J.*, **68**, 135 (1958).

(29) S. Sakakibara, Director, Protein Research Foundation, Osaka University, Osaka, Japan, private communications (1970).

phosgene, in the cold, with subsequent removal of excess phosgene under reduced pressure, and were then treated with glycine[26,28] or ethyl glycinate.[24] The product from glycine was acidified with a slight excess of sulfuric acid, extracted into ethyl acetate, dried over anhydrous sodium sulfate, and evaporated at low temperature. The product from ethyl glycinate was first saponified and then worked up similarly. Since these *N*-acylamino acids were oils, they were converted into the dicyclohexylammonium salts by reaction with dicyclohexylamine dissolved in ether.[24] These follow with their properties: (*R,S*)-*N*-(*sec*-butoxycarbonyl)-glycine DCHA, mp 128–129°, % N calcd 7.86 and found 7.55; (*R,S*)-*N*-(1-methylbutoxycarbonyl)glycine DCHA, mp 121.5–123°, % N calcd 7.56 and found 7.70; (*R,S*)-*N*-(2-methylbutoxycarbonyl)glycine DCHA, mp 121–122°, % N calcd 7.56 and found 7.31; (*S*)-*N*-(2-methylbutoxycarbonyl)glycine DCHA, mp 118–119.5°, % N calcd 7.56 and found 7.51.

Isolation of *N*-(Alkoxycarbonyl)glycines from Their Dicyclohexylammonium Salts.—The method was a modification of the directions outlined by the Protein Research Institute of Osaka University, Osaka, Japan. Ten grams of the powdered salt was placed in a separatory funnel with 100 ml of ethyl acetate and shaken for several minutes. Then, for each equivalent of salt there was added 1.2 equiv of 1 *N* H_2SO_4. The mixture was shaken until all of the salt had dissolved. The ethyl acetate layer was separated and the aqueous layer was extracted three more times, with the same volume of ethyl acetate each time. The combined ethyl acetate extracts were then washed once with about 25 ml of a saturated sodium chloride solution. Suction filtration was necessary to remove a small amount of insoluble precipitate. After separation of the ethyl acetate layer, it was dried over anhydrous sodium sulfate. The first addition of anhydrous salt produced an aqueous layer in contact with hydrated salt. Suction filtration of the entire mass was followed by separation of the ethyl acetate layer from the aqueous layer. More anhydrous sodium sulfate was added to the ethyl acetate layer and the mixture was shaken once more. The solid was removed by filtration and the ethyl acetate filtrate was placed over anhydrous sodium sulfate. The solid residue from these last two filtrations were extracted with about 50 ml of ethyl acetate and each extract was removed by filtration. These combined filtrates were added to the ethyl acetate that had been placed over anhydrous sodium sulfate. The mixture was shaken for several minutes and allowed to stand overnight. The solution was then removed by suction filtration. The solid was extracted with 30 ml of ethyl acetate and the ethyl acetate was removed by filtration and combined with the dried ethyl acetate layer. Flash evaporation was carried out from a 100-ml flask that was rapidly rotated. More solution was added from time to time. The flask, which contained two small pieces of glass rod to prevent bumping, had been previously weighed. Evaporation was continued to constant weight. A nearly quantitative yield of *N*-acylamino acid resulted as an oil. It was used directly, by dissolving in buffer, for the papain-catalyzed reactions. This isolation was also used with *N*-(*tert*-pentyloxycarbonyl)-L-alanine DCHA, purchased from Osaka University Protein Research Foundation.

General Procedures for Papain-Catalyzed Reactions.—Nearly all reaction mixtures contained 0.01 mol of the *N*-acylamino acid, 0.0100 mol of the substituted aniline, 0.500 g of L-cysteine·HCl·H_2O, 0.500 g of activated papain, and 100 ml of buffer (0.50 *M* HOAc), pH 4.5, placed in a 125-ml glass-stoppered flask. Incubation was started immediately at 40°. Insoluble products were removed by filtration at the end of appropriate periods of time, after which incubation was continued. In the cases of *N*-(*tert*-pentyloxycarbonyl)glycine *p*-anisidide and *N*-(*tert*-butoxycarbonyl)glycine *m*-anisidide it was necessary to induce crystallization by stirring vigorously in an ice bath after the first period of incubation, to change the oily product to a solid before filtration. Subsequent incubation yielded beautifully crystalline products without such treatment. For the reactions between *N*-(*tert*-pentyloxycarbonyl)-DL-alanine and *o*-fluoroaniline, *m*-anisidine, and *p*-anisidine, 0.0200 mol of the *N*-acylamino acid was used rather than 0.0100 mol. The other details were identical. Results for *N*-(*tert*-alkoxycarbonyl)amino acids are summarized in Table II. *o*-Anisidine, *o*-aminophenol, and *o*-fluoroaniline failed to give satisfactory reactions when substituted glycines were used.

Weights of Precipitates from Reaction between *N*-(*tert*-Alkoxycarbonyl)alanines and Substituted Anilines.—Precipitates were collected by suction filtration after various periods of incubation. The filtrate was returned to the incubator. Then the precipitate was washed, on the suction filter, with about 200 ml of distilled water. The solid, on the filter paper, was removed and dried near the vent of a hood with the hood turned on, for a period of 24 hr and then weighed. Purification for nitrogen analyses and for optical rotations was accomplished by dissolving the precipitates in methanol, adding a small amount of decolorizing carbon, and filtering four times, with careful rinsing with methanol each time to remove the solid completely. For the racemic *N*-acylamino acids, only the products from the 0–24 hr periods of incubation were used for purification. Carefully cleaned filter flasks and Buchner funnels were used for each repetitive filtration. The final filtrate was placed in a Petri dish with a slightly elevated watch glass and dried by evaporation under the hood. This was followed by drying in a vacuum desiccator over phosphorus pentoxide.

Three groups of weights are given, A, B, and C. For the A group, incubation periods in sequence were 0–24 and 24–48 hr; for the B group 0–24 hr only; for the C group 0–6, 6–12, 12–24, and 24–48 hr. Abbreviations for names of precipitates are those given in Table II. Group A. *t*-BOC-gly *m*-A: 1.162 g, 0.057 g; *t*-BOC-gly *p*-A: 1.752 g, 0.397 g; *t*-POC-gly *m*-A: 1.438 g, 0.188 g; *t*-POC-gly *p*-A: 1.157 g, 0.056 g. Group B. *t*-BOC-L-ala *p*-A: 0.882 g; *t*-BOC-ala *p*-A: 1.350 g. Group C. *t*-POC-L-ala *m*-A: 1.584 g, 0.092 g, 0.197 g, 0.186 g; *t*-POC-ala *m*-A: 2.225 g, 0.474 g, 0.219 g, 0.093 g; *t*-POC-L-ala *p*-A: 1.674 g, 0.178 g, 0.089 g, 0.031 g; *t*-POC-ala *p*-A: 1.325 g, 0.456 g, 0.266 g, 0.125 g; *t*-POC-L-ala *o*-F: 0.226 g, 0.186 g, 0.179 g, 0.178 g; *t*-POC-ala *o*-F: 0.108 g, 0.032 g, 0.027 g, 0.017 g.

Optical Rotations.—For optical rotations of products from *N*-(*tert*-alkoxycarbonyl)-DL- or -L-alanine, Eastman Spectro Grade pyridine was used, with a Rudolph Model 80 high precision polarimeter. Optical rotations of products from (*R,S*)-*N*-(alkoxycarbonyl)glycines, unless otherwise specified, were determined for purified products from the earliest incubation period in spectro grade pyridine at 25° (room temperature) and 589 nm with a Cary Model 60 recording spectropolarimeter at the University of California, Los Angeles. Zero settings were made for each measurement before and after the optical measurement was made, with pyridine in the polarimeter tube of 1-cm thickness. Solids were dissolved in pyridine in a 5.00-ml volumetic flask and the solutions were then filtered through sintered-glass suction tubes. After a zero reading with the solvent, the same polarimeter tube was rinsed with methanol and then ether and then dried with the use of a constricted glass tubing connected to a suction line. The polarimeter tube was filled with solution and optical rotation was taken. For a low optical rotation, a setting was used for 100 divisions/0.02°. For other rotations, a setting of 100 divisions/0.04° was used. Solutions involved ~0.1 to 0.6 g of *N*-acylamino acid/5 ml of solution. All were weighed to the nearest 0.1 mg.

Systematic Recording of Experimental Results for Reactions between *N*-(Alkoxycarbonyl)glycines and *o*- and *p*-Anisidines.—At the beginning of each incubation period, there would be equal quantities of *R* and *S* enantiomers when a racemic *N*-acylamino acid was used. However, their anisidide products would not ordinarily contain equal amounts of *R* and *S* enantiomers. Therefore, these products are designated as *R* and *S*, rather than *R,S*. For products from the essentially single (*S*)-*N*-acylamino acid, the symbol *S* is used. Hours of incubation are listed first, followed by the weight of product, and then the melting point. Optical rotations and nitrogen analyses are given at the end. A single asterisk (*) indicates that the purified product from that incubation period was used for both an optical rotation in pyridine as the solvent and for nitrogen analysis. A double asterisk (**) means that the purified product was used only for a nitrogen analysis, a triple asterisk (***) only for optical rotation.

I. (*R*)- and (*S*)-*N*-(*sec*-Butoxycarbonyl)glycine *m*-anisidides: 0–3 hr, 0.261 g*, 75–77°; 3–6 hr, 0.062 g, 76–77°; 6–12 hr, 0.002 g, 76–77°; 12–24 hr, 0.009 g, 74–75°; 24–48 hr, 0.005 g, 74–75° ($[\alpha]^{25}D$ −0.11°, % N calcd 9.99 and found 9.94). (*R*)- and (*S*)-*N*-(*sec*-Butoxycarbonyl)glycine *p*-anisidides: 0–3 hr, 0.140 g***, 117–119°; 3–6 hr, 0.243 g, 119–120°; 6–12 hr, 0.163 g**, 119–120°; 12–24 hr, 0.064 g, 119–120°; ($[\alpha]^{25}D$ −0.97°, % N calcd 9.99 and found 9.90).

II. (*R*)- and (*S*)-*N*-(1-Methylbutoxycarbonyl)glycine *m*-anisidides: 0–6 hr, 1.184 g*, 116–117°; 6–12 hr, 0.185 g, 119–120°; 12–24 hr, 0.179 g, 117–118°; 24–48 hr, 0.107 g, 116–118°; ($[\alpha]^{25}D$ +1.44°, % N calcd 9.51 and found 9.52).

III. (*S*)-*N*-(2-**Methylbutoxycarbonyl**)**glycine** *m*-**anisidide**: 0–6 hr, 1.190 g*, 102–103°; 6–12 hr, 0.117 g, 102–103°; 12–24 hr, 0.024 g 101–102°; ($[\alpha]^{25}D$ +1.20°, % N calcd 9.51 and found 9.62). (*R*)- **and** (*S*)-*N*-(2-**Methylbutoxycarbonyl**)**glycine** *m*-**anisidides**: 0–3 hr, 1.037 g*, 78–79°; 3–6 hr, 0.353 g, 76–77°; 6–12 hr, 0.199 g, 76–77°; 12–24 hr, 0.061 g, 76–77°; ($[\alpha]^{25}D$ +0.138°, % N calcd 9.51 and found 9.52, 55.8% *S* enantiomer in 0–3-hr product.

IV. (*S*)-*N*-(2-**Methylbutoxycarbonyl**)**glycine** *p*-**anisidide**: 0–6 hr, 1.168 g*, 116–118°; 6–12 hr, 0.346 g, 116–118°; 12–24 hr, 0.132 g, 116–118°; ($[\alpha]^{25}D$ +2.40°, % N calcd 9.51 and found 9.70). (*R*)- **and** (*S*)-*N*-(2-**Methylbutoxycarbonyl**)**glycine** *p*-**anisidides**: 0-3 hr, 0.856 g*, 111–112°; 3–6 hr, 0.456 g, 111–112°; 6–12 hr, 0.397 g, 110–111°; 12–24 hr, 0.174 g, 110–111°; 24–48 hr, 0.130 g, 107–109°; ($[\alpha]^{25}D$ +0.222°, % N calcd 9.51 and found 9.70, 54.6% *S* enantiomer in 0–3 hr product).

Registry No.—*N*-(*tert*-Butoxycarbonyl)glycine, 4530-20-5; *N*-(*tert*-pentyloxycarbonyl)glycine, 3588-44-1; *N*-(*tert*-butoxycarbonyl)-DL-alanine, 3744-87-4; *N*-(*tert*-pentyloxycarbonyl)-DL-alanine, 34885-82-0; (*R,S*)-*N*-(*sec*-butoxycarbonyl)glycine DCHA, 38435-97-1; (*R,S*)-*N*-(1-methylbutoxycarbonyl)glycine DCHA, 38435-98-2; (*R,S*)-*N*-(2-methylbutoxycarbonyl)glycine DCHA, 38435-99-3; (*S*)-*N*-(2-methylbutoxycarbonyl)glycine DCHA, 38436-00-9; (*R*)-*N*-(*sec*-butoxycarbonyl)glycine *m*-anisidide, 38436-01-0; (*S*)-*N*-(*sec*-butoxycarbonyl)glycine *m*-anisidide, 38436-02-1; (*R*)-*N*-(*sec*-butoxycarbonyl)glycine *p*-anisidide, 38436-03-2; (*S*)-*N*-(*sec*-butoxycarbonyl)glycine *p*-anisidide, 38436-04-3; (*R*)-*N*-(1-methylbutoxycarbonyl)glycine *m*-anisidide, 38436-05-4; (*S*)-*N*-(1-methylbutoxycarbonyl)glycine *m*-anisidide, 38436-06-5; (*S*)-*N*-(2-methylbutoxycarbonyl)glycine *m*-anisidide, 38436-07-6; (*R*)-*N*-(2-methylbutoxycarbonyl)glycine *m*-anisidide, 38436-08-7; (*S*)-*N*-(2-methylbutoxycarbonyl)glycine *p*-anisidide, 38436-09-8; (*R*)-*N*-(2-methylbutoxycarbonyl)glycine *p*-anisidide, 38436-10-1; papain, 9001-73-4.

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Purine *N*-Oxides. XLVI. Some Interesting Reactions of 3-Acetoxy-8-methylxanthine[1]

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The reactivities of 3-acetoxy-8-methylxanthine have been compared with corresponding reactivities of 3-acetoxyxanthine. The former undergoes a rearrangement in water to yield 8-hydroxymethylxanthine, and evidence is presented suggesting an intermediate possessing an exocyclic methylene group. In addition, some hydrolysis to 3-hydroxy-8-methylxanthine and some reduction to 8-methylxanthene occur, the latter apparently proceeding through a radical mechanism. 8-Methylguanine 3-oxide can also be rearranged to 8-hydroxymethylguanine. 3-Acetoxyxanthine reacts in aqueous solutions with many nucleophiles to yield a variety of 8-substituted xanthines. Under the same conditions 3-acetoxy-8-methylxanthine reacts only with the water to afford the 8-hydroxymethyl derivative. 3-Acetoxy-8-azaxanthine undergoes only the hydrolysis and reduction reactions.

Esters of the oncogenic 3-hydroxyxanthine react with nucleophiles under mild conditions *in vitro*,[3] and *in vivo*,[4] to form 8-substituted xanthines. Similar nucleophilic substitution reactions with macromolecules of the cell have long been offered as an explanation of the initiation of the cancer process by chemical oncogens.[5] A weak oncogenicity of 3-hydroxy-8-azaxanthine (**16**) and the possible similar activity of 3-hydroxy-8-methylxanthine (**1**)[4] prompted a comparative investigation of the chemical behavior of compounds with these distinct alterations of the 8 position of 3-hydroxyxanthine.

Treatment of 3-hydroxy-8-methylxanthine (**1**) with acetic anhydride in trifluoroacetic acid at room temperature afforded a monoacetyl derivative. The ir and nmr[6] spectra indicated the presence of an O-acetyl group, and the slow development of a purple color with ferric chloride provided further support for the 3-acetoxy-8-methylxanthine structure (**2**). Reaction of 3-hydroxy-8-methylxanthine (**1**) in hot acetic anhydride, followed by treatment with water, gave some 8-hydroxymethylxanthine (**10**) and extensive decomposition. The *O*-acetyl derivative of 3-hydroxy-8-methylguanine (**14**) was not isolable, but in acetic anhydride and trifluoroacetic acid at room temperature, followed

(1) This investigation was supported in part by funds from the National Cancer Institute, Grant No. CA 08748.

(2) D. R. S. is a Damon Runyon Memorial Fellow.

(3) N. J. M. Birdsall, U. Wölcke, T.-C. Lee, and G. B. Brown, *Tetrahedron*, **27**, 5969 (1971).

(4) G. B. Brown, M. N. Teller, I. Smullyan, N. J. M. Birdsall, T.-C. Lee, J. C. Parham, and G. Stöhrer, *Cancer Res.*, in press.

(5) J. A. Miller, *ibid.*, **30**, 559 (1970).

(6) A downfield shift of the nmr signal of the 8-methyl protons in 8-methylxanthine and guanine derivatives, when the solvent was TFA rather than DMSO-d_6, was attributed to protonation of the imidazole ring in the former solvent. This phenomenon has been observed previously in N-methylated xanthines.[7]

(7) D. Lichtenberg, F. Bergmann, and Z. Neiman, *J. Chem. Soc. C*, 1676 (1971).

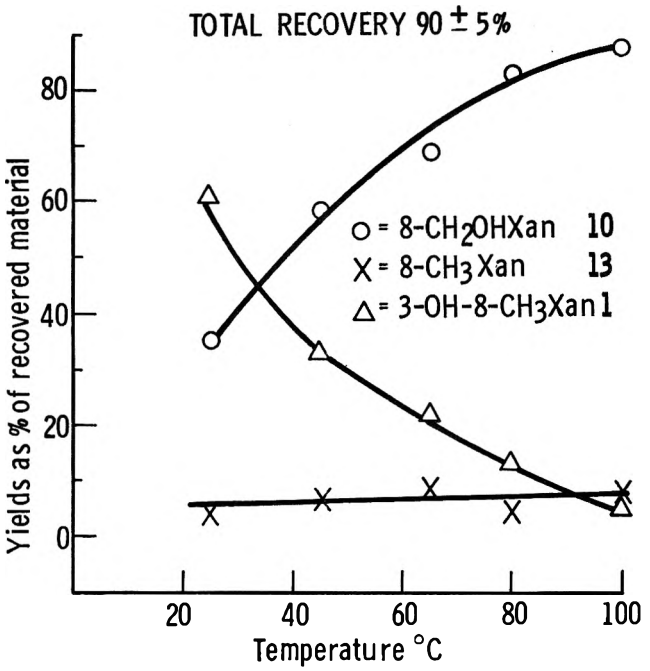
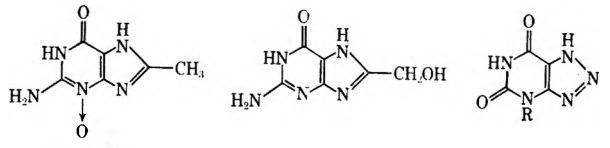


Figure 1.—Effect of temperature on yields of products.

by treatment with water, **14** was converted to 8-hydroxymethylguanine (**15**).



14 **15**

16, R = OH
17, R = OAc
18, R = H

If the treatment of 3-hydroxy-8-methylxanthine (**1**) with acetic anhydride and trifluoroacetic acid was prolonged, a solid could be isolated, the nmr (δ 5.82, two-proton singlet) and ir (carbonyl absorption at 1750 cm^{-1}) spectra of which indicated the presence of a trifluoroacetoxymethyl group.[8] On standing, this compound slowly reacted, presumably with atmospheric moisture, to give 8-hydroxymethylxanthine (**10**), which showed a two-proton singlet at δ 5.38. The difference in chemical shifts of the methylene protons of these two compounds is in agreement with the assigned 8-trifluoroacetoxymethylxanthine structure (**11**).[8] It has previously been observed that esters of this type are readily hydrolyzed by atmospheric moisture.[8]

In water at room temperature 3-acetoxy-8-methylxanthine (**2**) yielded 8-hydroxymethylxanthine (**10**), together with 3-hydroxy-8-methylxanthine (**1**) and 8-methylxanthine (**13**). Increase in temperature of this reaction (Figure 1) resulted in an increase in the amount of rearrangement to 8-hydroxymethylxanthine, with a corresponding decrease in the hydrolysis to 3-hydroxy-8-methylxanthine. The formation of 8-methylxanthine (**13**) showed little sensitivity to changes in reaction temperature.

Examination of the reactions of **2** in aqueous solution at different pH's (Figure 2) showed the preferential formation of the hydrolysis product 3-hydroxy-8-methylxanthine (**1**) below pH 5. Above pH 5 the

(8) D. R. Sutherland and G. Tennant, *J. Chem. Soc., Perkin Trans. 1*, in press.

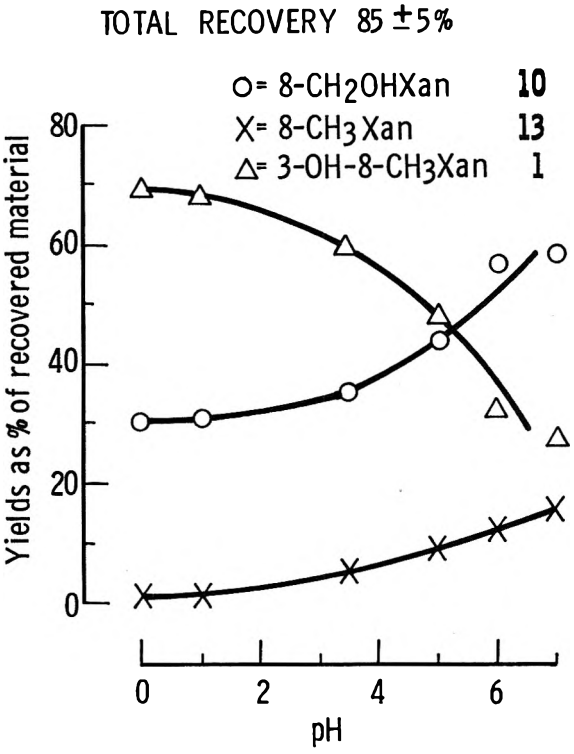


Figure 2.—Effect of pH on yields of products.

major product was 8-hydroxymethylxanthine (**10**). There was also a significant increase in the production of 8-methylxanthine (**13**) as the pH increased.

Investigation of changes in the polarity of the solvent on the reaction product distribution (Figure 3) showed that the amount of rearrangement to **10** increased, with a corresponding decrease in hydrolysis to **1**, as the polarity of the solvent decreased. In contrast, the solvent polarity had no effect on the production of 8-methylxanthine (**13**).

Treatment of 3-acetoxy-8-methylxanthine (**2**) with methanol or ethanol afforded, after evaporation, a product which was unstable in most solvents. Upon treatment with water it afforded 8-hydroxymethylxanthine (**10**), together with smaller quantities of 3-hydroxy-8-methylxanthine (**1**) and 8-methylxanthine (**13**). When the crude product from methanol or ethanol treatment was dissolved in trifluoroacetic acid, it showed an nmr signal at δ 4.95, attributable to an exocyclic methylene group[9] at C-8. However, this signal rapidly disappeared and a new signal developed at δ 5.82, identical with that assigned to the methylene protons of 8-trifluoroacetoxymethylxanthine (**11**). The latter signal also gradually disappeared and was replaced by the δ 5.38 signal of the hydroxymethyl derivative **10**. The nmr spectrum of the crude product also exhibited signals attributed to **13** and **1**, showing that both the reduction and the hydrolysis also occurred in alcohols. The uv spectrum of 3-acetoxy-8-methylxanthine (**2**) in methanol showed an initial absorption at 268 nm. This absorbance rapidly decreased threefold while shifting to 270 nm. The 270-nm absorption is identical with that exhibited by the

(9) (a) D. Meuche, M. Neuenschwander, H. Schaltegger, and H. U. Schlunegger, *Helv. Chim. Acta*, **47**, 1211 (1964); (b) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "Nmr Spectral Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962, No. 109, 132, and 180; (c) R. F. C. Brown, G. E. Gream, D. E. Peters, and R. K. Solly, *Aust. J. Chem.*, **21**, 2223 (1968).

product obtained from treatment of 2 with refluxing methanol. This product underwent a series of changes when treated with water. The initial absorption at 270 nm increased threefold in intensity within 10 min, and then decreased about fourfold over 2 hr to the final spectrum. That spectrum was the same as the ultimate spectrum of 2 in water, which was reached after a similar series of changes, and was that of a mixture of 8-hydroxymethylxanthine (**10**), 3-hydroxy-8-methylxanthine (**1**), and 8-methylxanthine (**13**). The acetoxy compound 2 in water initially showed a 272-nm maximum, which shifted in 60 sec to 269 nm with a slight increase in intensity. After 90 sec the absorption decreased threefold with a shift to 270 nm, and then showed changes identical with those described for the uv of the product from alcohol treatment.

The similarity of the uv spectra changes observed when 2 was treated with water or with alcohols indicated the presence of a similar intermediate in each solvent. Nmr evidence indicated the presence of an exocyclic methylene group in the product obtained after treatment of 2 with methanol or ethanol, suggesting that an intermediate such as **7** is involved in the rearrangement to **10**. Such intermediates have been invoked to explain the conversions of heterocyclic *N*-oxides to products acyloxylated in the nucleus or on a side chain.[10-12]

In marked contrast to the results with 3-acetoxyxanthine,[3] no reaction of 3-acetoxy-8-methylxanthine (2) with aqueous solutions of nucleophiles such as chloride, nitrite, or azide ion or methionine has been observed. The only products detected were those from the reaction of 2 with water.

There are, however, obvious similarities in the reactivities of 3-acetoxyxanthine[3] and 3-acetoxy-8-methylxanthine (2) in aqueous solutions. Each compound yields products resulting from three reactions: hydrolysis, reduction, and rearrangement. With each compound rearrangement became the major reaction pathway only as the pH increased (Figure 2). At lower pH's ester hydrolysis was the major reaction. These changes in the ratios of the products arising from the different reactions coincide with the pH of formation of the anion of 3-hydroxyxanthine,[13] and the same is apparently true for the 8-methyl compound **3**.[14]

It has been suggested that at lower pH's the rearrangement of 3-acetoxyxanthine to uric acid proceeds *via* a heterolytic cleavage of the *N*-acetoxy bond to give a nitrenium ion at N-3, which undergoes an allylic

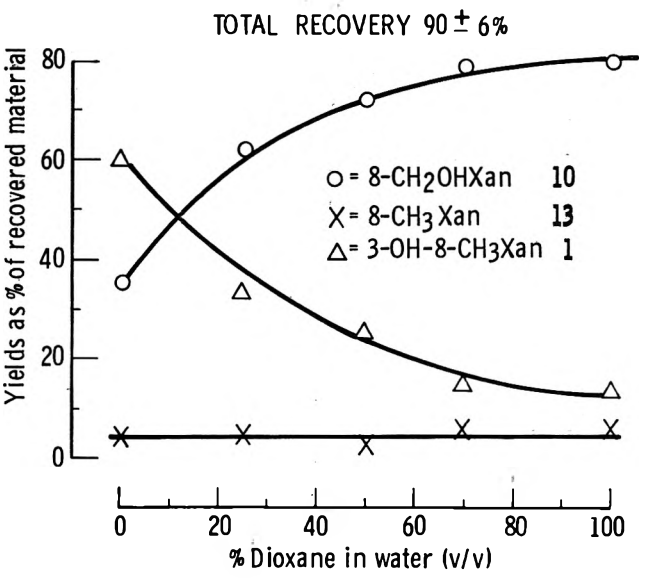
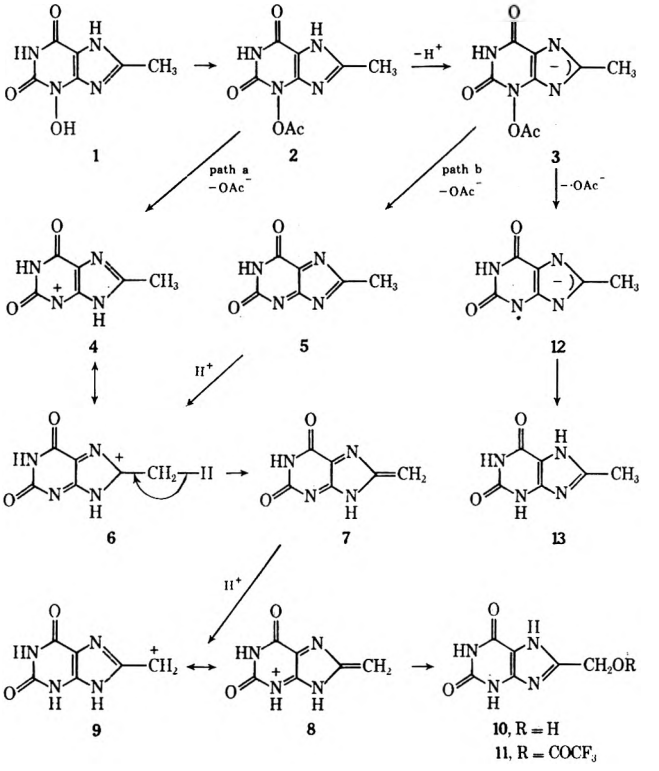


Figure 3.—Effect of solvent composition on yields of products.

shift to afford a more stable secondary carbonium ion at C-8. This intermediate undergoes nucleophilic attack to yield uric acid.[13] If this mechanism were true for the 8-methyl derivative 2 (see Scheme I),

SCHEME I



a more stable tertiary carbonium ion **6** would be formed at C-8 and a greater degree of rearrangement might be expected. In fact, the yield of the rearrangement product, 8-hydroxymethylxanthine, was at least four times greater than that of the uric acid derived from 3-acetoxyxanthine at pH's less than 5.

At higher pH's, where expulsion of the acetate ion was aided by the negative charge on the imidazole ring (**3**), the amount of rearrangement increased noticeably with a simultaneous decrease in the hydrolysis to 3-

(10) E. Ochiai, "Aromatic Amine Oxides," Elsevier, New York, N. Y., 1967.

(11) V. J. Traynellis in "Mechanisms of Molecular Migrations," Vol. 2, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1969, Chapter 1.

(12) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, N. Y., 1971.

(13) N. J. M. Birdsall, J. C. Parham, U. Wölcke, and G. B. Brown, *Tetrahedron*, **28**, 3 (1972).

(14) The pK_a of 3-acetoxy-8-methylxanthine was difficult to obtain because of the rapid and complex changes in the uv spectrum of the compound in aqueous solution. However, the influence of the 8-methyl group in similar compounds increased the pK_a of ionization of the imidazole proton by ~0.6 units.[15] Therefore, from the known pK_a of 3-acetoxyxanthine (6.8 ± 0.5)[16] it can be deduced that the pK_a of the 8-methyl derivative is ~7.4 ± 0.5.

(15) J. C. Parham, T. G. Winn, and G. B. Brown, *J. Org. Chem.*, **36**, 2639 (1971).

(16) N. J. M. Birdsall, T.-C. Lee, and U. Wölcke, *Tetrahedron*, **27**, 5961 (1971).

hydroxy-8-methylxanthine (1). At these higher pH's the proportion of rearrangement compared to hydrolysis was again higher than that observed in the reactions of 3-acetoxyxanthine. It is probable that the two pathways leading to the tertiary carbonium ion 6 are competitive in aqueous solution, with path b predominating at higher pH's and path a at lower pH's.

The rearrangement product obtained from 3-acetoxy-8-methylxanthine (2) was not truly analogous to that obtained from 3-acetoxyxanthine. The latter, uric acid, was formed by direct nucleophilic attack at C-8, whereas the former, 8-hydroxymethylxanthine, must be formed by attack at the carbon atom of the exocyclic methyl group. The absence of any product arising from direct attack at C-8 can be attributed to steric hindrance by the methyl group in the carbonium ion 6. The nmr evidence has suggested an intermediate with an exocyclic methylene group at C-8 (7). Such a species, presumably formed from the tertiary carbonium ion 6, could be protonated to give the cation 8, which could then react with water by a Michael addition type process to yield the hydroxymethyl compound 10. The primary carbonium ion 9 is less likely to be a contributing factor, since it should be less stable than the resonance-stabilized tertiary carbonium ion 6. If 9 is involved, preferential solvation of it by water molecules could explain the failure to find any evidence for reactions with other nucleophiles in aqueous solution. The absence of a reaction giving 8-methoxymethylxanthine in sodium methoxide in methanol infers that 7 does not undergo a Michael addition under such conditions. However, the strongly basic nature of sodium methoxide may cause ionization of the proton at N-9, thereby rendering the methylene group of 7 very resistant to nucleophilic attack. Treatment of 2 with methanol in the presence of Dowex-50 (H^+), which might have aided nucleophilic attack by protonating 7, did not result in formation of the methoxymethyl derivative.

At lower pH's (Figure 2) and in solutions of high polarity (Figure 3), there was a significant amount of rearrangement, but hydrolysis to 3-hydroxy-8-methylxanthine (1) was favored, which suggests an $A_{Ac}2$ hydrolysis mechanism.[17]

The yield of 8-methylxanthine (13) obtained from 3-acetoxy-8-methylxanthine (2) in aqueous solutions was found to be relatively insensitive to changes in solvent polarity and temperature. These observations, like those with 3-hydroxyxanthine,[13] suggest that the reduction occurs by a free-radical mechanism. In aqueous solutions of the acetoxy compound 2 the presence of iodide ion, but not chloride ion, caused a large increase in the production of the reduced compound. In another study it has been noted that uv irradiation of 3-hydroxy-8-methylxanthine (1) or of its acetoxy derivative 2 in the solid state afforded a free radical.[18]

Since the production of 8-methylxanthine (13) in aqueous solution became significant only at higher pH's (Figure 2), it appears that formation of the radical proceeds from the anion 3. A radical (12) derived by homolytic cleavage of the N–O bond of the 8-methylxanthyl anion will abstract hydrogen from water and then protonate to give 8-methylxanthine (13).

A by-product in the reactions of 3-acetoxyxanthine in nearly neutral aqueous solutions was an unstable and highly insoluble blue compound.[3,13] It may be significant to the structure of that product that no evidence was found for the formation of such a compound from 3-acetoxy-8-methylxanthine (2), in which the 8 position is blocked.

3-Hydroxy-8-azaxanthine (16), in which the 8 position is altered in a different manner, was also investigated. It decomposed in refluxing acetic anhydride. The preparation of 3-acetoxy-8-azaxanthine (17)[16] from 3-hydroxy-8-azaxanthine was improved by the use of acetic anhydride in trifluoroacetic acid at room temperature. In water at room temperature the 3-acetoxy derivative 17 hydrolyzed quantitatively to the *N*-hydroxy compound 16. No reactions could be observed with nucleophiles in solution. Treatment of the acetoxy compound 17 with hot methanol gave 3-hydroxy-8-azaxanthine (16) as the major product, but it also yielded a small amount of the reduction product, 8-azaxanthine (18), in analogy to the reduction of 3-acetoxy-8-methylxanthine (2) in methanol under comparable conditions.

Whether these chemical properties of 3-hydroxy-8-methylxanthine and 3-hydroxy-8-azaxanthine are related to the process of tumor induction remains to be seen. The observations that each of these, like 3-acetoxyxanthine, are reduced, in part, by a reaction which may proceed through a radical mechanism add to the evidence encouraging serious consideration of the possibility that a free-radical reaction mechanism may be involved in oncogenicity.[4]

Experimental Section

Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. The uv and ir spectra were recorded with Unicam SP800A and Perkin-Elmer Model 137B Infracord (Nujol suspension) spectrophotometers, respectively. Nmr spectra were measured at 60 MHz using a Varian A-60 spectrometer, in dimethyl sulfoxide-d_6 or trifluoroacetic acid, at 35°, with tetramethylsilane as the internal standard.

3-Acetoxy-8-methylxanthine (2).—3-Hydroxy-8-methylxanthine[19] (1) (250 mg) was stirred in trifluoroacetic acid (15 ml) and acetic anhydride (10 ml) at room temperature for 3 hr. This was poured into dry ether (100 ml) and the resulting solution was concentrated to 10 ml. Treatment of the concentrate with dry ether (100 ml) and overnight refrigeration afforded the acetoxy compound 2, which was washed with dry ether and dried under vacuum at room temperature overnight: yield 72%; nmr (TFA) δ 2.90 (s, 3, CCH_3), 2.53 (s, 3, $NOCOCH_3$); nmr (DMSO-d_6) δ 13.40 (br, 1, NH), 11.65 (br, 1, NH), 2.42 (s, 3, CCH_3), 2.37 (s, 3, $NOCOCH_3$); ir (Nujol) 3100–3400, 2600–2750 (NH), 1810 ($NOCOCH_3$), 1670 cm^{-1} (CO). The ir and nmr spectra also exhibited absorption attributable to acetic acid and the analysis corresponded to a hemiacetate.

Anal. Calcd for $C_8H_8N_4O_4 \cdot 0.5CH_3CO_2H$: C, 42.3; H, 4.3; N, 19.7. Found: C, 41.9; H, 4.1; N, 19.3.

If the reaction is continued for 3 days before work-up, the nmr spectrum of the crude product shows the presence of 3-acetoxy-8-methylxanthine (2), 8-methylxanthine (13)[20] [nmr (TFA) δ 2.93 (s, 3, CCH_3)], 3-hydroxy-8-methylxanthine (1) [nmr (TFA) δ 2.97 (s, 3, CCH_3)], 8 trifluoroacetoxymethylxanthine (11) [nmr (TFA) δ 5.82 (s, 2, CH_2OCOCF_3); ir (Nujol) 1750 cm^{-1} ($OCOCF_3$)], and 8-hydroxymethylxanthine (10)[21] [nmr (TFA) δ 5.38 (s, 2, CH_2OH)].

(17) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969.

(18) J. C. Parham, I. Pullman, and G. B. Brown, unpublished results.

(19) N. J. M. Birdsall, T.-C. Lee, T. J. Delia, and J. C. Parham, *J. Org. Chem.*, **36**, 2635 (1971).

(20) H. C. Koppel and R. K. Robins, *ibid.*, **23**, 1457 (1958).

(21) H. Bredereck, E. Siegel, and B. Föhlisch, *Chem. Ber.*, **95**, 403 (1962).

Examination of the reaction mixture by nmr spectroscopy at 60-min intervals showed that formation of 8-trifluoroacetoxymethylxanthine (11) began after 4 hr, before the formation of the hydroxymethyl compound 10.

8-Hydroxymethylxanthine (10). A.—3-Acetoxy-8-methylxanthine (2) (250 mg) was refluxed in water (25 ml) for 1 hr, the solution was evaporated, and the residue was crystallized from water to yield 80% of 10, identical with an authentic sample.[21]

B.—3-Hydroxy-8-methylxanthine (1) (250 mg) was refluxed in acetic anhydride (60 ml) for 30 min. The dark solution was evaporated, and the residue was crystallized from water to yield 11% of 10. The nmr spectrum of the crude residue did not show signals assignable to methylene protons. Evaporation of the aqueous crystallization liquors afforded a complex mixture, inseparable by column chromatography, and showing only end absorption in the uv.

8-Hydroxymethylguanine (15).—8-Methylguanine 3-oxide (14)[16] (250 mg) was stirred in trifluoroacetic acid (25 ml) and acetic anhydride (15 ml) for 24 hr at room temperature. The resulting solution was evaporated under vacuum at room temperature to a gum, which was crystallized from water to yield 29% of 15, identical with an authentic sample.[22] Temperatures above 30° caused decomposition to products possessing only end absorption in the uv.

Reactions of 3-Acetoxy-8-methylxanthine (2) in Aqueous Solutions (See Figures 1–3).—3-Acetoxy-8-methylxanthine (2) (11.2 mg) was dissolved in the solvent (25 ml) and at the temperature specified. The solutions were stirred for 16 hr, after which no further reaction occurred as shown by lack of change in optical density of diluted aliquots. Aliquots (5 ml) were analyzed with an 8 × 1 cm column of Dowex-50 [H^+], 200–400 mesh, eluted with 0.1 *N* HCl, and with the uv absorption of the effluent recorded by an ISCO UA2 monitor. The elution volumes follow: 8-hydroxymethylxanthine, 125 ml; 3-hydroxy-8-methylxanthine, 170 ml; 8-methylxanthine, 360 ml. The fractions were evaporated and dissolved in aqueous solutions of the required pH. The yields were calculated from the volume and absorbance of each fraction with the following reference values: 8-hydroxymethylxanthine, pH 13, λ_{max} 286 nm (ϵ 11,000);[21] 3-hydroxy-8-methylxanthine, pH 13, λ_{max} 297 nm (ϵ 8050); 8-methylxanthine, pH 1, λ_{max} 265 nm (ϵ 7800).[20] For reactions in dioxane and water the solvent was evaporated under vacuum, and the residues were dissolved in water for analysis.

3-Acetoxy-8-methylxanthine (2) (11.2 mg) was added to a solution of sodium iodide (15 mg) in water (30 ml) and stirred for 16 hr. The reaction mixture was extracted with chloroform, and the aqueous fraction was analyzed to yield 11% of 3-hydroxy-8-methylxanthine (1), 10% of 8-hydroxymethylxanthine (10), and 46% of 8-methylxanthine (13). In a similar experiment with sodium chloride, the yield of 8-methylxanthine (13) was 8%.

Under conditions that led to numerous 8-substituted products of 3-hydroxyxanthine,[3] 2 was treated with aqueous solutions of sodium azide, sodium nitrite, sodium chloride, or methionine. Upon column chromatography 1, 10, and 13 were found in each case, but no other products representing substitution by these nucleophiles were detected. The nmr spectra of the crude reaction residues showed no signals attributable to 8-substituted products, other than 10.

Treatment of 3-Acetoxy-8-methylxanthine (2) with Methanol and Ethanol.—3-Acetoxy-8-methylxanthine (2) (250 mg) was refluxed in dry methanol or ethanol (100 ml) for 1 hr, and the solution was evaporated. The nmr spectrum (TFA) of the residue initially showed a singlet at δ 4.95, which disappeared with the concomitant appearance of a signal at 5.82, identical with that of 8-trifluoroacetoxymethylxanthine (11). The spectrum also showed signals in the CH_3 region (δ 2–3), that could be assigned to 3-hydroxy-8-methylxanthine (1), 8-methylxanthine (13), and acetic acid. The residue from the methanol reaction upon treatment with water and chromatographic separation afforded 28% of 1, 7% of 13, and 49% of 10. 3-Acetoxy-8-methylxanthine was treated with methanol as above, in the presence of dry Dowex-50 [H^+] (1 g). The Dowex resin was removed by filtration and the filtrate was treated as above to give 33% of 1, 5% of 13, and 42% of 10.

Treatment of 3-Acetoxy-8-methylxanthine (2) with Sodium Methoxide.—3-Acetoxy-8-methylxanthine (2) (225 mg) was stirred with a solution of sodium (115 mg) in methanol (250 ml) for 2 hr at room temperature. The solvent was evaporated, and the residue was dissolved in water. The resulting solution was adjusted to pH 5 with 1 *N* HCl. Column chromatography with Dowex-50 [H^+] afforded 21% of 13, 23% of 1, and 31% of 10, together with some material possessing only end absorption in the uv.

3-Acetoxy-8-azaxanthine (17).—3-Hydroxy-8-azaxanthine (16)[23] (250 mg) was stirred in trifluoroacetic acid (12 ml) and acetic anhydride (5 ml) at room temperature for 17 hr. The solution was evaporated at room temperature, and the residue was stirred in dry methanol (100 ml) for 24 hr to give, after evaporation, 78% of 17, identical with an authentic sample.[16]

Treatment of 16 with refluxing acetic anhydride caused immediate decomposition to a tar, which showed only end absorption in the uv.

Reaction of 3-Acetoxy-8-azaxanthine (17) in Methanol.—3-Acetoxy-8-azaxanthine (17) (50 mg) was refluxed in dry methanol (10 ml) for 4 hr. The solution was evaporated and the residue was dissolved in water. After column chromatography with Dowex-50 [H^+], 91% of 3-hydroxy-8-azaxanthine (16) and 3% of 8-azaxanthine (18) were obtained.

Registry No.—1, 22888-28-4; 2, 38605-78-6.

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o-Nitrophenyl Esters in Solid Phase Peptide Synthesis

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Stepwise synthesis of the heptapeptide amide, L-Leu-L-Gln-L-Asn-L-Cys(Bzl)-L-Pro-L-Leu-Gly-NH_2 has been carried out by the solid phase method (a) with *o*-nitrophenyl esters as acylating agents and (b) with DCC as coupling reagent at each chain-lengthening step. Countercurrent distribution revealed only minor impurities in the product obtained with active esters, but not insignificant amounts of by-products in the material prepared by the DCC method.

Nitrophenyl esters,[1] in spite of their pronounced reactivity in aminolysis, are not the best acylating agents in reactions involving derivatives of single amino acids or dipeptides as amino components. Diketopiperazine formation competes with the desired acylation, particularly in the case of dipeptides where the ring closure, an unimolecular reaction, competes with the desired bimolecular acylation. However, many advantages of active esters, such as unequivocal reactions or the ease of removal of excess reagent, fully emerge when an already existing shorter or longer peptide chain needs to be lengthened by the addition of a single amino acid residue. These observations and the general concern about racemization during coupling led to the stepwise strategy first demonstrated on a synthesis of oxytocin.[2] The then new approach, stepwise synthesis of peptides with active esters,[3] was considered by Merrifield[4] to be ideal for solid phase peptide synthesis (SPPS), but was immediately abandoned for technical reasons. After Bodanszky and Sheehan[5] proved that active esters are indeed applicable in SPPS, the *p*-nitrophenyl esters of protected asparagine and glutamine became accepted tools of solid phase peptide chemists. A more general use of active esters in SPPS was reported only in a few cases.[6] Probably because of the moderate rates of acylation of resin-bound amino components,[7] the pronounced solvent dependence of these rates, and incomplete reactions with hindered amino acids,[8] coupling with dicyclohexylcarbodiimide (DCC)[9] remained the most widely used method in SPPS. Carbodiimides and several other coupling reagents[10] are highly efficient and can provide the desired amides even in minutes,[11] but they suffer from the disadvantage of overactivation[12] and can lead to undesired side reactions. One of these, the formation of ninhydrin-positive impurities in the reaction of DCC with *tert*-butyloxycarbonyl (Boc) amino acids, was recently reported.[13] More importantly, the high reactivity of intermediates such as *o*-acylisoureas or symmetrical anhydrides[14] necessitates global protection. Side chain hydroxyl and carboxyl groups must be protected. Selective acylation of amino groups can be achieved only at the expense of reactivity and, hence, of speed. Yet, with unprotected hydroxyl and carboxyl functions, there is a considerable gain in the freedom of planning of syntheses (*e.g.*, with free side chain carboxyl groups, the absence of esters permits the removal of completed chains from the resin by aminolysis,[5] hydrazinolysis,[15] or ester exchange[16]).

The advantages of selective acylation prompted a reexamination[17] of different active esters with respect to their usefulness in SPPS. It soon became clear that rate measurements carried out in solution are not necessarily valid when the amino component is attached to an insoluble support. The matrix of the resin itself is the cause of serious steric hindrance, which is subsequently compounded by the hindrance from the growing peptide chain.[13,18] It is understandable, therefore, that bulky activating groups, such as the one in pentachlorophenyl esters,[19] render the corresponding derivative, that was highly active in solution, quite inefficient in SPPS. The initially applied[5] *p*-nitrophenyl esters are better in this respect, but not particularly fast. On the other hand, *o*-nitrophenyl esters, while only somewhat more reactive in solution than their para isomers, were found quite promising in SPPS. An additional advantage of *o*-nitrophenyl esters is that, in contrast to the para isomers, their reaction rates are only slightly solvent dependent.[13]

To test the applicability of *o*-nitrophenyl esters in actual SPPS, the heptapeptide amide L-leucyl-L-glutaminyl-L-asparaginyl-*S*-benzyl-L-cysteinyl-L-prolyl-

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L-leucylglycinamide[20] was synthesized first by the exclusive use of *o*-nitrophenyl esters, and then, for comparison, also by DCC couplings in each step. The aminobenzhydryl resin described by Rivaille and his associates[21] was acylated by *tert*-butyloxycarbonylglycine *o*-nitrophenyl ester (Boc-Gly-ONO). The protecting group was removed with trifluoroacetic acid (TFA) and the resulting amine was treated with Boc-L-Leu-ONO. This procedure was followed until the complete chain of the heptapeptide was assembled. The acylation steps were monitored by measurements (uv absorption) of the released *o*-nitrophenol. The completeness of these reactions was checked by the ninhydrin method of Kaiser and his coworkers.[22] In the alternative procedure, the rapid method proposed by Corley, Sachs, and Anfinsen[11] was followed. The weight increase of the resin was about the same in the two syntheses. The crude heptapeptide amide, removed by the prolonged action of TFA,[23] was secured in both cases as the trifluoroacetate in amounts that correspond to the capacity of the resin. In view of the use of all reagents in considerable excess, the calculation of yields in the manner conventional in organic syntheses may not be justified.[24]

Countercurrent distribution[25] of the crude heptapeptide amide trifluoroacetate, prepared *via* active esters in the solvent system 1-butanol–ethanol–0.1% acetic acid (4:1:5) through 60 transfers, resulted in the distribution curve shown in Figure 1. A detailed study of the main distribution band revealed only slight amounts of impurities, apparently formed during the cleavage of the peptide from the resin by acidolysis.

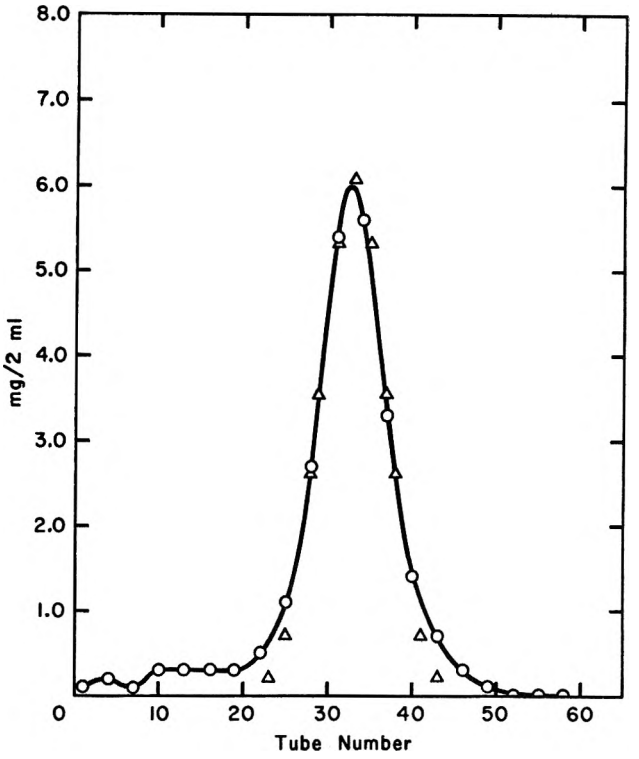

Figure 1.—Countercurrent distribution of crude heptapeptide amide I, prepared *via* *o*-nitrophenyl esters (O, experimental values; Δ, calculated values).

From tubes no. 30–40, on evaporation of the solvent, the trifluoroacetate of I was obtained in crystalline form. This material was shown to be chromatographically and analytically pure. A second sample of the same crude peptide trifluoroacetate was converted to the free base and was crystallized from water.

Distribution of the crude heptapeptide amide obtained by the rapid method[11] with DCC revealed (Figure 2) the presence of a considerable amount of impurities. This comparison clearly demonstrates that the active ester approach, although not particularly fast, can lead to products of good quality that can be easily purified. Further information is expected from our continued use of *o*-nitrophenyl esters in the SPPS of peptides containing residues with functional (OH, COOH) side chains.

Experimental Section

Capillary melting points are reported uncorrected. On thin layer chromatograms, the protected peptides were revealed by *tert*-butyl hypochlorite–KI–starch reagents. The following solvent systems were applied for development: A, *n*-BuOH–AcOH–H_2O (4:1:1); B, $CHCl_3$–MeOH (9:1). For paper chromatography, *n*-BuOH–pyridine–AcOH–H_2O (30:24:6:20)[26] was used.

For amino acid analyses, polymer-bound samples were hydrolyzed with propionic acid–6 *N* HCl (1:1 v/v)[27] in evacuated, sealed ampoules at 130° for 24 hr, and analyzed by the Spackman–Stein–Moore method[28] on a Beckman Spinco 120C amino acid analyzer. All other samples were hydrolyzed with constant-boiling HCl in evacuated, sealed ampoules at 110° for 16 hr.

tert-**Butyloxycarbonylglycine** *o*-**Nitrophenyl Ester.**—*t*-Boc-Gly (4.81 g, 27.5 mmol) and *o*-nitrophenol (6.95 g, 50 mmol) were dissolved in pyridine (75 ml) and cooled in an ice–water bath.

(20) Initially the synthesis of oxytocin was planned. After the incorporation of the seventh residue, amino acid analysis revealed that, instead of L-isoleucine, L-leucine was added to the hexapeptide chain. The error was traced to a preparation of Boc-L-Leu mislabeled by the supplier as Boc-L-Ile. The material was checked by us only for homogeneity but not for identity and therefore the error was detected too late. A possible continuation of the synthesis, that would have resulted in the hormone analog 3-L-leucine oxytocin, was briefly considered. However, instead of persisting in the preparation of oxytocin or one of its analogs, it seemed more attractive to terminate the chain building at this point. From the point of view of exploration of advantages and disadvantages of *o*-nitrophenyl esters in SPPS, the heptapeptide amide I is not inferior, as a model, to oxytocin, in which complicating factors arise from ring closure, dimerization, etc. A question about the incorporation of the isoleucine residue was settled in separate experiments (with the participation of Mr. A. Chang): complete acylation of resin-bound valine was achieved with (*Z*)-L-Ile-ONO.

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(22) E. Kaiser, R. L. Colescott, C. D. Bossinger, and P. I. Cook, *Anal. Biochem.*, **34**, 595 (1970).

(23) Removal of the completed peptide amide from the resin with TFA is probably too slow for many practical purposes. Furthermore, short-column analysis of unhydrolyzed compound I in its crude form revealed two by-products, with maxima at 19 and 27 min, and therefore less basic than compound I, which is eluted at 46 min. During the slow process of cleavage, some hydrolysis of asparagine and/or glutamine residues seems to have occurred, probably owing to the presence of traces of water. Indeed, when samples of the protected heptapeptidyl resin (10 mg) were treated with TFA (0.5 ml) for periods from 1 to 16 days, not only a gradual increase in the amount of the by-product(s) that give a peak at 27 min and in the area of the ammonia peak was observed, but also a corresponding decrease in the size of the principal product peak at 46 min. An increase with time in the least basic peak at 19 min was also noted. These less basic by-products result therefore from hydrolysis during cleavage and are not the consequence of side reactions in the chain-building procedures.

(24) In the active ester approach, the amount of the Boc-amino acids used for the preparation of 1 mmol of crude heptapeptide amide I (trifluoroacetate) totalled 21 mmol. The rapid acylation procedure (with DCC) required 110 mmol of Boc-amino acid for the same amount of crude material. Because of the considerable difference in the quality of the crude peptides obtained by the two methods, the economy of the active ester method would become even more pronounced if the calculations would be based on purified products. For a detailed discussion of this question, *cf.* ref 18.

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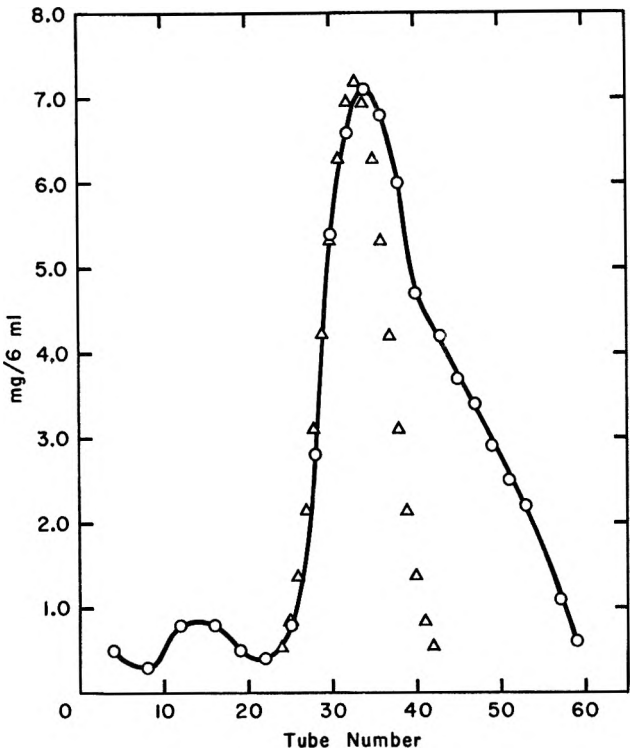

Figure 2.—Countercurrent distribution of crude heptapeptide amide I with DCC applied in all coupling steps (O, experimental values; Δ, calculated values).

DCC (5.15 g, 25 mmol) was added to the stirred solution and rinsed in with more pyridine (25 ml). After 30 min of stirring, the ice bath was replaced with a bath at room temperature. The reaction was followed by the disappearance of the diimide band at 4.8 μ in the ir spectrum. After a total of 4 hr, the *N,N'*-dicyclohexylurea (DCU) was removed by filtration and the pyridine by evaporation *in vacuo* below room temperature. The resulting oil was dissolved in ether and filtered to remove some more DCU. The solvent was evaporated and the crystalline residue was dissolved in $CHCl_3$ (100 ml). The solution was extracted with 5% citric acid (75 ml in three portions), and then with small volumes of 0.1 *N* NaOH. The first few extracts were yellow, the subsequent ones red. When the extracts were again light in color (orange), the washing with alkali was discontinued and the organic layer was washed with water (100 ml). The solution was dried over $MgSO_4$ and filtered, and the solvent was evaporated *in vacuo*. The crystalline solid was dissolved in warm 95% EtOH (75 ml). On cooling, long, white needles formed. The crystals were collected in the cold room, washed with cold 95% EtOH, and dried in air and finally in a desiccator *in vacuo* to give 5.73 g (78%): mp 96.5–98°; tlc R_fA 0.85, R_fB 0.63; active ester carbonyl, 5.62 μ.[29]

Anal. Calcd for $C_{13}H_{16}N_2O_6$ (296.4): C, 52.7; H, 5.4; N, 9.5. Found: C, 52.8; H, 5.4; N, 9.4.

***tert*-Butyloxycarbonyl-L-Leucine *o*-nitrophenyl ester** was prepared according to the procedure described above. The crude oil from a 65-mmol preparation was taken up in warm (35°) petroleum ether (bp 37–50°). Cooling to room temperature produced long, fine, white needles. After a night in a cold room, the crystals were collected, washed with cold petroleum ether, and dried. The active ester, 20.0 g (87%), melts at 56–57°: $[\alpha]^{25}D$ −68° (*c* 1, DMF); tlc R_fA 0.87, R_fB 0.65; active ester carbonyl, 5.62 μ.

Anal. Calcd for $C_{17}H_{24}N_2O_6$ (352.5): C, 57.9; H, 6.9; N, 8.0. Found: C, 58.0; H, 6.7; N, 8.1.

***tert*-Butyloxycarbonyl-L-proline *o*-nitrophenyl ester** was prepared as described for the above active esters. The crude oil from a 10-mmol preparation was taken up in ether; the solution was filtered and evaporated *in vacuo*. The residual oil slowly solidified on standing at room temperature. One-half of the crude solid was dissolved in warm (35°) 95% EtOH (12 ml), cooled, and seeded with the crude crystals. After the addition of water (3 ml), large, yellowish crystals grew over a 2-day period. The crystals were filtered, washed with cold 95% EtOH, and dried *in vacuo* to give 0.30 g, mp 61–70°. The filtrate was concentrated to an oil that, when combined with the rest of the crude solid, was taken up in warm (35°) 95% EtOH. Water was added to turbidity, and the solution was seeded and placed in the cold room. The crystals were collected, washed with cold 90% EtOH, and dried in air to give 1.7 g: mp 63–70° (a third crop weighed 0.73 g, mp 58–62.5°); $[\alpha]^{25}D$ −83° (*c* 1, DMF, 1% AcOH); tlc R_fA 0.84, R_fB 0.66; active ester carbonyl, 5.67 μ. A sample of the active ester was dissolved in hexane and filtered, and the filtrate was concentrated to an oil. The oil was triturated with a small volume of hexane until it solidified, and dried for analysis *in vacuo* over P_2O_5.

Anal. Calcd for $C_{16}H_{20}N_2O_6$ (336.4): C, 57.1; H, 6.0; N, 8.3. Found: C, 57.0; H, 6.2; N, 8.1.

***tert*-Butyloxycarbonyl-*S*-benzoyl-L-cysteine *o*-nitrophenyl ester** was prepared according to the procedure described for the active ester of glycine. The crude oil from a 10-mmol preparation was dissolved in warm 95% EtOH. On cooling, long white needles formed, which were then collected, washed with cold 95% EtOH, and dried to give 3.3 g (77%): mp 103–105°; $[\alpha]^{25}D$ −74° (*c* 1, DMF, 1% AcOH); tlc R_fA 0.82, R_fB 0.67; active ester carbonyl, 5.62 μ.

Anal. Calcd for $C_{21}H_{24}N_2O_6S$ (432.6): C, 58.3; H, 5.6; N, 6.5; S, 7.4. Found: C, 58.1; H, 5.5; N, 6.8; S, 7.6.

***tert*-Butyloxycarbonyl-L-asparagine *o*-nitropheny. ester** was prepared according to the procedure described for Z-Asn-ONP.[30] From a 38-mmol preparation, 8.5 g of crude product was obtained, mp 137–141°, $[\alpha]^{25}D$ −48.0° (*c* 2, DMF). Trituration with EtOAc gave 6.7 g, mp 146–149°. Dissolution in DMF and precipitation by the addition of water yielded 5.6 g, mp 147.5–150°, $[\alpha]^{25}D$ −49.8° (*c* 2, DMF). Recrystallization from hot EtOAc produced 4.2 g (36%): mp 144.5–146.5; $[\alpha]^{25}D$ −52.0°; tlc R_fA 0.77, R_fB 0.41.

Anal. Calcd for $C_{15}H_{19}N_3O_7$ (353.3): C, 51.0; H, 5.4; N, 11.9. Found: C, 50.8; H, 5.6; N, 11.6.

***tert*-Butyloxycarbonyl-L-glutamine *o*-nitrophenyl ester** was prepared according to the procedure described in ref 30. From a 68-mmol preparation, the yield of crude product was 15.3 g, mp 132–137°. Trituration with EtOAc gave 14.9 g, mp 149–151°, $[\alpha]^{25}D$ −53.0° (*c* 2, DMF). Precipitation with water from DMF yielded 14.0 g, mp 149.5–151°, $[\alpha]^{25}D$ −52.3° (*c* 2, DMF). Recrystallization from hot EtOAc gave 8.7 g (without additional purification): mp 148.5–151°; $[\alpha]^{25}D$ −52.3° (*c* 2, DMF); tlc R_fA 0.79, R_fB 0.40.

Anal. Calcd for $C_{16}H_{21}N_3O_7$ (367.4): C, 52.3; H, 5.8; N, 11.4. Calcd for $C_{16}H_{21}N_3O_7 \cdot {}^1/_2H_2O$ (376.4): C, 51.1; H, 5.9; N, 11.2. Found: C, 51.3; H, 5.9; N, 11.3.[31]

Benzhydrylamine Resin.—The hydrochloride (3.0 g)[21] was treated with a mixture of triethylamine (4 ml) and dichloromethane (26 ml) in a sintered glass funnel. After about 1–2 min, the solvent was removed and the same treatment was repeated, this time for 5 min. The resin was washed with dichloromethane (160 ml in eight portions) and with methanol (60 ml in three portions) and dried *in vacuo* at room temperature. The incorporation of Boc-Gly, as determined by amino acid analysis, varied between 0.7 and 1.0 mmol per gram of resin. Amino acid analysis, after acylation of the resin with Boc-Gly-ONO as described below, gave similar results. However, in both procedures the increase in weight corresponds to an uptake of about 1.4 mmol of Boc-glycine by 1 g of aminobenzhydryl resin.

Reaction Vessel.—The stem of a sintered glass filter funnel (60 ml, F) was equipped with a two-way stopcock. This allowed the rapid interchange of N_2 (dried over KOH and $CaCl_2$) used for gentle agitation of the resin and aspiration used for filtration. A mercury regulator ensured constant N_2 pressure. The filter was kept loosely covered with a polyethylene stopper. The reagents were added manually.

Chain Building with *o*-Nitrophenyl Esters.—Aminobenzhydryl

(29) In the ir spectrum, the active ester carbonyl band of *o*-nitrophenyl esters appears at a lower wavelength (5.62 μ) than the corresponding band of the para isomers (5.65 μ). This is in harmony with the higher reactivity of the ortho derivatives.

(30) M. Bodanszky, G. S. Denning, Jr., and V. du Vigneaud, *Biochem. Prep.*, **10**, 122 (1963).

(31) The analytical sample was dried over P_2O_5 at 40° and *ca.* 0.1 mm for 2 hr. Drying at a higher temperature was not attempted because of the lack of stability of active esters of glutamine.

TABLE I

A STUDY OF POOLED FRACTIONS FROM COUNTERCURRENT DISTRIBUTION OF CRUDE COMPOUND I FROM ACTIVE ESTER SYNTHESIS

Pooled fraction (tube no.)	Tlc (R_fA)	Paper chromatogram	Area of peaks, cm² [a] 19 min	22 min	27 min	46[c] min	50 min	Amino acid analysis[b] Asp	Glu	Pro	Gly	Leu	Bzl-Cys
0–19	0.38 (w)[d]		6	0.5	0.5		1	0.8	0.9	0.7	1.0	1.4	
20–24	0.41[e]	0.75 (w)[d]						0.9	0.95	1.2	1.0	1.5	0.3
	0.32 (m)	0.71 (m)											
	0.21 (m)	0.61 (m)											
		0.50 (w)											
25–29	0.36[e] (s)	0.75 (s)			3	14		1.0	1.0	1.05	1.0	1.9	0.6
		0.61 (w)											
30–34	0.36 (s)	0.75 (s)			0.7	30		1.0	0.9	1.2	1.0	2.3	0.9
35–40	0.36 (s)	0.75 (s)				25		1.2	0.9	1.1	1.0	1.9	0.9
41–50	0.57 (w)	0.89 (t)				1		0.9	0.85	0.9	1.0	1.3	0.8
	0.39 (m)	0.77 (w)											
51–60	0.62 (w)							0.5	0.4	1.0	1.0	1.3	0.4
	0.41 (w)												

[a] 0.5 mg of unhydrolyzed sample was applied to the short column of the amino acid analyzer. 18 min, etc., indicates the elution time measured at the maxima. [b] Of hydrolysates. [c] Compound I. [d] Intensity: s, strong; m, medium; w, weak; t, trace. [e] Tailed.

resin (2.67 g) was placed into the reaction vessel and covered with a solution of *t*-Boc-Gly-ONO (1.18 g, 4 mmol) in DMF (20 ml, dried over Linde 4A Molecular Sieve) and gently agitated with a slow stream of N_2. Samples (5 μl) were removed at about hourly intervals and diluted to 10 ml with 95% EtOH containing 1% 1 *N* HCl. Absorption at 350 mμ (ε 2600) was used to measure the liberated *o*-nitrophenol. When no increase in the optical density was observed, the solution was removed by suction and the resin was washed with DMF (25 ml), followed by CH_2Cl_2 (60 ml in three portions). Small samples of the peptidyl resin were used for the ninhydrin test[22] (*ca.* 2 mg) and amino acid analysis (10 mg). Any remaining amino groups were acetylated with Ac_2O (0.5 ml) in CH_2Cl_2 (20 ml) for 45 min. The Boc group was removed by treatment with 25% TFA in CH_2Cl_2 (20 ml) for 1 min and by a second treatment for 25 min. The resin was then washed with CH_2Cl_2 (100 ml in four portions). Liberation of the amino groups was accomplished by treatment of the resin with triethylamine (TEA) in CH_2Cl_2 (2.5 ml/17.5 ml) for 1 min, removal of the solution by suction, and a second treatment, this time for 5 min, followed by washing with CH_2Cl_2 (240 ml in eight portions). The removal of Boc-protecting groups and the liberation of amino groups was carried out in the same manner throughout subsequent chain-lengthening steps. Acylation with the remaining protected active esters was carried out in DMF as follows. Boc-L-Leu-ONO (5 mmol) was added in three portions (two portions of 2 mmol each, followed by a 1-mmol portion), Boc-L-Pro-ONO (4.6 mmol) in three portions (3, 1, and 0.6 mmol), Boc-*S*-Bzl-L-Cys-ONO (4.5 mmol) in two portions (3.5 and 1 mmol), Boc-L-Asn-ONO (5.2 mmol) in three portions (3.2 mmol, and two portions of 1 mmol), Boc-L-Gln-ONO (5 mmol) in three portions (3 mmol, and two portions of 1 mmol), and Boc-L-Leu-ONO (8 mmol) in two portions (6 and 2 mmol). The final addition, with the exception of the asparagine active ester, led to no measureable reaction. The incorporation of the first two amino acids required only a few hours; the subsequent reactions were allowed to proceed overnight. At the completion of chain building, the protected amino acyl resin weighed 5.64 g, an increase of 2.97 g (without correction for samples removed). This corresponds to 3.25 mmol of protected heptapeptide or 1.2 mmol per gram of aminobenzhydryl resin. Amino acid analysis: Asp, 1.0; Glu, 0.95; Pro, 1.2; Gly, 1.0; Leu, 1.9, Bzl-Cys, 0.9.

Chain Building *via* Coupling with DCC.—Aminobenzhydryl resin (1.0 g), liberated from the hydrochloride as described above, was acylated with 2 mmol of Boc-Gly and 2 mmol of DCC, the latter applied in two equal portions. After the resin was washed alternately with CH_2Cl_2 and CH_3OH several times, the possibly remaining amino groups were acetylated with Ac_2O (0.5 ml) in CH_2Cl_2 (20 ml). The subsequent washings, deprotection and the incorporation of the next amino acid, etc., were carried out according to the procedure described in ref 11, except that a sintered glass filter (*cf.* above) was used as reaction vessel. The heat loss due to evaporation of CH_2Cl_2 was compensated by gentle warming of the filter with a warm air stream. The Boc derivatives of asparagine and glutamine were dissolved in CH_2Cl_2 with the addition of a small volume of DMF. All Boc-amino acids, with the exception of Boc-Gly, were applied in 20-mmol amounts. The weight increase after the completion of the synthesis of the protected heptapeptidyl resin, 1.06 g, corresponds to about 1.16 mmol of protected heptapeptide. Amino acid analysis: Asp, 1.0; Glu, 0.8; Pro, 0.9; Gly, 1.0; Leu, 1.9; Bzl-Cys, 0.8.

Acidolytic Removal of the Peptide Amide I from the Resin.—One-third (1.88 g) of the protected heptapeptidylaminobenzhydryl resin was treated with trifluoroacetic acid (TFA, 10 ml) overnight. The solution was separated from the resin by filtration and the latter was washed with TFA (10 ml) and CH_2Cl_2 (20 ml). Evaporation *in vacuo* left an oily residue that on trituration with ether (20 ml) afforded an off-white solid; this was dried *in vacuo* over KOH, 157 mg, mp 195–207°. A second treatment of the resin, for 24 hr, yielded 134 mg; a third and a fourth treatment, each for 24 hr, yielded 109 and 89 mg, respectively. Further exposure to TFA, for about 1 week each time, gave 239, 93, 27, and 18 mg, respectively. A total of 866 mg was collected. The first five fractions (a total of 728 mg) were found to be indistinguishable from each other on paper chromatograms (R_f 0.75 and a faint spot at R_f 0.61) and were pooled. On the short column of the amino acid analyzer, the unhydrolyzed material (0.5 mg) showed the peak corresponding to compound I at 46 min (20 cm²). Impurities emerged at 19 and 27 min with areas of 0.4 and 1 cm², respectively. An aliquot of this material was used for countercurrent distribution, as described below.

On completion of the second synthesis, in which DCC was used for coupling, a 67% aliquot of the protected heptapeptidylaminobenzhydryl resin (1.39 g) was cleaved similarly. The crude trifluoroacetate was collected in 513-, 128-, and 51-mg fractions after three exposures lasting for 5 days each. A total of 692 mg was collected. Paper chromatography of the largest fraction showed the major product at R_f 0.75, a slight impurity at R_f 0.62, and also a by-product at R_f 0.89. A sample (0.5 mg) applied unhydrolyzed to the short column revealed impurities at 27 and 66 min, with areas of 0.8 and 0.3 cm², respectively. The main product appeared with its maximum at 46 min (10 cm²).

Conversion of the Trifluoroacetate of Heptapeptide Amide I to the Free Amine.—This was carried out by following the procedure of Jost, Rudinger, and Šorm[32] described for the hydrobromide of a similar heptapeptide. From a sample of compound I (0.50 g) prepared *via* active esters, the free amine was obtained in crystalline form[33] (0.24 g): mp 179–182°; $[\alpha]^{25}D$ −54° (c 1, DMF); tlc R_fA 0.36. The unhydrolyzed material (0.5 mg) applied to the short column of the amino acid analyzer produced a single peak with its maximum emerging at 47 min. Amino acid analysis: Asp, 1.0; Glu, 0.95; Pro, 0.9; Gly, 1.05; Leu, 2.0; Bzl-Cys, 0.8; NH_3, 3.2.

Countercurrent Distribution of Compound I.—A sample (0.65 g) of I (trifluoroacetate) dissolved in the lower phase (10 ml) of the system 1-BuOH–EtOH–1% AcOH (4:1:5) was placed into the tube no. 0 of a 60-tube Craig apparatus and distributed with

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TABLE II

A STUDY OF POOLED FRACTIONS FROM COUNTERCURRENT DISTRIBUTION OF CRUDE COMPOUND I FROM SYNTHESIS USING DCC FOR COUPLING

Pooled fraction (tube no.)	Tlc (R_fA)	Paper chromatogram	Area of peaks, cm² [a] 19 min	22 min	27 min	46[c] min	52 min	62 min	66 min	Amino acid analysis[b] Asp	Glu	Pro	Gly	Leu	Bzl-Cys
0–7	0.33 (w)[d]									1.0	1.0		0.3	0.8	
	0.24 (w)			2											
	0.12 (w)														
8–20	0.56 (m)	0.53 (w)[d]	0.3	1.5	0.2		2		3	1.4	1.0	0.3	0.5	1.8	*f*
	0.46 (s)	0.33 (w)													
	0.30 (s)	0.26 (w)													
	0.12 (m)														
24–33	0.44 (m)	0.89 (m)			2	18				0.9	0.8	0.8	1.0	1.7	0.6
	0.36[e] (s)	0.75 (s)													
		0.61 (m)													
34–44	0.59 (m)	0.89 (m)				16				0.85	0.75	0.9	1.0	2.0	0.9
	0.36 (s)	0.75 (s)													
45–50	0.57 (w)	0.90 (s)						10		0.9	0.7	1.0	1.0	1.8	0.9
	0.51 (m)														

[a–e] For references *a–e*, *cf.* Table I. [f] This fraction contains sulfur. Thus the absence of Bzl-Cys in the amino acid analysis should be due to some side reaction involving this residue, and not to a lack of its incorporation.

10-ml phases through 60 transfers. A weight curve was determined by evaporation of samples from selected tubes, from the lower phase up to tube no. 30 and from the upper phase beyond this tube. The distribution curve is shown in Figure 1. A sample (0.40 g) of the crude trifluoroacetate from the DCC-mediated synthesis was distributed in the same system; the distribution curve is shown in Figure 2.

Samples from different areas of these distributions were examined on paper chromatograms, on tlc, and on the short column of the amino acid analyzer and also by quantitative amino acid analysis of their hydrolysates. The results of this study are summarized in Tables I and II.

A sample (8 mg) of fractions 45–50 from the distribution of the crude product of the second synthesis (with DCC, *cf.* Figure 2) was dissolved in liquid NH_3 (*ca.* 50 ml) and treated with CH_3OH (0.3 ml) and Na[34] to produce a blue color which persisted for about 20 min. After evaporation of the ammonia, the residue was dissolved in H_2O (4 ml) and an aliquot (1 ml) was evaporated with a stream of N_2 with warming. The residue was stored *in vacuo* over H_2SO_4 overnight and then hydrolyzed with 6 *N* HCl for amino acid analysis in the usual way. No significant decrease of aspartic acid content was observed and only very small amounts of basic amino acids appeared. Thus, the presence of the fast-moving component cannot be explained by nitril formation from the asparagine or glutamine residues; the question about the nature of this by-product remained unresolved.

Purified material from the active ester synthesis was obtained by pooling the contents of tubes 30–40 (0.40 g): mp 195–207°; $[\alpha]^{25}D$ −78° (*c* 2, H_2O); tlc R_fA 0.36; paper chromatogram *R* 0.75. Amino acid analysis: Asp, 1.0; Glu, 0.85; Pro, 1.0; Gly, 1.0; Leu, 2.0; Bzl-Cys, 0.9.

Anal. Calcd for $C_{40}H_{61}N_{10}O_{11}SF_3$ (947.0): C, 50.7; H, 6.5; N, 14.8; S, 3.4; F, 6.0. Calcd for $C_{40}H_{61}N_{10}O_{11}SF_3 \cdot H_2O$ (965.1): C, 49.8; H, 6.6; N, 14.5; S, 3.3; F, 5.9. Found: C, 49.6; H, 6.6; N, 14.0; S, 3.5; F, 6.1.

Registry No.—I free amine, 38605-53-7; I trifluoroacetate salt, 38605-54-8; *t*-Boc-Gly *o*-nitrophenyl ester, 38606-09-6; *t*-Boc-Gly, 4530-20-5; *o*-nitrophenol, 88-75-5; *t*-Boc-L-Leu *o*-nitrophenyl ester, 24868-52-8; *t*-Boc-L-Pro *o*-nitrophenyl ester, 38605-56-0; *t*-Boc-*S*-benzyl-L-Cys *o*-nitrophenyl ester, 38605-57-1; *t*-Boc-L-Asp *o*-nitrophenyl ester, 38605-58-2; *t*-Boc-L-Gln *o*-nitrophenyl ester, 38605-59-3.

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Intramolecular and Divalent Metal Ion Catalysis. The Hydrolytic Mechanism of O-Phenyl N-(Glycyl)phosphoramidate

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The pH–rate profile for the hydrolysis of O-phenyl N-(glycyl)phosphoramidate (II) reveals intramolecular catalysis by the neighboring carboxylate function which serves to accelerate greatly the rate of P–O bond cleavage. In fact, P–O bond fission in the reference compound, O-(phenyl)phosphoramidate (I), is not detected. The catalysis of II is further enhanced ($>10^2$) by the addition of Zn^{2+} or Mg^{2+} ions, which do not affect the rate of hydrolysis of I. A mechanism is postulated featuring formation of a five-membered cyclic acyl phosphate (product studies in hydroxylamine buffer) which decomposes *via* water attack on phosphorus rather than carbon (^{18}O tracer experiments). These findings suggest that two types of biologically important catalysis may be incorporated into a model system in order to confer dramatic reactivity on a normally unreactive phosphate diester. These results contrast with the Cu(II)-catalyzed hydrolysis of salicyl phosphate, which apparently is of the general-acid type with carboxylate merely serving as a coordinating ligand.

Intramolecular models for biological phosphoryl transfer reactions at the diester level have been particularly useful in defining the probable existence of intermediate pentacovalent species on these pathways.[2,3] Previous quantitative investigations had focused mainly on the behavior of O-phosphate diesters and featured nucleophilic carboxyl or carboxylate catalysis.[3,4] A striking stereochemical aspect of carboxylate catalysis in the intramolecular diester systems is the preferential exocyclic group expulsion by an *o*-carboxylate, *e.g.*, loss of phenol during hydrolysis of phenyl (2-carboxyphenyl)phosphate, despite the relative leaving group pK_a values. This phenomenon has been attributed to a restricted pseudorotation of the dianionic pentacovalent intermediate.[4,5]

We posed several questions: (1) will the substitution of nitrogen for oxygen affect the stereochemical course; (2) will metal ions alter the mode of decomposition of the presumed intermediate; and (3) is a synergistic acceleration of the rate of hydrolysis by both intramolecular and metal ion catalysis feasible?[6] Answers to these questions compose the major thesis of this paper.

Experimental Section

Microanalyses for nitrogen and phosphorus were performed by Midwest Microlab. Twice distilled deionized water, D_2O (99.8% Diaprep) and $H_2{}^{18}O$ (8.1 atom %, Bio-Rad) were employed as solvents. Reagent-grade buffer materials, metal nitrates, and other solvents were used without further purification, except where noted. Descending paper chromatography was run on Schleicher and Schuell orange ribbon 589c paper in 0.1 *M* aqueous K_2CO_3–absolute ethanol (3.5:6.5) and developed with Hanes and Isherwood spray[7] (phosphate) and 1% ninhydrin spray (glycine). Nmr spectra in D_2O were measured on a Varian Associates A-60 spectrometer using sodium 2,2-dimethyl-2-silapentane-5-sulfonate as the internal standard. Uv spectra were obtained on a Cary 14 recording spectrophotometer. Mass spectra were measured on an MA 902-AEI spectrometer.

The monopotassium salt of O-(phenyl)phosphoramidate (I) was prepared from the diphenyl phosphoramidate precursor $[NH_2PO_3(C_6H_5)_2]$ by the method of Stokes,[8] uv $\lambda_{max}^{0.1\ M\ KOH}$ 262 mμ (ε 440).

Anal. Calcd for $C_6H_7N_1P_1O_3K\cdot H_2O$: N, 6.12; P, 13.52. Found: N, 6.40; P, 13.50.

The dipotassium salt of O-phenyl N-(glycyl)phosphoramidate (II) was prepared by an adaptation of the method of Zervas, *et al.*[9] Diphenyl phosphorochloridate (0.044 mol) was added dropwise to a rapidly stirring, ice-cold suspension of glycine ethyl ester hydrochloride (0.040 mol) in anhydrous pyridine (30 ml). The mixture was stirred for 2 hr and poured into ice water (100 ml). The diphenyl derivative separated as an oil that crystallized upon scratching. The white crystals were collected by filtration, washed with water, dried under vacuum, and recrystallized from ether, *m/e* 335 (calcd, 335), mp 76–77° (uncorrected).

A suspension of the diphenyl derivative (0.0057 mol) in 0.40 *N* potassium hydroxide (35 ml) was stirred for 6 hr at room temperature. The reaction mixture was filtered and the filtrate was titrated to pH 7 with glacial acetic acid. The solution was evaporated under vacuum to 3 ml and cold absolute ethanol (10 ml) was added. Precipitation of the desired salt was accomplished by the dropwise addition of cold acetone (10 ml). The product was isolated by filtration and further purified by dissolving in water (1 ml) and adding absolute ethanol (5 ml) followed by precipitation again with acetone. The compound was dried *in vacuo* and stored at −10°. The overall yield was approximately 50% and no attempts were made to maximize the yield. II showed nmr (D_2O) δ 3.48 (d, 2 H, $-NCH_2CO_2-$) and 7.33 (broad multiplet, 5 H, C_6H_5-), at pH 6; $\lambda_{max}^{0.1\ M\ KOH}$ 262 mμ (ε 480). Paper chromatography revealed one spot, R_f 0.53, which developed for phosphate, glycine, and phenol (visualized by uv irradiation).

Anal. Calcd for $C_8H_8N_1P_1O_5K_2\cdot H_2O$: N, 4.33; P, 9.58. Found: N, 4.42; P, 9.57.

Salicyl phosphate (III) was prepared according to the procedure of Chanley, *et al.*[10]

Dissociation Constants.—Values for dissociation constants for I and II were determined in a Metrohm cell (EA 662) at 25°, μ 0.2, KNO_3. Hydrogen ion corrections were applied as described by Albert and Serjeant[11] (Table I).

Apparatus.—Instrumentation used in this study has been described previously.[12] Kinetic runs were carried out in Kimax (No. 45066) screw-cap tubes whose threads were wrapped with Teflon tape to prevent evaporation. Tubes were maintained at reaction temperature (±0.1°) by immersion in a circulating water bath.

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Kinetics.—Kinetic experiments were initiated by the addition of a 1-ml aliquot from a freshly prepared aqueous stock solution (0.01 *M*) of the phosphoramidate to 9 ml of the preequilibrated buffer solution or by the direct addition of the phosphoramidate (10^{-5} mol) to 10 ml of preequilibrated buffer solution.

Hydrolysis of I was monitored by analysis for ammonia employing the following modification of the Weatherburn method.[13] The aliquot (0.2 ml) to be analyzed (0–6 μmol in ammonia) was added to 5.0 ml of reagent A, which consists of 5.0 g of phenol and 25 mg of sodium nitroprusside made up to 500 ml with water. The tube was covered with Parafilm and shaken vigorously to mix. To this solution, 5 ml of reagent B, which consists of 2.5 g of sodium hydroxide and 4.2 ml of commercially available Clorox made up to 500 ml with water, was added. The tube was thoroughly mixed and the intensity was read at 625 mμ after 20 min of incubation at 35°. Compound I gave no initial reading so that apparently no hydrolysis occurred under the assay conditions. Duplicate runs agreed within ±5%.

The spontaneous and metal ion catalyzed hydrolysis of II, at pH >6, was monitored by measuring phenoxide ion at 285 mμ by withdrawing 1-ml aliquots and adding 1 ml of 1 *N* potassium hydroxide. An alternative analysis measured the production of orthophosphate by the method of Martin and Doty,[14] as modified by Jencks.[15] Duplicate runs agreed within ±4%. In the presence of magnesium ion, the addition of KOH precipitated $Mg(OH)_2$, which was removed by centrifugation prior to measurement of the absorption.

The disappearance of II at pH <6 was monitored by measuring the liberation of phenoxide ion at 285 mμ by the following procedure. A 1-ml aliquot was added to 1 ml of 1 *N* potassium hydroxide and the absorbance was measured. This solution was sealed into a breakseal ampoule and incubated in a 75° water bath for 24 hr, and the absorbance at 285 mμ was again measured. Under the assay conditions the dianion of phenyl phosphate—a competing product at pH <6—is stable, so that any increase in absorbance at 285 mμ arises from phenolate due to the total hydrolysis of the remainder of II. The concentration of II at a given time therefore is proportional to ΔOD_t, the difference between the two absorbance readings at 285 mμ. Hydrolysis of phenyl phosphate monoanion (10^{-3} min^{-1}, 75°),[16] a competing reaction at pH <6, therefore does not interfere. The observed first-order rate constants for the hydrolysis of II, at pH <6, were calculated from slopes of log ΔOD_t against time. All plots were linear to at least three half-lives and duplicate runs agreed within ±4%.

The hydrolysis of III at 25° was monitored by measuring orthophosphate release by the method of Martin and Doty. Initial ester concentrations were *ca.* 5×10^{-3} *M*.

Acyl trapping reactions with II were carried out in 0.67 *M* hydroxylamine hydrochloride, recrystallized prior to use, at pH 7.2, 75°. The rate was determined by measuring the production of phenoxide ion at 285 mμ as described above. With hydroxylamine in excess, pseudo-first-order kinetics were observed. Similar trapping experiments were attempted with III employing 0.4 *M* hydroxylamine (as free base) at pH 5.6, 25°, in the absence and presence of metal ion.

Buffers employed in the spontaneous hydrolysis of I and II were nitric acid (pH <1.5), oxalate (0.2 *M*, pH 1.5–2.0), glycine (0.1 *M*, pH 2.0–3.0), citrate (0.033 *M*, pH 3.0–4.0), acetate (0.2 *M*, pH 4.0–5.5), phosphate (0.033 *M*), pH 6.0–7.0), and Tham (0.2 *M*, pH 7.2–9.0) with μ 0.2, KNO_3. Buffers used in the metal ion catalyzed hydrolysis of II were acetate (0.002 *M*, pH 4.0–5.5) and Tham (0.002 *M*, pH 7.2–9.2) with μ 0.2, KNO_3. Acetate buffer (0.4 *M*, μ 1.0, KCl) was employed for the spontaneous and metal ion catalyzed hydrolysis of III.

Buffer effects in both the spontaneous and metal ion catalyzed hydrolysis were negligible over a 0.1 *M* change in buffer concentration. The pH was measured at 25° (glass electrode) upon initiation and after completion of the kinetic runs; those exhibiting pH drift greater than ±0.05 unit were discarded. Buffer corrections were applied to those runs at 75° employing the apparent heats of ionization from data in ref 17. Deuterium oxide buffers were *ca.* 98% D_2O after correction for addition of hydrogen acids and bases. The kinetic deuterium solvent isotope effect (pH 6.6) was calculated utilizing rates measured in identical H_2O and D_2O buffers in the pH-independent region.

^{18}O Tracer Experiments.—The dipotassium salt of II (15 mg) was hydrolyzed to completion (*i.e.*, to glycine, inorganic phosphate, and phenol) in 2 ml of 8.1% ^{18}O-enriched acetate buffer (pH 5.8, μ 0.1, 75°) or 0.4 *M* chloroacetate buffer (pH 2.9, μ 0.2, 75°). The solution was added to an Amberlite IR-120 column (1 × 5 cm) in the ammonium form, and eluted first with water (40 ml) and then 1 *N* ammonium hydroxide (40 ml). The fraction eluted with water contained inorganic phosphate (Martin and Doty method) and phenol (spectrophotometric assay at 285 mμ). Isolation of inorganic phosphate and conversion of the oxygens to carbon dioxide has been described previously.[18,19] The fraction eluted with ammonium hydroxide was evaporated *in vacuo* to dryness.

A fraction of the residue was dissolved in a minimal amount of water and chromatographed according to the procedure of Fieser for the identification of glycine.[20] The remainder was redissolved in 0.1 ml of 0.01 *M* ammonium hydroxide and the silver glycinate precipitated upon the addition of solid silver nitrate (10% excess). Pyrolytic decarboxylation of silver glycine in a vacuum train yielded carbon dioxide, isolated by the method in ref 19.

The dipotassium salt of II (15 mg) was hydrolyzed to completion in 2 ml of 8.1% ^{18}O-enriched acetate buffer (pH 6.0, μ 0.1, 35°) in the presence of 0.5 *M* $Zn(NO_3)_2$. The resulting white precipitate, $Zn_3(PO_4)_2$, which formed, was isolated by centrifugation, washed with 95% ethanol and absolute ether, and dried *in vacuo*. The zinc phosphate was converted to potassium dihydrogen phosphate by the method of Haake and Westheimer.[21] The oxygen of potassium dihydrogen phosphate was converted to carbon dioxide according to the method of Boyer, *et al.*[19]

The relative isotopic abundances occurring in the carbon dioxide were determined on an MS 902 AEI mass spectrometer by measuring peak heights directly from the ion signal collector. Tank carbon dioxide was run as a standard prior to determinations.

Products.—The products of hydrolysis of I and II at t_∞ were identified by paper chromatography utilizing glycine, R_f 0.50, inorganic phosphate, R_f 0.12, and phenyl phosphate (uv visualization and Hanes and Isherwood spray) as standards. The observed product of hydrolysis of I at pH 2.0 was phenyl phosphate. The observed products of hydrolysis of II at pH 2.0 were glycine and phenyl phosphate, and a trace amount of inorganic phosphate, and at pH >6 in the absence and presence of metal ions were glycine, phenol, and inorganic phosphate at all temperatures.

Spectrophotometric scanning (340–210 mμ) at t_∞ of the reaction solutions of II at pH >6 disclosed ultraviolet spectra identical with quantitative liberation of phenol. Below pH 6, the products of hydrolysis are pH dependent and the mole fraction of phenol produced *via* P–O bond cleavage was calculated from the ratio of the phenol concentrations measured at t_∞ to the initial concentration of II obtained by total hydrolysis to phenol. In practice this was accomplished by starting with a known concentration of II and measuring the OD of phenolate ion (see above) against time until successive readings at *ca.* 1–3-hr intervals agreed within experimental error. Since the hydrolysis of phenyl phosphate to phenol and inorganic phosphate was a competing reaction, the mole per cent of phenol was calculated for only those runs at pH values in which II hydrolyzed at least 50-fold faster than phenyl phosphate.

The products of the hydrolysis of III in the absence and pres-

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(18) (a) S. J. Benkovic and E. J. Sampson, *J. Amer. Chem. Soc.*, **93**, 4009 (1971). (b) The decomposition of IV is given by the expression $k_p = k_{obsd}K_ak_{-b}k_h/k_bk_{-h}$, where $K_a = 10^{-4}$ *M*, $k_b/k_{-h} \cong 10^{-6}$ (approximation for the steady-state concentration of IV), and $k_{-h}/k_h = 10^{-13}$ *M*. The latter is estimated from the equation of Branch and Calvin: G. E. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1941. The calculated value of $k_p \cong 10^9$ sec^{-1} should be compared to that deduced for k_{-h} (*ca.* 10^{-2} sec^{-1}), since k_h is diffusion controlled. Implicit in the above preequilibrium derivation is the assumption that $k_h[H^+] \gg k_p$, which is untenable at pH ≧ 7 in view of the calculated value of k_p.

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(21) P. Haake and F. Westheimer, *J. Amer. Chem. Soc.*, **83**, 1102 (1961).

TABLE I
RATE AND DISSOCIATION CONSTANTS OF I AND II

Compd	k_H, M^{-1} min^{-1}	k_1, min^{-1}	$k_2 \times 10^3$, min^{-1}	$k_3 \times 10^3$, min^{-1}	pK_{a_1}[a]	pK_{a_2}[a]
I[b]	25	0.15			2.23 ± 0.1	
II[b]		1.25	8.1	8.77	1.9 ± 0.2	4.12 ± 0.03
II[c]	1.78	0.023	0.71	0.12	1.9 ± 0.2	4.12 ± 0.03

[a] Dissociation constants were determined at 25° (μ 0.2). [b] Rate constants were determined at 75°. [c] Rate constants were determined at 35°.

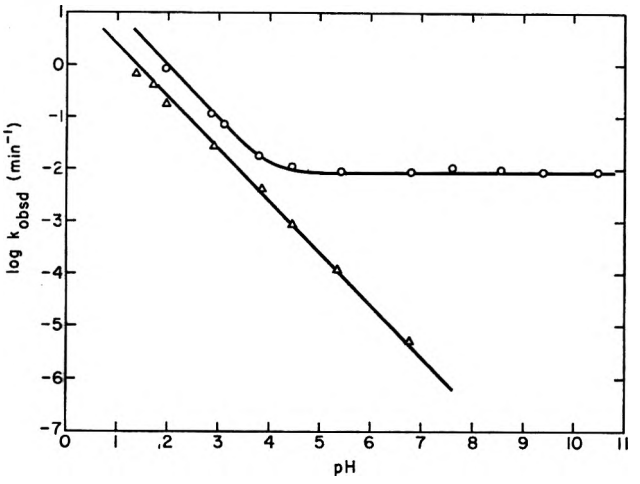


Figure 1.—The log k_{obsd}–pH rate profile for the hydrolysis of I, △, and II, O, at 75°, μ 0.2. Solid lines are theoretical curves calculated from values listed in Table I.

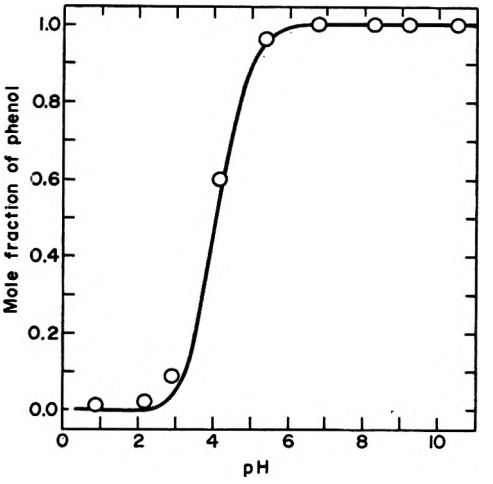


Figure 2.—Plot of the mole fraction of phenol liberated at t_∞ *vs.* pH, for the hydrolysis of II at 35°, μ 0.2. The solid line is the theoretical curve calculated from eq 3 utilizing pK_{a2} = 4.12.

ence of metal ion previously have been shown to be salicylic acid and inorganic phosphate.[22,23]

The mole fraction of glycylhydroxamic acid produced in the acyl trapping experiment described above was calculated from the ratio of hydroxamic acid concentrations measured at t_∞ to the value observed for the total solvolysis of glycine ethyl ester hydrochloride under identical conditions (0.015 *M* substrate, 0.67 *M* hydroxylamine, pH 7.2, 75°). Hydroxamic acid was developed by the procedure of Lippman and Tuttle.[24] Glycine controls revealed no significant hydroxamic acid formation at identical reagent concentrations (0.015 *M*). Duplicate runs agreed within ±15%.

Results and Discussion

The pH–rate profiles for the hydrolysis of *O*-(phenyl)-phosphoramidate (I) and *O*-phenyl *N*-(glycyl)phosphoramidate (II) are shown in Figure 1. The products of hydrolysis of I are ammonia and phenyl phosphate over the pH range investigated. The solid line for I was calculated from eq 1, where k_H is the second-order

$$k_{obsd} = (k_H a_H + k_1)\left(\frac{a_H}{K_{a_1} + a_H}\right) \quad (1)$$

rate constant associated with hydronium ion catalyzed hydrolysis of the neutral species, k_1 is the first-order rate constant for the spontaneous hydrolysis of the neutral species, K_{a_1} is the dissociation constant for the neutral species, and a_H is the activity of hydrogen as measured by the glass electrode. The solid lines for the pH–rate profiles (Figure 1, 75°, Figure 3, 35°) and pH product distribution profile (Figure 2) for II were calculated from eq 2 and 3, respectively, where k_H, k_1, and K_{a_1} are defined as above, K_{a_2} is assigned to the dissociation

$$k_{obsd} = \frac{a_H^2(k_H a_H + k_1) + K_{a_1}(k_2 a_H + K_{a_2} k_3)}{a_H(a_H + K_{a_1}) + K_{a_1}K_{a_2}} \quad (2)$$

$$\text{Mole fraction of phenol} = \left(\frac{K_{a_2}}{K_{a_2} + a_H}\right) \quad (3)$$

constant of the carboxyl function, and K_2 and k_3 are first-order rate constants associated with the hydrolysis of the mono- and dianion, respectively. Values of the rate and dissociation constants utilized in eq 1, 2, and 3 appear in Table I.

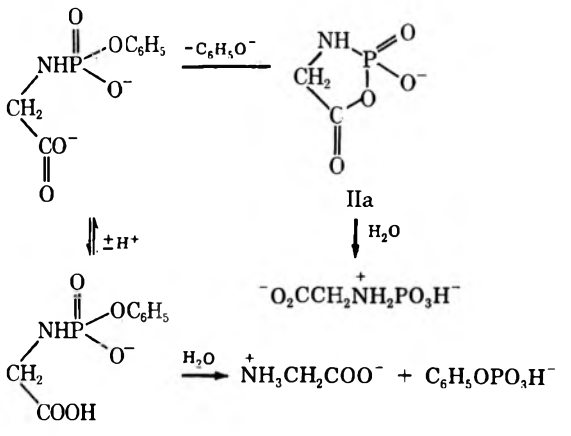
At pH <2, hydrolysis of II proceeds *via* P–N bond cleavage with concomitant formation of glycine and phenyl phosphate. The mechanisms of hydronium ion and spontaneous hydrolysis of the neutral species of mono- and unsubstituted phosphoramidates have been investigated previously;[25,26] therefore the subsequent study has been restricted to the pH-independent region where the observed catalysis is maximum. At pH 6–11, phenol, inorganic phosphate (quantitative formation), and glycine (qualitative) are observed as the products of hydrolysis. Presumably the P–O bond is preferentially cleaved, forming phenol and *N*-phosphorylglycine. The subsequent hydrolysis of *N*-phosphorylglycine to glycine and inorganic phosphate is anticipated to be 30-fold faster at 75° than the hydrolysis of II based on the structure–reactivity correlation for the hydrolysis of phosphoramidate monoester monoanions and the estimated pK_a of glycine (9.6, 75°).[18] Alternatively, the formation of phenol by sub-

(22) M. L. Bender and J. H. Lawlor, *J. Amer. Chem. Soc.*, **85**, 3010 (1963).
(23) R. Hofstetter, Y. Murakami, G. Mont, and A. E. Martell, *ibid.*, **84**, 3041 (1962).
(24) F. Lippman and C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945).
(25) I. Oney and M. Caplow, *J. Amer. Chem. Soc.*, **89**, 6972 (1967).
(26) S. J. Benkovic and P. A. Benkovic, *ibid.*, **90**, 2646 (1968), and references cited therein.

sequent hydrolysis of phenyl phosphate as a result of P–N bond cleavage appears unlikely, since phenyl phosphate dianion hydrolyzes 10^6 fold less rapidly than II.[16]

The involvement of the neighboring carboxylate anion in the hydrolysis of II is supported by (1) the broad pH-independent region at pH >6, (2) the large rate enhancement for P–O fission observed at pH >7, *ca.* 10^4, even though amine expulsion in I is at least a factor of 10^2 faster than phenol,[18] and (3) the change in products resulting from the titration of a group (pK_a 4.1) as shown in Figure 2. A small deuterium solvent kinetic isotope effect observed at pH 6.6 for II, $k_H/k_D = 1.2$, suggests that a proton transfer is not involved in the rate-determining step. Furthermore, the entropy of activation in the pH-independent region is −15 eu. This $\Delta S^{\pm}$ value is identical with those reported for benzyl phosphoenolpyruvate[3] and phenyl-(2-carboxyphenyl)phosphate,[4] in which nucleophilic catalysis by a neighboring carboxyl and/or carboxylate group has been implicated. These collective data appear to be in accord with the mechanism shown in Scheme I.

SCHEME I



In an attempt to trap the cyclic acyl intermediate IIa, the solvolysis of II was conducted in 0.67 *M* hydroxylamine.[3] A small but detectable concentration of hydroxamic acid (8 ± 2% of the theoretical) was produced. However, the observed rate of phenol release was *ca.* tenfold greater (0.086 min^{-1}, 75°) in the presence of hydroxylamine than for the spontaneous hydrolysis. This finding may be rationalized in terms of preferential nucleophilic attack on phosphorus by hydroxylamine prior to formation of IIa. Competing intermolecular catalysis by hydroxylamine is further supported by the observation of similar processes at rates that would be competitive for both *O*-phosphate diesters and phosphoramidate monoesters in the presence of added nucleophiles.[27,28]

The results of the total hydrolysis of II in 8.1% ^{18}O-enriched acetate buffer (pH 5.8) are shown in Table II. These data are interpreted as indicating the incorporation of two oxygen atoms of solvent per molecule of inorganic phosphate and no incorporation of excess ^{18}O into the carboxyl moiety of glycine during the hydrolysis of II. A control experiment with glycine and inorganic phosphate revealed that no exchange with the solvent occurred with either product during the time of the hydrolysis.

(27) A. J. Kirby and M. Younas, *J. Chem. Soc. B*, 1165 (1970).
(28) G. W. Jameson and J. M. Lawlor, *ibid.*, 53 (1970).

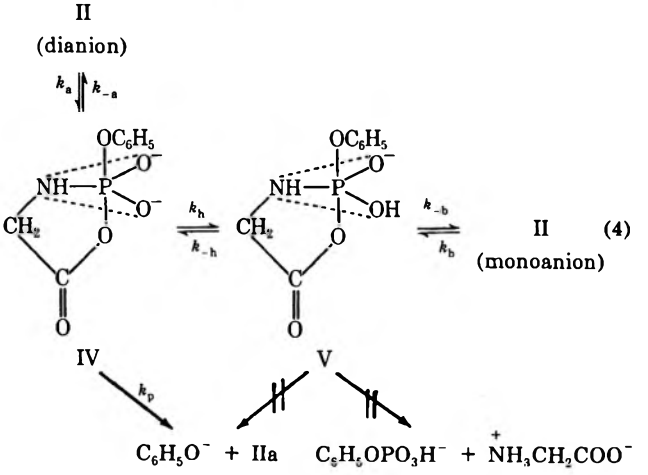
TABLE II
^{18}O TRACER STUDIES ON THE HYDROLYSIS OF II[a]

Compd	^{18}O excess	Atoms of solvent incorporated per molecule of product[b]
II (pH 5.8)	3.8 (in KH_2PO_4)	1.9[c]
II (pH 5.8)	0.0 (in glycine)	0
II + Zn^{2+} (0.5 *M*, pH 5.8)	3.6 (in KH_2PO_4)	1.8[c]
KH_2PO_4 (pH 5.8)	0.0	0
Glycine (pH 5.8)	0.0	0
Glycine (pH 2.9)	0.0	0

[a] 8.1% ^{18}O-enriched buffer. [b] Error bounds ±7%. These values were corrected for the natural abundance of ^{18}O. [c] These results suggest that 2.0 atoms of solvent are incorporated per molecule of inorganic phosphate. Similar small discrepancies in ^{18}O tracer studies have been observed in other cases, *e.g.*, P. C. Haake and F. H. Westheimer, *J. Amer. Chem. Soc.*, **83**, 162 (1961)

The incorporation of two atoms of solvent per molecule of inorganic phosphate may be viewed as occurring in two consecutive hydrolysis steps. Ring closure followed by preferential attack by water on the phosphoryl center of IIa would introduce the first atom of solvent. Incorporation of the second atom of solvent presumably occurs during the subsequent hydrolysis of *N*-phosphorylglycine. We have previously shown that P–N bond cleavage in the hydrolysis of *N*-(*n*-butyl)phosphoramidate results in the incorporation of only one oxygen atom of solvent per molecule of inorganic phosphate.[18a] These results are in accord with the mechanism in Scheme I.

Although Scheme I is written without explicitly invoking pentacoordinate intermediates, previous studies have implicated their presence.[3,4] Furthermore, their decomposition in this case is anticipated to be rate limiting, since expulsion of carboxylate or carboxyl should be orders of magnitude greater than amine or phenolate. The two probable species, in accord with the preference rules, are IV and V.[5]



The hydrolysis of the monoanion through preequilibrium formation of species V and IV followed by the latter's decomposition is kinetically indistinguishable from hydrolysis of the dianion. However, the calculated rate coefficient, k_p, for collapse of IV to IIa and phenoxide greatly exceeds that for either deprotonation or protonation of V, *i.e.*, k_{-h} and $k_h[H^+]$, invali-

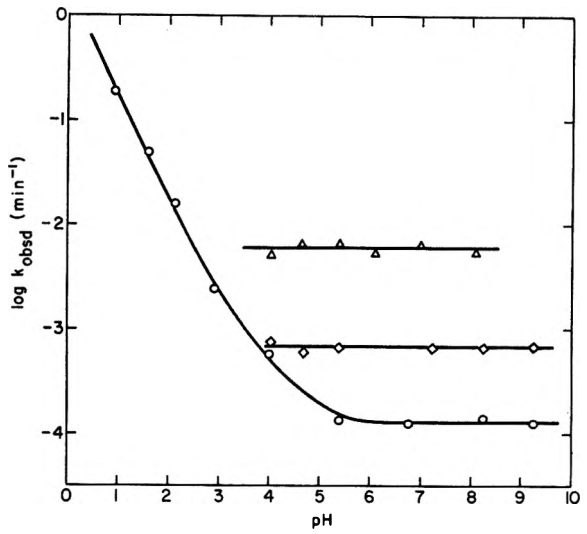


Figure 3.—The log k_{obsd}–pH rate profile for the spontaneous (O), Mg^{2+} (10^{-2} M) catalyzed (◇), and Zn^{2+} (10^{-2} M) catalyzed (△) hydrolysis of II (10^{-3} M) at 35°, μ 0.2.

dating the required preequilibrium assumption.[18b] It is also unlikely that the proton transfer step to solvent is in itself rate determining in view of the high sensitivity of the k_3 term to changes in the para substituent of the phenol.[4]

At pH 2.9 the observed kinetic terms k_1 and k_2 assigned to the neutral and monoanionic species of II comprise 90% of k_{obsd}. However, the appearance of glycine and phenyl phosphate as products upon protonation of II is not accompanied by incorporation of ^{18}O into glycine at pH 2.9, which would be diagnostic of an intermediate acyclic acyl phosphate arising from carboxyl attack which then decomposes *via* C–O bond cleavage. Hence V is either not in prototropic equilibrium with IV as suggested above or the former reacts mainly through k_{-b}. The formation of glycine and phenyl phosphate as products therefore may be assigned to the operation of a competing intermolecular pathway owing to the increased reactivity of the P–N relative to the P–O bond toward acid-catalyzed hydrolysis. Species similar to V, however, are competent in neighboring carboxyl catalysis in *O*-phosphate diester hydrolyses.[3,4]

The pH–rate profiles for the metal ion catalyzed hydrolysis of II in the presence of Zn^{2+} and Mg^{2+} at a [metal]/[substrate] = 10 are shown in Figure 3. Catalysis by such metal ions has not been observed with phosphate diesters previously and was not observed with I. Throughout the pH region of interest the reactive forms of the metal ions presumably are $[Zn(H_2O)^6]^{2+}$ and $[Mg(H_2O)^6]^{2+}$. As before, phenol was released quantitatively.

Plots of log k_{obsd} *vs.* [M_T] for both Zn^{2+} and Mg^{2+} ions are shown in Figure 4. The theoretical curves are calculated from eq 6 based on a scheme assuming preequilibrium formation of a reactive 1:1 ester–metal ion complex ME, where [ME] $\ll$ [M^{2+}]. Given eq 5 it

$$M^{2+} + E \underset{}{\overset{K}{\rightleftharpoons}} ME \xrightarrow{k_M} \text{products} + M^{2+} \qquad (5)$$

(k_0)

may be shown that k_{obsd} is described by eq 6, where [M_T] is the initial stoichiometric concentration of

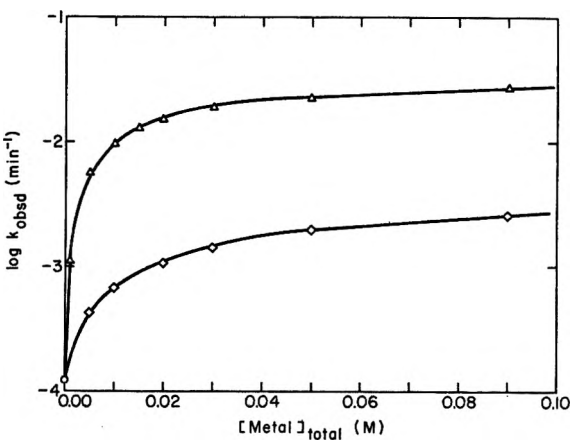


Figure 4.—Plot of log k_{obsd} *vs.* [M_T] for the metal ion catalyzed hydrolysis of II (10^{-3} M), at 35°, μ 0.2, pH 5.5, Mg^{2+} (◇), and Zn^{2+} (△). [M_T] is the initial stoichiometric concentration of the metal ion.

TABLE III
RATE AND ASSOCIATION CONSTANTS FOR THE METAL ION CATALYZED HYDROLYSIS OF II (35°, μ 0.2)

Metal ion	k_M[a] × 10^3, min^{-1}	k_0[b] × 10^4, min^{-1}	K,[c] M^{-1}
Zn	36	1.2	35
Mg	4.8	1.2	13.5

[a] k_M is the first-order rate constant associated with the hydrolysis of the ester–metal ion complex. [b] k_0 is the first-order rate constant for the spontaneous hydrolysis of II. [c] K is the association constant for formation of the ester–metal ion complex.

metal ion; k_0, k_M, and K are defined in Table III. The values of k_{obsd} calculated from eq 6 utilizing the

$$k_{obsd} = \frac{k_0 + K[M_T]k_M}{1 + K[M_T]} \qquad (6)$$

rate constants and dissociation constants in Table III are in satisfactory agreement with the experimentally determined points (see Figure 4). The values of K suggest metal–oxygen ion complexes, implying that ME may represent an initial metal ion–carboxylate complex.[29]

The ^{18}O data (Table II) confirm that two atoms of solvent are incorporated per molecule of inorganic phosphate product during the Zn^{2+}-catalyzed hydrolysis of II. We interpret this finding as indicating that the integrity of the mechanism of bond breaking and bond formation at the phosphorus center of II is unaffected by the presence of metal ions (see above).

The spontaneous and Cu(II) ion catalyzed hydrolysis of salicyl phosphate has been partially reexamined particularly in view of an earlier postulation which featured nucleophilic attack by carboxylate on phosphorus in the presence of the metal ion.[23] This mechanism contrasts with the generally accepted view of general acid catalysis by carboxyl in the spontaneous reaction.[22] Such a scheme requires the intermediacy of a cyclic acyl phosphate (salicyloyl phosphate) and/or an acyclic acyl phosphate (*O*-hydroxybenzoyl phosphate). Either species should lead to a salicyl hydroxamate in the presence of hydroxylamine. The observed rate constants, 2.8×10^{-7} and 3.5×10^{-6} min^{-1} [5×10^{-3} M Cu(II)], are in satisfactory agree-

(29) L. Sillen and A. E. Martell, "Stability Constants of Metal-Ion Complexes," Special Publication 25, Chemical Society, London, 1964.

ment with earlier measurements.[22,23] However, no hydroxamate could be detected during the course of the metal ion catalyzed hydrolysis. The observation of hydroxamate products in other related di- and triester phosphate hydrolyses catalyzed by neighboring carboxyl or carboxylate groups warrants its presence.[30] From this result one may infer that nucleophilic catalysis by carboxylate is limited to di- and triester systems, as for II, and that the occurrence of metal ion catalysis in salicyl phosphate hydrolysis may be attributed to an amplification of the general acid catalysis observed in the absence of metal ion.

One may postulate several alternative mechanisms for the role of the metal ion in the catalysis of II. The metal ion may serve to neutralize the negatively charged phosphoryl oxygen, thereby reducing the electrostatic repulsion encountered by the carboxylate anion, and facilitating displacement. The importance of this effect, however, is apparently a factor of tenfold. This estimate is based on the ratio of the rate constants for phenoxide expulsion by carboxylate from the triester, diphenyl(2-carboxyphenyl) phosphate, and the diester, phenyl(2-carboxyphenyl) phosphate, the latter as the dianion, after correction for differences in the sensitivity of phosphorus to nucleophilic attack in the two systems.[31] Alternatively, the metal ion may act as an effective acid catalyst, lowering the pK_a of the departing phenol.[6] The structure–reactivity correlation for the hydrolysis of substituted aryl(2-carboxyphenyl) phosphates reveals a very high dependency (β −1.26) on the basicity of the leaving phenol.[4] Therefore, a change of 2 pK_a units in the pK_a of the leaving phenol, owing to chelation of the metal ion with the ether oxygen, would rationalize the rate acceleration. However, the pK_a of the stronger La^{3+}–phenolate complex is only 2 units below that for phenol, implying that this rationale is not entirely satisfactory.[29] A third and final argument invokes stabilization of the possible intermediate pentacovalent species by the metal ion and the associated transition states leading to and from this species. The plausibility of this latter suggestion will be the subject of a future communication.

Model systems which feature intramolecular catalysis or catalysis by biologically important Zn^{2+} or Mg^{2+} ions are of particular interest, since the interactions involved may closely resemble those in an enzyme–substrate complex.[32] The results of this study indicate that both of these types of catalysis may be integrated into one model system to confer dramatic reactivity to a normally unreactive phosphate diester.

Registry No.—I, 38401-04-6; II, 28401-05-7; diphenylphosphorochloridate, 2524-64-3; glycine ethyl ester hydrochloride, 623-33-6; diphenyl *N*-(glycyl)-phosphoramidate, 38401-06-8.

Acknowledgment.—This work was supported by a grant from the National Institutes of Health, GM 13306.

(30) S. J. Benkovic in "Comprehensive Chemical Kinetics," C. H. Banford and C. F. Tipper, Ed., American Elsevier, New York, N. Y., 1972.

(31) R. H. Bromilow, S. A. Khan, and A. J. Kirby, *J. Chem. Soc., Perkin Trans. 2*, 911 (1972).

(32) G. J. Lloyd and B. S. Cooperman, *J. Amer. Chem Soc.*, **93**, 4883 (1971). These authors recently have described a model system which features phosphoryl transfer from phosphoryl imidazole to the Zn^{2+}–pyridine-2-carbaldoxime anion *via* a ternary complex.

Phosphorus Derivatives of Nitrogen Heterocycles. 3. Carbon–Phosphorus Bonding in Pyridyl-2- and -4-phosphonates[1]

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A postulate that the extent of d_π–p_π conjugation for a phosphorus substituent on a pyridyl ring is greater for attachment at the 4 position than at the 2 position has been examined in a series of pyridyl-2- and -4-phosphonates by measurement of several physical properties. Although the ^{31}P nmr spectra of the pyridylphosphonate esters suggest the presence of d_π–p_π conjugation for attachment at the 4 position, ultraviolet and mass spectra of these esters and pK_a determinations on the corresponding acids argue strongly against such conjugation. The general conclusion that all the pyridylphosphonates show an absence of d_π–p_π conjugation is based on a comparison of physical properties with those of phenylphosphonates, a system in which d_π–p_π conjugation has been shown to be absent by other workers.

There exists considerable current interest concerning the extent of d_π–p_π bonding in the C–P bond of phosphorus substituents attached to aryl and heteroaryl rings.[2] From the ultraviolet and proton magnetic resonance spectra it has been concluded that d_π–p_π bonding exists in the C–P bonds of furan, thiophene, and pyrrole derivatives but that it is probably absent in pyridine derivatives. Although the spectra for pyridyl-2-phosphonates support this view, the corresponding pyridyl-4-phosphonates give indications of some d_π–p_π interaction.[2,3] To examine this possibility a more detailed examination has been made of the ^{31}P nmr spectra of the esters and acids, the mass spectra of esters, and pK_a and uv measurements for pyridyl phosphonic acids.

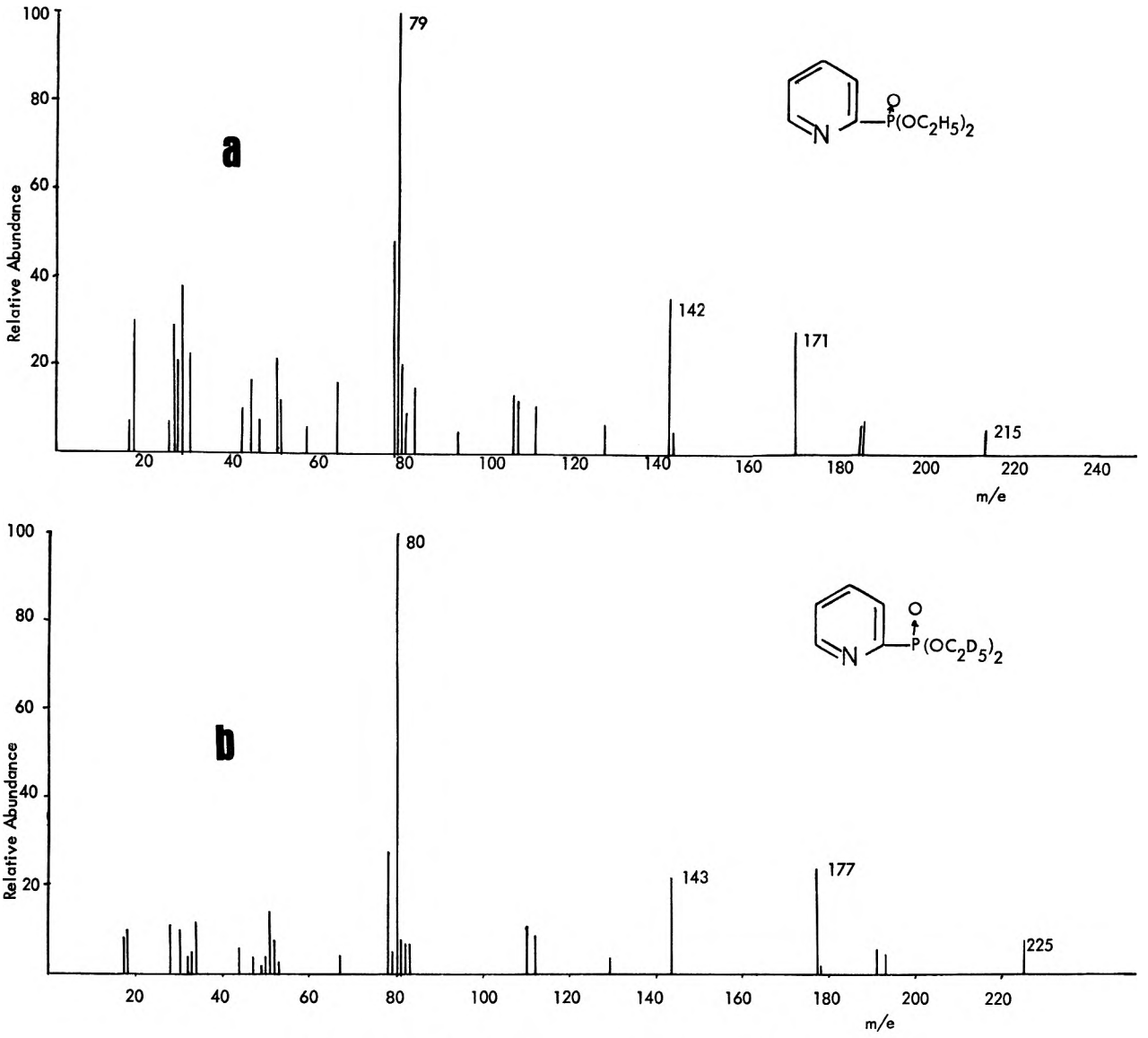
P^{31} Nmr Spectra.—The magnitude of the ^{31}P chemical shift of the phosphonate group can be correlated with the electron-donating ability of the attached organic radical.[4] It should be possible, therefore, to

(1) This work was presented, in part, at the 7th Midwest Regional Meeting of the American Chemical Society, St. Louis, Mo., Oct 1971. The present interpretation of the data differs considerably from this earlier presentation.

(2) D. Redmore, *Chem. Rev.*, **71**, 315 (1971).

(3) D. Redmore, *J. Org. Chem.*, **35**, 4114 (1970).

(4) J. G. Riess, J. R. Van Wazer, and J. Letcher, *J. Phys. Chem.*, **71**, 1925 (1967); C. C. Mitsch, L. D. Freedman, and C. G. Moreland, *J. Magn. Resonance*, **3**, 446 (1970).



Figures 1a and 1b.—Mass spectra of pyridylphosphonates.

TABLE I
^{31}P CHEMICAL SHIFTS OF PYRIDYLPHOSPHONATES AND RELATED COMPOUNDS

Phosphonate	Chemical shift *vs.* H_3PO_4, ppm
Diethyl pyridyl-2-phosphonate (1)	−8.2
Diethyl 4,6-dimethylpyridyl-2-phosphonate (2)	−10.5
Diethyl 3,5-dimethylpyridyl-2-phosphonate (3)	−11.4
Diethyl 3-chloropyridyl-2-phosphonate (4)	−7.7
Diethyl 2,6-dimethylpyridyl-4-phosphonate (5)	−15.0
Diethyl 2-thienylphosphonate	−10.9[a]
Diethyl phenylphosphonate	−16.7[a]
Pyridyl-2-phosphonic acid (6)	+2.3
2,6-Dimethylpyridyl-4-phosphonic acid (7)	−5.6

[a] Reference 5.

determine whether there are differences in the interaction for a phosphonate group attached to the 2 and 4 positions on the pyridine ring on the basis of the ^{31}P chemical shift. The stronger electron-donating groups will show less shielding of the phosphorus nucleus.[4,5] The data summarized in Table I show that chemical shift differences do exist in the pyridylphosphonates. It can be seen from the ^{31}P chemical shifts that the pyridyl ring in the 4-phosphonate **5** is more strongly electron donating than the pyridyl ring in the isomeric 2-phosphonates **2** and **3**. This is precisely the effect that one would predict if a phosphonate group at the 4 position enters into greater d_π–p_π conjugation than at the 2 position.

Mass Spectra.—The mass spectra of diethyl pyridyl-2-phosphonate (**1**), the perdeuterioethyl ester of **1**, diethyl 4,6-dimethylpyridyl-2-phosphonate (**2**), and diethyl 2,6-dimethylpyridyl-4-phosphonate (**5**) have been determined at 70 eV and are represented in Figure 1. The fragmentation patterns observed for the pyridylphosphonates differ considerably from those observed for diethyl alkylphosphonates.[6] The base peak in the latter appears at M − 55 and represents $[RP(OH)_3]^+$, which is a fragment of low abundance for all the pyridylphosphonates. The base peak for the pyridyl-2-phosphonates **1** and **2** is M − 136 (loss of $C_4H_9O_3P$) and for the perdeuterioethyl ester of **1** M − 145 (loss of $C_4D_9O_3P$). In the case of diethyl 2,6-dimethyl-

(5) D. W. Allen, B. G. Hutley, and M. T. J. Mellor, *J. Chem. Soc., Perkin Trans. 2*, 63 (1972).

(6) J. L. Occolowitz and G. L. White, *Anal. Chem.*, **35**, 1179 (1963); see also J. G. Pritchard, *Org. Mass Spectrom.*, **3**, 163 (1970).

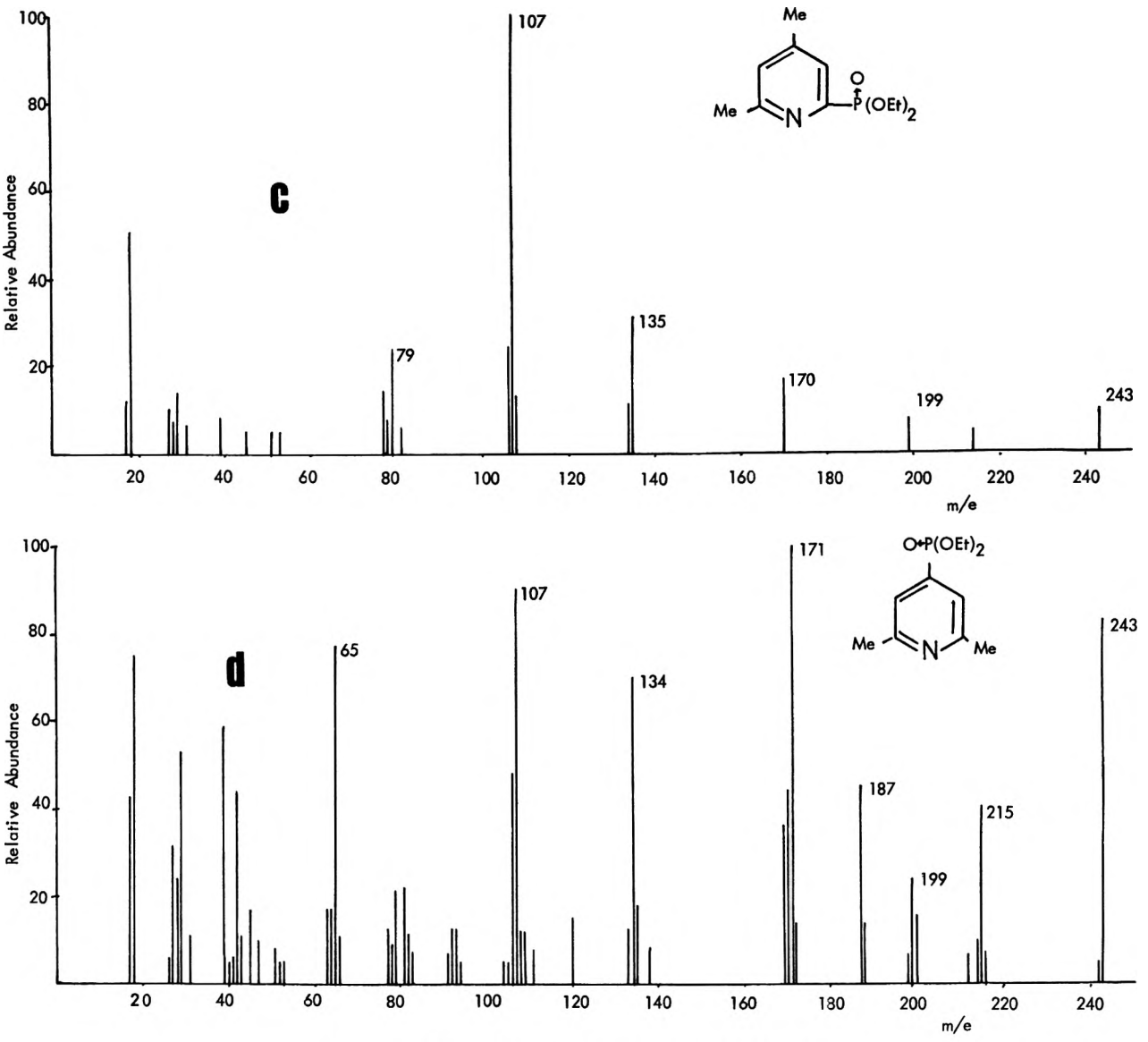


Figure 1c and 1d.—Mass spectra of pyridylphosphonates.

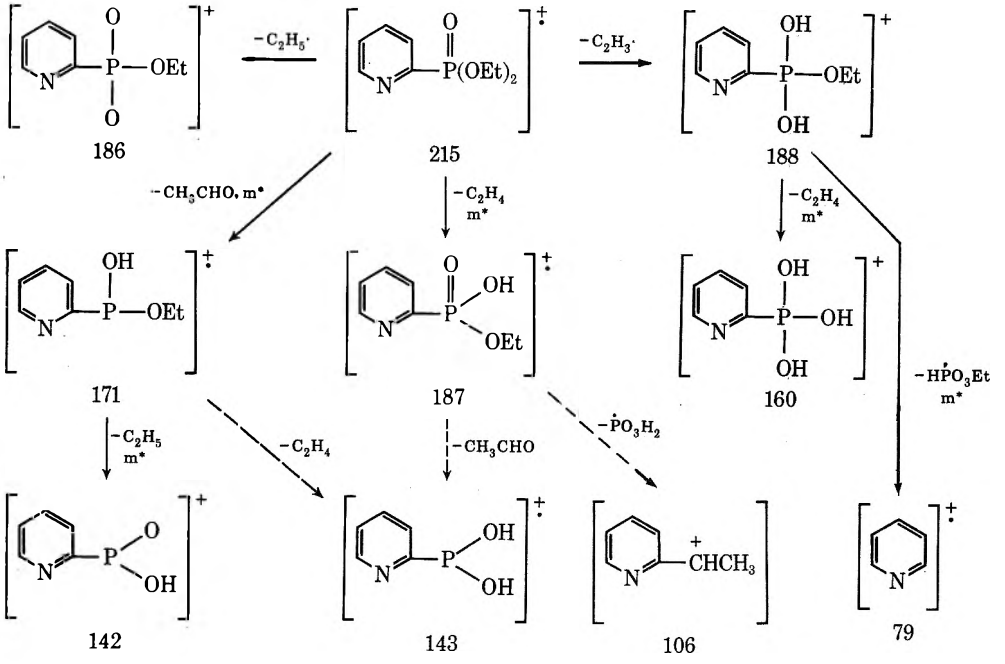
pyridyl-4-phosphonate (**5**) the base peak is M − 72, although M − 136 is still a fragment of high relative intensity (90%). Schemes I and II represent the postulated fragmentation pathways for compounds **1** and **5**, respectively. In these schemes fragmentations for which there are good precedents or for which the appropriate metastable peaks are observed (indicated by m*) are shown by a solid arrow, while the broken arrow is used where strong evidence is lacking. However, the structures shown in these schemes are firmly established; the spectrum of the perdeuterated ester was particularly important in this respect. In both **1** and **5** the loss of C_2H_4 and CH_3CHO is a well-established fragmentation identified by the presence of the appropriate metastable peaks. The genesis of the phosphorus-free ions, *m/e* 107, 106, and 79 in Scheme I and *m/e* 134 and 107 in Scheme II, is not unequivocally established. For diethyl pyridyl-2-phosphonate (**1**) ion *m/e* 79 appears to come from ion *m/e* 188, as indicated by a metastable peak at *m/e* 33.2. The corresponding ion at *m/e* 107 for phosphonate **5** appears to come from ion *m/e* 171 (metastable at *m/e* 66.9). The ions of *m/e* 107 and 106 in Scheme I are "ethylated" pyridines, since in the perdeuterio compound they appear at *m/e* 112 and 110, respectively, and thus involve a rearrangement. The appearance of a metastable peak at *m/e* 83.5 for compound **5** suggests that "ethylated" pyridine *m/e* 134 arises from ion *m/e* 215, Scheme II.

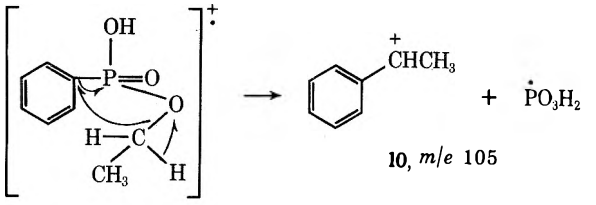
In an attempt to clarify the structures of the ions *m/e* 107 and 106 derived from **1**, the mass spectrum of diethyl phenylphosphonate (**8**) was measured as shown in Figure 2. The base peak for this ester has *m/e* 158 (M − 56) and, as in the case of the pyridylphosphonates, "ethylated" aryl peaks are present at *m/e* 106 and 105 with relative intensities of 5 and 43%. The presence of these ions in the phenyl ester shows that the "ethyl" group can be carbon bound and that this is not a feature unique to the pyridylphosphonates. It is suggested that ion **10**, *m/e* 105, in the phenylphosphonate arises by fragmentation and rearrangement of ion **9** as shown.

In examining Figures 1 and 2 it can be seen that fragmentation patterns for these aryl phosphonates differ considerably. In the 2-pyridylphosphonates **1** and **2** the base peak is the pyridinium ion, and no ions retaining the C–P bond have a higher relative intensity than 35%. On the other hand, in the 4-phosphonate **5** many ions retaining the C–P bond have a high relative

SCHEME I

FRAGMENTATION PATHWAY FOR DIETHYL PYRIDYL-2-PHOSPHONATE





intensity, including the molecular ion. Table II, which lists the relative intensity of the main fragments of the

TABLE II

RELATIVE INTENSITIES OF THE MAJOR FRAGMENTS OF THE PHOSPHONATE ESTERS

Ion	1	2	5	8	—Perdeuterio 1—	
M	6	10	83	75	M	8
M − 27	2	2	8	19	M − 30	2
M − 28	8	2	41	19	M − 32	5
M − 29	7	5	11	14	M − 34	6
M − 44	28	8	24	18	M − 48	24
M − 55	4	2	14	66	M − 62	2
M − 56	2	2	45	100	M − 64	2
M − 72	5	4	100	77	M − 80	2
M − 73	36	17	43	90	M − 82	22
M − 108	12	32	18	5	M − 113	9
M − 109	14	11	70	43	M − 115	11
M − 136	100	100	90	46	M − 145	100
M − 137	48	24	48	59	M − 147	27

phosphonates studied, brings out these differences and further shows that the 4-phosphonate **5** is much more like diethyl phenylphosphonate (**8**) in its fragmentation than are the 2-phosphonates.

We conclude, therefore, from the mass spectra that the C–P bonding in pyridyl-2- is different from that in pyridyl-4-phosphonates and that the 4-phosphonate is a typical aryl phosphonate by comparison with phenylphosphonate. Since other types of measurements have indicated an absence of d_π–p_π bonding in phenylphosphonates,[7] the difference in the mass spectra

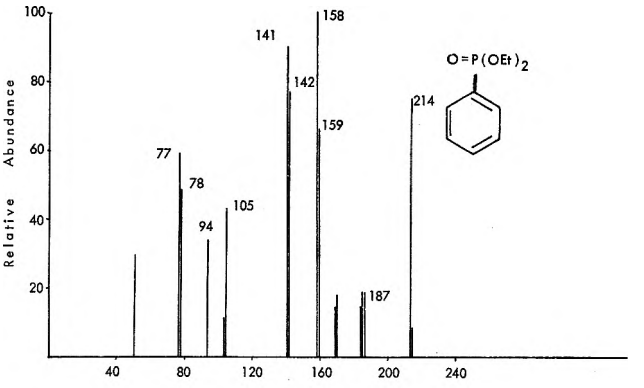
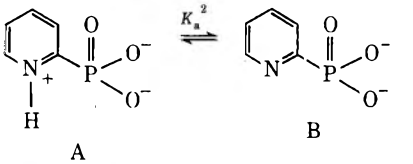


Figure 2.

of 2- and 4-pyridylphosphonates is not ascribable to d_π–p_π bonding. In fact, the differences in ease of C–P cleavage in the mass spectra would appear to arise from its facilitation by adjacent nitrogen in the 2-phosphonates rather than from C–P bond strengthening by d_π–p_π conjugation in the pyridyl-4-phosphonates.

pK_a Determinations on Pyridylphosphonic Acids.—Pyridylphosphonic acids are high-melting solids existing as zwitterions which titrate as dibasic acids. The pK_a values of these acids have been determined by potentiometric titration with 0.1 *N* sodium hydroxide and are presented in Table III.

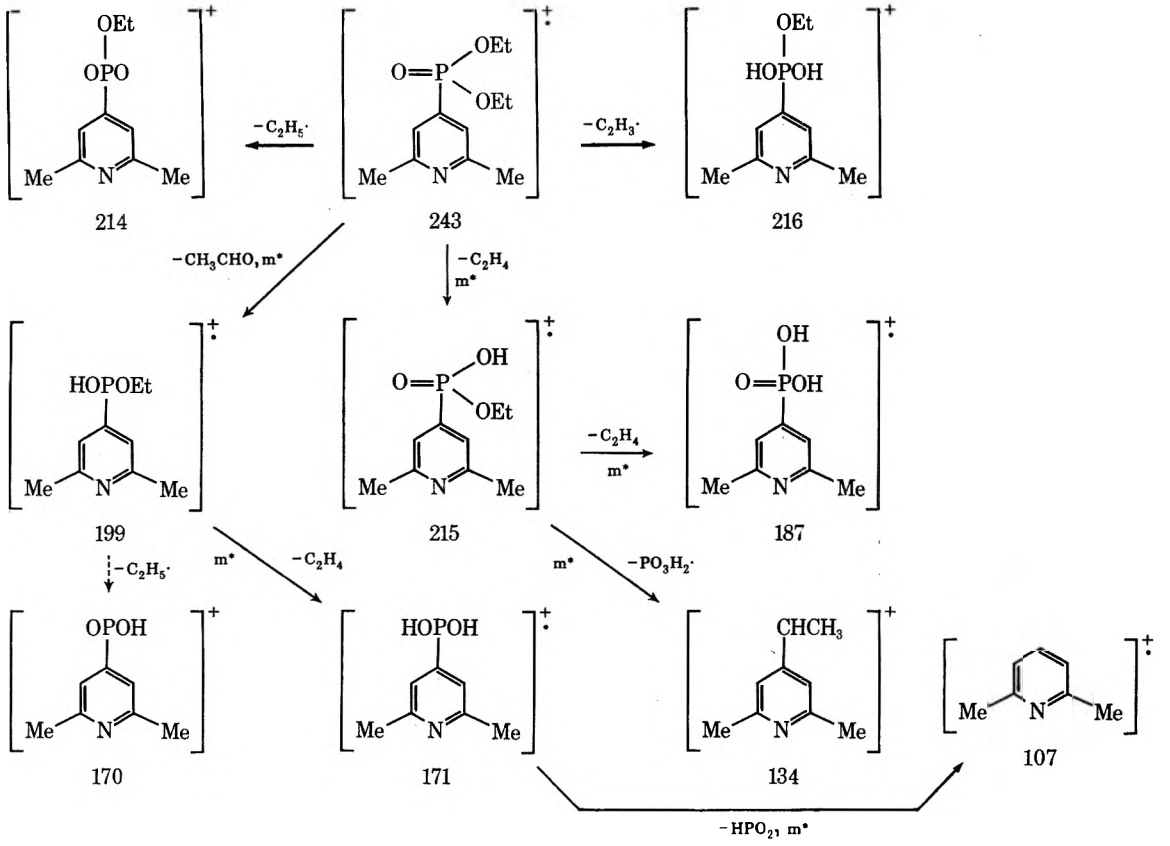
The correlation obtained by plotting the pK_a^2 values for the pyridylphosphonic acids against the pK_a of the parent pyridines (Figure 3) shows that the second ionization step is A ⇄ B.



(7) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, London, 1965, pp 67–85.

SCHEME II

FRAGMENTATION PATHWAY FOR DIETHYL 2,6-DIMETHYLPYRIDYL-4-PHOSPHONATE



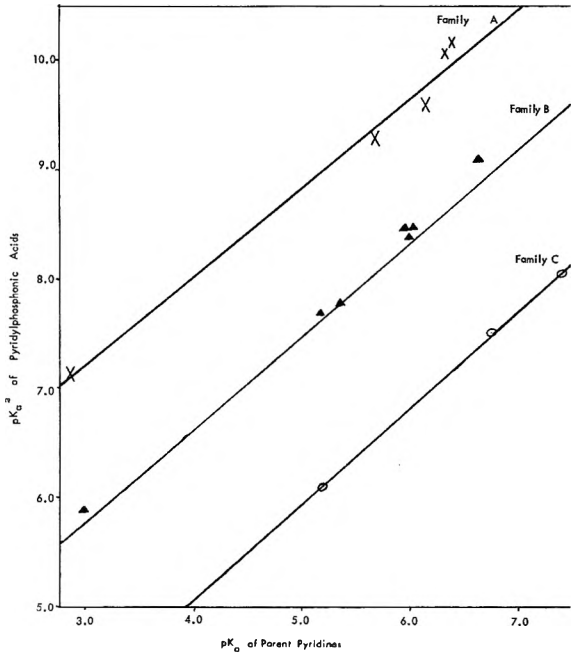


Figure 3.

The phosphonic acids are seen to fall into three families (Figure 3), which from the least squares method of analysis are described by the following equations: family A, $pK_A = 4.81 + 0.81\ pK_p$, correlation coefficient $r = 0.993$; family B, $pK_A = 3.24 + 0.85\ pK_p$, $r = 0.925$; family C, $pK_A = 1.58 + 0.88\ pK_p$, $r = 0.999$, where pK_p is the pK_a of the pyridine and pK_A is pK_a^2 for the pyridylphosphonic acid.

TABLE III

pK_a OF PYRIDYLPHOSPHONIC ACIDS[a]

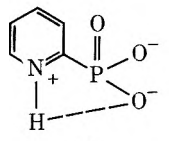
Phosphonic acid		pK_a^1	pK_a^2	pK_a of parent pyridine
Pyridyl-2-	6	4.13	7.71	5.17[b]
6-Methylpyridyl-2-	11	4.31	8.49	5.94[c]
4-Methylpyridyl-2-	12	4.25	8.47	6.03[c]
4-Phenylpyridyl-2-	13	4.24	7.80	5.35[d]
4-*tert*-Butylpyridyl-2-	14	4.44	8.41	5.99[c]
4,6-Dimethylpyridyl-2-	15	4.64	9.10	6.63[b]
4-Benzylpyridyl-2-	16	4.28	7.04	5.59[d]
3-Fluoropyridyl-2-	17	2.38	5.90	2.97[c]
3-Methylpyridyl-2-	18	4.39	9.32	5.67[c]
3,5-Dimethylpyridyl-2-	19	4.75	9.60	6.14[d]
3-Ethyl-6-methylpyridyl-2-	20		10.07	6.33
3,6-Dimethylpyridyl-2-	21	4.41	10.17	6.40[c]
3-Chloropyridyl-2-	22	3.49	7.15	2.84[c]
2,6-Dimethylpyridyl-4-	7	5.12	7.52	6.75[b]
2,3,6-Trimethylpyridyl-4-	23	5.06	8.04	7.40[e]
Pyridyl-4-	24		6.10[f]	5.17[b]

[a] These values are nonthermodynamic. Strictly speaking, these dissociation constants should be designated pK_{a_2} and pK_{a_3}, since further protonation to $C_6H_4NH^+P{=}O(OH)_2$ (pK_{a_1}) could be brought about in strong acid. [b] A. Albert in "Physical Methods in Heterocyclic Chemistry," Vol. 1, Academic Press, New York, N. Y., 1963. [c] "Handbook of Tables for Organic Compound Identification," 3rd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1967. [d] A. Fischer, W. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3591 (1964). [e] N. Ikekawa, Y. Sato, and T. Maeda, *Chem. Pharm. Bull.*, **2**, 205 (1950); *Chem. Abstr.*, **50**, 994 (1956). [f] Calculated value; *vide infra*.

Family C, the least basic, is a family of pyridyl-4-phosphonates; family B and family A both are 2-phosphonates, the latter all bear 3 substituents.

Several groups of workers have applied the Hammett equation to the basicity of pyridines and have obtained excellent correlations.[8] Using the value 5.77 for the reaction constant (ρ) in the pyridine protonation[8a] with σ_{para} for PO_3^{2-} of -0.16,[9] the calculated pK_a^2 for 4-pyridylphosphonic acid (**24**) is 6.10. Unfortunately, the synthesis of this acid has so far been unsuccessful so that the calculated pK_a^2 has been used in Figure 3 to obtain the line for family C. The excellent fit of this calculated value with the experimental values for **7** and **23** indicates that the 4-pyridylphosphonic acids and phenylphosphonic acid have equal d_π–p_π conjugation in their C–P bonding. Further, we can conclude that this contribution of d_π–p_π bonding is zero since the pK_a^2 value for phenylphosphonic acid calculated from the Taft–Ingold relationship $\log K_2 = -7.77 + 1.177\sigma^*$ determined for aliphatic phosphonic acids (and hence purely inductive) is precisely the experimentally determined value.[10] Justification for the use of the Hammett relationship to calculate the pK_a^2 for **24** is obtained by the result of its application to 4-trimethylsilylpyridine. Using a σ_{para} value for $SiMe_3$ of -0.07 (determined from benzoic acid ionization in water),[11] the calculated pK_a for 4-trimethylsilylpyridine is 5.57, exactly equal to the experimental value.[12] The absence of a d_π–p_π conjunctive contribution from the $-SiMe_3$ group in 4-trimethylsilylbenzoic acid has been cogently argued on the basis of the thermodynamic parameters for the dissociation process.[13]

Since it was concluded that there is no d_π–p_π conjugation in the 4-pyridylphosphonic acids, the higher basicity of the pyridyl ring in the 2-phosphonates compared with the 4-phosphonates must arise from an effect other than d_π–p_π conjugation, since this is a base-weakening effect. Intramolecular hydrogen bonding as in **26**, stabilizing the N-protonated form and hence



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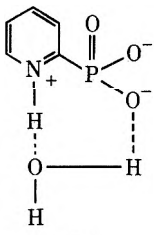

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increasing the pK_a, offers a reasonable explanation of this higher basicity. It would appear that the geometry in **26** is somewhat unfavorable for H bonding[14] and that interpolation of a water molecule as in **27** may be desirable.

The higher basicity of 3-substituted pyridyl-2-phosphonic acids (family A) compared with unsubstituted pyridyl-2-phosphonic acids (family B) can be explained by hindrance to solvation of the PO_3^{2-} by this substituent, bringing about a strengthening of the intramolecular hydrogen bonding. Hindrance to solvation of $-PO_3^{2-}$ ions by adjacent groups has been proposed to explain the lower than expected acidities in aliphatic acids.[10]

Ultraviolet Spectra.—Ultraviolet spectra have been used in a number of compounds to determine the presence of d_π–p_π conjugation between an unsaturated system and an attached phosphorus substituent.[7] In electron-rich aryl or heteroaryl phosphonates, bathochromic shifts have been observed, providing evidence for d_π–p_π interaction.[2]

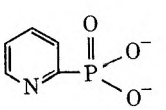
The uv spectra of pyridyl-2-phosphonic acid (**6**) and 2,6-dimethylpyridyl-4-phosphonic acid (**7**) and their ethyl esters **1** and **5** have been measured in water and the data are summarized in Table IV. The spectral data for the parent pyridines also are included as reference points. From the data it can be seen that for both **6** and **7** there is only a slight bathochromic shift from the parent pyridines. Thus, there is no evidence for a difference in conjugative interaction in the two series.

TABLE IV
ULTRAVIOLET SPECTRA OF PYRIDYLPHOSPHONATES

Compd	Absorption, nm (ϵ)
Pyridine (0.1 *N* NaOH)	262 (1800), 257 (2750),[a] 251 (2450)[a]
Pyridine (0.1 *N* HCl)	256 (5300)[a]
Pyridyl-2-phosphonic acid (pH 10)	268 (4050), 262 (5660), 256 (4700)
Pyridyl-2-phosphonic acid (pH 6.0)	264 (6570)
Pyridyl-2-phosphonic acid (pH 2.0)	263 (8410)
Diethyl pyridyl-2-phosphonate	267 (1970), 259 (2790)
2,6-Lutidine (0.1 *N* NaOH)	267 (4510)[a]
2,6-Lutidine (0.1 *N* HCl)	270 (8540)[a]
2,6-Dimethylpyridyl-4-phosphonic acid (pH 10.0)	280 (3560) (s), 273 (4330)
2,6-Dimethylpyridyl-4-phosphonic acid (pH 6.30)	283 (6410) (s), 278 (7380)
2,6-Dimethylpyridyl-4-phosphonic acid (pH 3.0)	283 (6510) (s), 278 (7420)
Diethyl 2,6-dimethylpyridyl-4-phosphonate	279 (3200)

[a] H. C. Brown and X. R. Mihm, *J. Amer. Chem. Soc.*, **77**, 1723 (1955).

From the measurements on the acids at different pH's it can be seen that the position of the absorption maximum is almost independent of pH. From the pK_a determinations we know that at pH 10 the acid exists in form **28** and at pH 2 in form **29** (or possibly further



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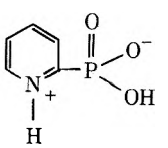

29

protonated). In form **29** the opportunity for d_π–p_π conjugation is minimal, since both protonation of the nitrogen and the inductive effect of the PO_3H^- group[9] will reduce electron density in the pyridyl ring. However, in **28** the pyridyl ring is unprotonated and the substituent $-PO_3^{2-}$ is electron donating,[9] favoring d_π–p_π conjugation. Since both species show almost identical absorption properties, we conclude that there

(8) (a) H. H. Jaffe and H. L. Jones, *Advan. Heterocycl. Chem.*, **3**, 209 (1964). (b) A. Fischer, W. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3591 (1964).

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

(10) D. J. Martin and C. E. Griffin, *J. Organometal. Chem.*, **1**, 292 (1964).

(11) R. A. Benkeser and H. R. Krysiak, *J. Amer. Chem. Soc.*, **75**, 2421 (1953).

(12) D. G. Anderson, J. R. Chipperfield, and D. E. Webster, *J. Organometal. Chem.*, **12**, 323 (1968).

(13) J. M. Wilson, A. G. Briggs, J. E. Sawbridge, P. Tickle, and J. J. Zuckerman, *J. Chem. Soc. A*, 1024 (1970).

(14) G. C. Pimental and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman, San Francisco, Calif., 1960, pp 263–265; P. A. Kollman and L. C. Allen, *Chem. Rev.*, **72**, 283 (1972).

is an absence of d_π–p_π bonding between the pyridyl ring and the phosphorus substituent.

Conclusions.—Although the ^{31}P nmr chemical shift data can be interpreted as supporting d_π–p_π conjugation in pyridyl-4-phosphonates, all other measurements, mass spectra, ultraviolet spectra, and pK_a measurements, offer no evidence for any d_π–p_π conjugation in pyridylphosphonates.

Experimental Section

Melting points, determined on a Fisher-Johns melting point apparatus, and boiling points are uncorrected. The elemental analyses were performed by Clark Microanalytical Laboratory, Urbana, Ill., and the staff of Dr. F. J. Ludwig, Petrolite Corp., Physical-Analytical Section. Proton nmr spectra were obtained with a Varian Associates A-60 spectrometer, using TMS as an internal standard. ^{31}P nmr spectra were obtained with a Varian HR-100 spectrometer operating at 40.5 MHz, using H_3PO_4 as an external reference or with a Joel spectrometer operating at 24.3 MHz, using P_4O_6 as a reference. Infrared spectra were determined on a Beckman IR-4 spectrometer.

Mass spectra of the pyridylphosphonates were determined by West Coast Technical Service with a Hitachi Perkin-Elmer Model RMU-6D spectrometer at 70 eV. The mass spectrum of diethyl phenylphosphonate (8) was determined at Washington University through the courtesy of Dr. C. D. Gutsche with a Varian M-66 spectrometer at 70 eV. The ultraviolet spectra were determined on a Beckman DK-2 spectrometer.

All new pyridylphosphonate esters used in this study were prepared by the general method previously described.[3] In many cases these esters were not characterized but converted directly to the corresponding acids by hydrolysis in the normal manner.[3] The analytical data used in the characterization of the pyridylphosphonic acid derivatives are summarized below.

Diethyl 4,6-Dimethylpyridyl-2-phosphonate (2).—This ester was obtained in 40% yield: bp 110–112° (0.03 mm); nmr (neat) δ 1.32 (t, 6, J = 7 Hz, CH_3CH_2O), 2.35 (s, 3, CH_3Ar at C_4), 2.52 (s, 3, CH_3Ar at C_6), 4.25 (quintet, 4, J = 7 Hz, OCH_2CH_3), 7.30 (s, 1, H at C_5), 7.68 (d, 1, J = 7.5 Hz, H at C_3).

Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76; P, 12.76. Found: C, 54.09; H, 7.22; N, 5.92; P, 12.79.

4,6-Dimethylpyridyl-2-phosphonic Acid (15).—Hydrolysis of the above ester (2) yielded 4,6-dimethylpyridyl-2-phosphonic acid (15) after crystallization from aqueous ethanol, mp <300°.

Anal. Calcd for $C_7H_{10}NO_3P$: C, 44.92; H, 5.35; N, 7.49; P, 16.58. Found: C, 44.89; H, 5.00; N, 7.64; P, 16.66.

Disodium 3-Ethyl-6-methylpyridyl-2-phosphonate.—3-Ethyl-6-methylpyridine N-oxide was converted into diethyl 3-ethyl-6-methylpyridyl-2-phosphonate in 18% yield and subjected to hydrolysis in 18% hydrochloric acid in the normal manner. The product obtained upon crystallization from aqueous ethanol, mp 278–284°, was not the expected acid but rather the corresponding anhydride on the basis of the following data: ir (KBr disc) 1195 (P=O), 920 (POP), and 740 cm^{-1} (POP).[15]

Anal. Calcd for $C_{16}H_{22}N_2O_5P_2 \cdot H_2O$: C, 47.76; H, 5.97; N, 6.96; P, 15.42. Found: C, 48.36; H, 6.42; N, 6.90; P, 15.11; equiv wt (KOH titration) 205 (calcd 201); pK_a 4.16 (one break only).

Dissolution of the above anhydride (1 g) in water (25 ml) containing sodium hydroxide (0.4 g) gave disodium 3-ethyl-6-methylpyridyl-2-phosphonate after evaporation of the solvent. Recrystallization from aqueous ethanol yielded the pure salt: mp >300°; nmr (D_2O) δ 1.24 (t, 3, J = 8 Hz, CH_3CH_2–), 2.53 (s, 3, CH_3 at C_6), 3.09 (q, 2, J = 8 Hz, CH_3CH_2–), 7.31 (m, 1, H at C_5), 7.75 (m, 1, H at C_4).

Anal. Calcd for $C_8H_{10}NO_3PNa_2$: C, 39.18; H, 4.08; N, 5.71. Found: C, 39.09; H, 3.58; N, 5.78.

Disodium 3,6-Dimethylpyridyl-2-phosphonate.—Diethyl 3,6-dimethylpyridyl-2-phosphonate, obtained from 2,5-dimethylpyridine N-oxide in 40% yield, was hydrolyzed with 18% hydrochloric acid. The product, mp 296–302°, crystallized from aqueous ethanol, was the anhydride of 3,6-dimethylpyridyl-2-phosphonic acid: ir (KBr disc) 1185 (P=O), 926 (POP), and 746 cm^{-1} (POP).[15]

Anal. Calcd for $C_{14}H_{18}N_2O_5P_2 \cdot H_2O$: C, 44.92; H, 5.35; N, 7.49; P, 16.58. Found: C, 45.00; H, 5.47; N, 7.69; equiv wt (KOH titration) 190 (calcd 187); pK_a 4.20.

Dissolution of the above anhydride (1 g) in water (25 ml) containing sodium hydroxide (0.4 g) gave disodium 3,6-dimethylpyridyl-2-phosphonate upon evaporation of the solvent. Recrystallization from aqueous ethanol gave the pure salt: mp <300°; nmr (D_2O) δ 2.54 (s, 3, CH_3Ar at C_3), 2.58 (s, 3, CH_3Ar at C_6), 7.30 (m, 1, H at C_5), 7.67 (m, 1, H at C_6).

Diethyl 3-Chloropyridyl-2-phosphonate (4).—This ester was obtained in 63% yield: bp 125–126° (0.2 mm); nmr (neat) δ 1.45 (t, 6, J = 7 Hz, CH_3CH_2O), 4.40 (quintet, 4, J = 7 Hz, CH_3CH_2O), 7.72 (m, 1, ArH at C_5), 8.15 (m, 1, ArH at C_4), 8.90 (m, 1, ArH at C_6); ir (liquid film) 1250 (P=O), 790 cm^{-1} (3 adjacent aryl hydrogen).

Anal. Calcd for $C_9H_{13}ClNO_3P$: C, 43.29; H, 5.21; N, 5.61; P, 12.42: Found: C, 43.59; H, 5.43; N, 5.34; P, 12.56.

3-Chloropyridyl-2-phosphonic Acid (22).—This acid was obtained by hydrolysis of ester 4, mp 252–254° (aqueous ethanol).

Anal. Calcd for $C_5H_5ClNO_3P$: C, 31.01; H, 2.58; Cl, 18.35; N, 7.24; P, 16.02. Found: C, 30.12; H, 2.65; Cl, 18.11; N, 7.07; P, 15.61.

Diethyl 3-Fluoropyridyl-2-phosphonate.—3-Fluoropyridine N-oxide, mp 61–64° (lit.[16] mp 64°), was converted into diethyl 3-fluoropyridyl-2-phosphonate in 68% yield: bp 124–127° (0.1 mm); nmr ($CDCl_3$) δ 1.39 (t, 6, J = 7 Hz, CH_3CH_2O), 4.40 (quintet, 4, J = 7 Hz, CH_3CH_2O), 7.83 (m, 2, H at C_4 and C_5), 8.50 (m, 1, H at C_6).

Anal. Calcd for $C_9H_{13}FNO_3P$: C, 46.35; H, 5.58; N, 6.01; P, 13.30. Found: C, 45.25; H, 5.68; N, 5.97; P, 13.98.

3-Fluoropyridyl-2-phosphonic Acid (17).—Hydrolysis of the above ester and crystallization from aqueous ethanol yielded 3-fluoropyridyl-2-phosphonic acid, mp 220–222°.

Anal. Calcd for $C_5H_5FNO_3P \cdot {}^1/_2H_2O$: C, 32.26; H, 3.23; N, 7.52; P, 16.67. Found: C, 32.08; H, 3.44; N, 7.55; P, 16.33.

4-Phenylpyridyl-2-phosphonic Acid (13).—Hydrolysis of the corresponding ethyl ester yielded pure acid upon crystallization from aqueous ethanol, mp 268–271°.

Anal. Calcd for $C_{11}H_{10}NO_3P$: C, 56.17; H, 4.68; N, 5.96; P, 13.19. Found: C, 56.44; H, 4.38; N, 5.90; P, 13.35.

Di(perdeuterioethyl) Pyridyl-2-phosphonate.—Phosphorus pentachloride (20.8 g, 0.1 mol) was added to diethyl pyridyl-2-phosphonate (10.8 g, 0.05 mol) at 60° during 0.5 hr. Evolution of gas (ethyl chloride) was vigorous during the addition. The mixture was heated at 165–170° for 6 hr, during which time 11 g of distillate ($POCl_3$) was collected. The residue was distilled under reduced pressure to yield pyridyl-2-phosphonic dichloride (3.5 g, 33%), bp 88–90° (0.1 mm), ir (liquid film) 1270 cm^{-1} (P=O).

To pyridyl-2-phosphonic dichloride (3.4 g, 0.016 mol) in benzene (25 ml) was added a solution of ethanol-d_6 (1.8 g, 0.032 mol) and triethylamine (3.2 g, 0.032 mol) in benzene (30 ml) during 1 hr at 20°. After filtration of the precipitated amine hydrochloride the benzene solution was washed with sodium carbonate solution. Evaporation of the benzene yielded an oil which, upon distillation, yielded pure di(perdeuterioethyl) pyridyl-2-phosphonate: bp 93–95° (0.03 mm); ir (liquid film) 3050 (aryl CH), 2230 (CD_3), 2155 (CD_2), 2120 (CD_3?), 2080 (CD_3),[17] 1260 cm^{-1}; mass spectrum M^+ 225 (see Figure 1b).

4-Benzylpyridyl-2-phosphonic Acid (16).—4-Benzylpyridine N-oxide (49 g, 0.26 mol) was converted in the normal manner to diethyl 4-benzylpyridyl-2-phosphonate, which was purified by chromatography on alumina and elution with benzene, yield 12.7 g (16%). This oil was subjected to hydrolysis with 18% hydrochloric acid without further purification. The resulting oil was crystallized from aqueous ethanol to yield pure 4-benzylpyridyl-2-phosphonic acid: mp 269–272°; yield 2.1 g (20%); nmr (D_2O) δ 4.13 (s, 2, CH_2Ph), 7.50 (s, 5, PhH), 7.3 (m, 1, H at C_5), 7.9 (m, 1, H at C_3), 8.5 (m, 1, H at C_6).

Anal. Calcd for $C_{12}H_{12}NO_3P$: C, 57.83; H, 4.82; N, 5.62; P, 12.45. Found: C, 58.15; H, 5.27; N, 5.75; P, 12.68.

(15) The anhydride absorptions are absent in the spectra of other pyridylphosphonic acids, for example, the spectrum of pyridyl-2-phosphonic acid recorded on Documentation of Molecular Spectroscopy card no. 21442.

(16) M. Bellas and H. Suschitzky, *J. Chem. Soc.*, 4007 (1963).

(17) The infrared absorptions of the CD_3CD_2 group are given by B. Nolin and R. N. Jones, *J. Amer. Chem. Soc.*, **75**, 5626 (1953).

Registry No.—**1**, 23081-78-9; **1** perdeuterioethyl ester, 38605-80-0; **2**, 38605-81-1; **3**, 26384-92-9; **4**, 38605-83-3; **5**, 26384-85-0; **6**, 26384-86-1; **7**, 26394-19-4; **8**, 1754-49-0; **13**, 38605-87-7; **15**, 38605-88-8; **16**, 38605-89-9; **16** diethyl ester, 38605-90-2; **17**, 38605-91-3; **17** diethyl ester, 38605-92-4; **20**, 38605-93-5; **20** anhydride, 38605-94-6; **20** diethyl ester, 38605-95-7; **20** disodium salt, 38605-96-8; **21** anhydride, 38605-97-9; **21** diethyl ester, 38605-98-0; **21** disodium salt, 38605-99-1; **22**, 38606-00-7; 3-ethyl-6-methylpyridine *N*-oxide, 768-44-5; 2,5-dimethylpyridine *N*-oxide, 4986-05-4; 3-fluoropyridine *N*-oxide, 695-37-4; phosphorus pentachloride, 10026-13-8; pyridyl-2-phosphonic dichloride, 38606-04-1; 4-benzylpyridine *N*-oxide, 7259-53-2.

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Nuclear Magnetic Resonance Spectroscopy. Carbon-13 Nuclear Magnetic Resonance for Some Six-Membered Aromatic Nitrogen Heterocycles[1a]

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High-resolution, natural-abundance ^{13}C spectra have been obtained for pyridine, pyridazine, pyrimidine, pyrazine, and *s*-triazine and some methyl derivatives. Geminal and vicinal carbon–proton coupling has been related to proton–proton coupling in substituted ethylenes.

Although one-bond carbon–proton coupling constants in aromatic systems are well characterized,[2,3] long-range carbon–proton coupling constants have not been extensively studied. Direct observation of the inner satellites in the proton spectrum is hampered by the strong resonances from molecules having no ^{13}C. If the proton spectrum is particularly simple, these satellites can be observed,[4] but they cannot always be assigned to a particular carbon. The analysis of the outer satellites is dependent on the differences in the long-range carbon–proton coupling constants, but the magnitudes cannot be determined.[5] Homonuclear tickling of the inner satellites while observing the outer satellites gives all the transitions for a complete iterative analysis.[6] If all the proton–proton coupling constants are known (from studies of the unlabeled materials), all the carbon–proton coupling constants can be determined from the ^{13}C spectrum.

Lauterbur[2] has measured the ^{13}C chemical shifts of six-membered nitrogen heterocycles, but the spectra were low resolution and long-range couplings were not resolved. High-resolution ^{13}C spectra of pyridine have been published but not interpreted in detail.[7] Long-range carbon–proton coupling constants of benzene[8] and the five-membered heterocycles[9] have been reported. This paper concerns the nmr spectra of six-membered nitrogen heterocycles.

Experimental Section

All samples were obtained from commercial sources. Liquid samples were diluted with 5% acetone for an internal lock. Spectra of solid samples were taken as saturated acetone solutions. The spectra were obtained with the previously described Varian DFS-60 spectrometer.[8,9] Theoretical spectra were calculated by trial and error using the computer programs NMRIT, or by iteratative techniques with the LAOCOON programs.[10]

Results

The ^{13}C spectra of pyridine, pyridazine, and pyrazine are shown in Figures 1–6. The ^{13}C spectra of all of the carbons of pyrimidine and *s*-triazine are first order. Only the low field half of the pyrazine spectrum is shown because the high field half is simply its mirror image. The carbon–proton coupling constants for the parent heterocycles are summarized in Table I. Long-range coupling constants are accurate to ±0.2 Hz.

TABLE I

CARBON–PROTON COUPLING CONSTANTS IN THE SIX-MEMBERED NITROGEN HETEROCYCLES

Compound	Registry no.	Carbon	H-2	H-3	H-4	H-5	H-6
Pyridine	110-86-1	2	175.3	3.3	6.4	±1.6	10.9
		3	8.7	162.5	1.0	6.4	±1.6
		4	6.4	0.0	169.2	0.0	6.4
Pyridazine	289-80-5	3		182.5	6.5	2.0	−1.4
		4		6.7	169.9	0.0	5.2
Pyrimidine	289-95-2	2	202.7		10.3	0.0	10.3
		4	9.1		182.8	1.9	5.3
		5	1.9		9.5	166.2	9.5
Pyrazine	290-37-9		182.7	10.4		−1.5	9.8
s-Triazine	290-87-9		207.5		7.95		7.95

(1) (a) Supported by the Public Health Service, Research Grant No. GM-11072 from the Division of General Medical Sciences, and by the National Science Foundation; (b) National Science Foundation Predoctoral Fellow, 1965–1968.

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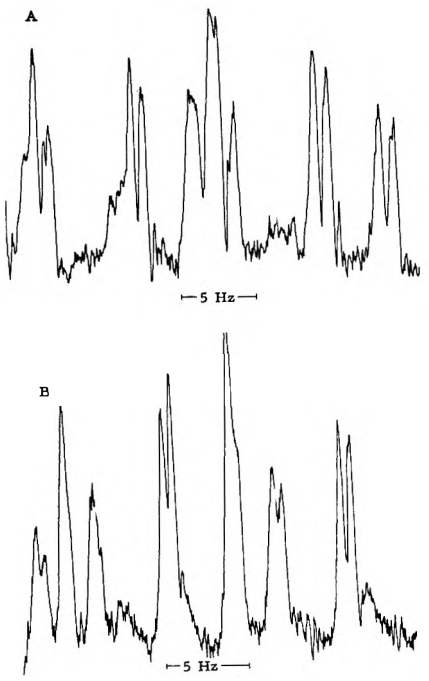


Figure 1.—Low (A) and high (B) field segments of the α-^{13}C resonance of pyridine at 15.0 MHz, 500 scans at a sweep rate of 0.25 Hz/sec.

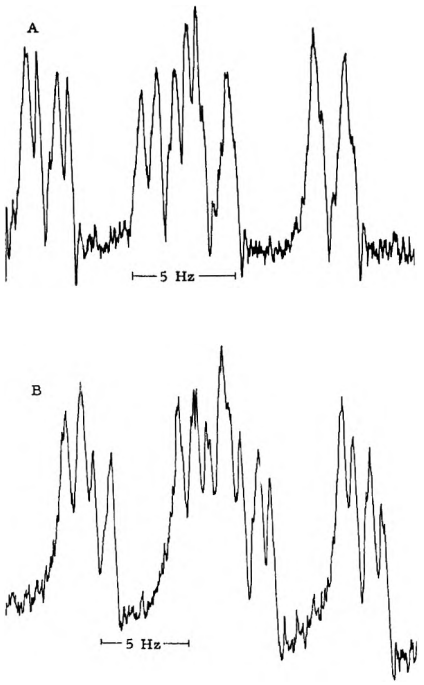


Figure 2.—Low (A) and high (B) field segments of the β-^{13}C resonance of pyridine at 15.09 MHz, 500 scans at a sweep rate of 0.25 Hz/sec.

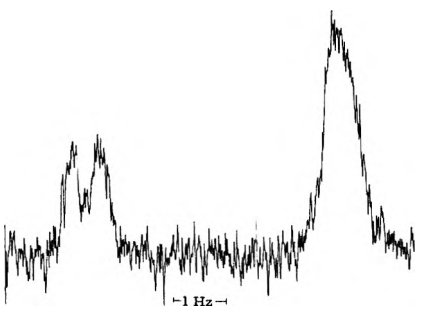


Figure 3.—Part of the ^{13}C spectrum of the γ carbon of pyridine at 15.09 MHz, 100 scans.

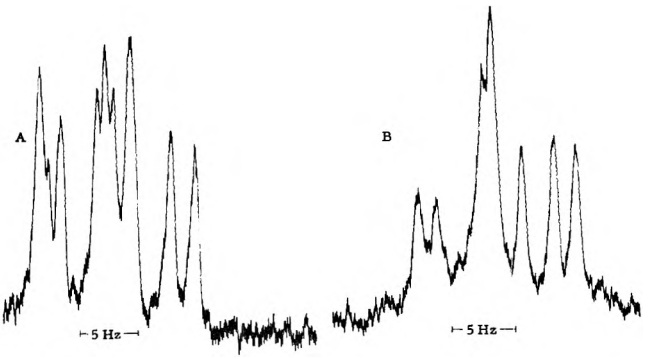


Figure 4.—Low (A) and high (B) field segments of the α-^{13}C resonance of pyridazine at 15.09 MHz, taken with 400 and 300 scans, respectively.

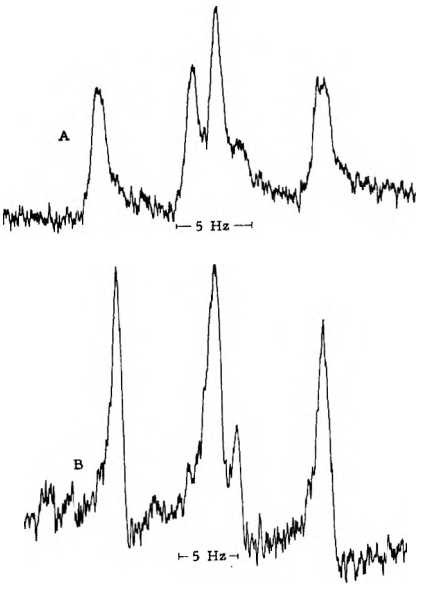


Figure 5.—Low (A) and high (B) field segments of the α-^{13}C resonance of pyridazine at 15.09 MHz, taken with 400 and 300 scans, respectively.

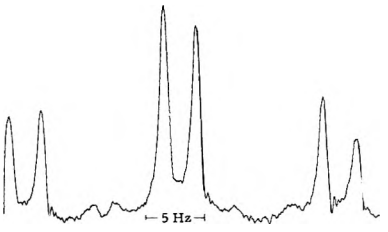


Figure 6.—Half of the ^{13}C spectrum of pyrazine at 15.09 MHz, 300 scans. The other half is the mirror image of this one.

Because of the complexity of the spectra of some of the parent compounds, methyl derivatives were examined and their carbon–proton couplings applied to the analysis of the parent compounds. Selective decoupling of the methyl protons was necessary to observe the long-range couplings to the aromatic protons. The decoupling power was quite critical: too much, and the coupling to the aromatic protons was perturbed; too little, and the coupling from the methyl protons was not completely eliminated. The carbon–proton coupling constants determined by this technique are best taken as lower limits to the true values. The long-range carbon–proton coupling constants in the methyl-substituted heterocycles are given in Table II.

TABLE II
LONG-RANGE CARBON-PROTON COUPLING IN HERTZ FOR METHYL-SUBSTITUTED NITROGEN HETEROCYCLES

Compound	Registry no.	Carbon	H-2	H-3	H-4	H-5	H-6
2-Methylpyridine	109-06-8	2		2.4	6.7	0.0	11.2
		3			0.0	6.5	1.5
		4		0.0		0.0	6.3
		5		6.3	0.0		8.7
		6		0.0	6.5	3.8	
3-Methylpyridine	108-99-6	2			5.25	0.0	10.95
		3	6.7		0.0	6.7	0.0
		5	1.45		0.0		10.2
		6	10.6		6.4	2.1	
4-Methylpyridine	108-89-4	2		4.2		−0.7	10.6
		3	8.7			5.6	1.6
		4	6.35	0.0		0.0	6.35
3,5-Dimethylpyridine	591-22-0	2			5.8		11.2
		3	7.7		0.0		1.6
		4	5.3				5.3
2,6-Dimethylpyridine	108-48-5	2		2.5	6.4	−0.7	
		3			0.0	5.1	
		4		<0.3		<0.3	
2,4-Dimethylpyridine	108-47-4	2		11.3		1.6	11.3
		4		0.0		0.0	6.7
		5		5.5			8.6
		6		0.0		4.0	
2,4,6-Trimethylpyridine	108-75-8	3				5.1	
3-Methylpyridazine	1632-76-4	4				0.0	5.5
		5			0.0		7.45
		6			*a*	*a*	
5-Methylpyrimidine	2036-41-1	2			10.6		10.6
		4	9.1				4.35
2,5-Dimethylpyrazine	123-32-0	2		9.4			9.4
		3					1.4
2,6-Dimethylpyrazine	108-50-9	2		9.95		1.25	
		3				9.7	
Mesitylene[b]	108-67-8	1	0.0		0.0		0.0
		2			6.4		6.4

[a] The average of these two coupling constants is 4.7 Hz. [b] The geminal carbon–proton coupling to the methyl protons is 6.0 Hz; the vicinal carbon–proton coupling is 4.25 Hz.

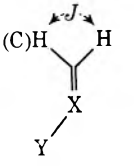
Two slightly different sets of proton–proton coupling constants have been reported for pyridine.[11,12] Both give good agreement with a 100-MHz spectrum of pyridine and both can be used equally well to match the ^{13}C spectrum. To a first-order approximation, the spectrum of C-4 is a doublet (H-4) of triplets (H-2, H-5). However, with the extremely slow passage conditions of Figure 3, an additional splitting is resolved. The splitting, however, is consistent with a value of 0.0 ± 0.1 Hz for the coupling with H-3 and H-5.

The ^{13}C(α)–H couplings in pyridazine were obtained using the proton–proton coupling constants derived from the ^{13}C satellites of the proton spectrum.[13] The best fit to the experimental spectrum of the α carbon was obtained with a ^{13}C isotope effect on the chemical shift of the directly attached and nearest neighbor proton of 2.0 and 1.7 Hz, respectively, relative to the shifts of the more remote protons.

The proton–proton coupling constants in pyrazine were assumed to be the same as those of the monomethyl derivative.[14]

The 25-MHz ^{13}C spectrum of C-1 of mesitylene[15] shows a 1:3:3:1 quartet from coupling with the methyl protons. Coupling with the geminal ring protons was zero. The undecoupled ^{13}C spectrum of C-2 is a broad doublet (J = 160 Hz) with no obvious fine structure. On decoupling the methyl protons, a triplet with J = 6.4 Hz is seen from coupling with the vicinal ring pro-

TABLE III
A COMPARISON OF PROTON–PROTON COUPLINGS $^2J_{HH}$ IN SUBSTITUTED ETHYLENES WITH CARBON–PROTON COUPLINGS $^2J_{CH}$ IN AROMATIC HETEROCYCLES



X	Y	J_{CCH}, Hz (pred)[a]	Reference	Compd	J_{CCH}, Hz (obsd)
C	H_2	−1.0	*b*	Benzene	+1.0
C	CH_3	−0.8	*c*	Mesitylene	0.0
N	C	−6.4	*d*	Pyridine, C-3	+8.7
N	N	−4.4	*d*	Pyridazine, C-4	6.4
C	N, H	0.0	*e*	Pyridine, C-4	0.0
C	H	6.4	*e, f*	Pyridine, C-4	6.4

[a] In Hz, from $J_{CCH} = 0.4J_{HCH}$. [b] Reference 18. [c] Reference 19. [d] B. L. Shapiro, S. L. Ebersole, G. J. Karabatsos, F. M. Vane, and S. L. Manatt, *J. Amer. Chem. Soc.*, **85**, 4041 (1963). These coupling constants are solvent dependent. [e] W. Brügel, Th. Ankel, and F. Krückeberg, *Z. Elektrochem.*, **64**, 1121 (1960). [f] The comparison here is between $^3J_{CCCH}$ and $^3J_{HCCH}$ (trans).

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(12) J. B. Merry and J. H. Goldstein, *J. Amer. Chem. Soc.*, **88**, 5560 (1966).
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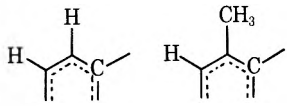
tons. On weak irradiation of the ring protons, each half of the doublet becomes a septet (J = 4.25 Hz) from the vicinal coupling to two adjacent methyl groups.

Discussion

Karabatsos and coworkers[16] have extended the valence-bond treatment of geminal proton–proton couplings[17] to geminal carbon–proton couplings. Such comparisons explain many trends in geminal and vicinal carbon–proton coupling in benzene[8] and the five-membered nitrogen heterocycles[9] if proper models are chosen. Some models and predicted and observed coupling constants are given in Table III. Although the quantitative agreement with Karabatsos' theory is best for benzene, the qualitative trends are correctly predicted throughout the heterocyclic series.

Vicinal carbon–proton couplings across a methyl group are approximately 0.9 times the corresponding couplings in compounds without the methyl. The ratio is the same as for the trans proton–proton couplings in ethylene (19.1 Hz)[18] and propene (16.8 Hz).[19]



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The Synthesis of Aryl Isocyanates from Nitro Compounds and Carbon Monoxide

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The $PdCl_2$-catalyzed reaction of nitrobenzenes and the thermal reaction of phenyl azides with CO show similar variations of isocyanate yields with pressure and similar by-products. The by-products from 4-fluoronitrobenzene, diphenylurea, triphenylbiuret, and an imidazolinone **3a** may arise from proton abstraction from a nitrene-like intermediate. Labelling of a phenyl with a 4-fluorine gives convenient quantitative analysis of crude reaction mixtures, but is unreliable as a single method for qualitative analysis.

The formation of phenyl isocyanate from nitrobenzene[1] or phenyl azide[2] and carbon monoxide in the presence of $PdCl_2$ is of both academic and practical interest.[3] The only by-products described have been diphenylurea and azobenzene, and the urea has been presumed to arise from reaction of the isocyanate with water.[1] The results presented here suggest that side reactions of nitrene-like intermediates are responsible for the by-products.[4]

$$ArNO_2 + 3CO \xrightarrow{PdCl_2} ArNCO + 2CO_2$$

Results

Over the range of 50–600 atm, the yield of 4-chlorophenyl isocyanate increases linearly with the square root of pressure (Table I). Yields are independent of temperature or palladium concentration (Table II). High pressure slows the reaction, but on extended heating the yield improvement is maintained.

The diphenylurea from pentadeuteronitrobenzene gave after sublimation infrared bands which were attributed to nitrogen–deuterium stretching vibrations.

An extensive study was made using 4-fluoronitrobenzene as substrate because ^{19}F nmr provided convenient analyses of the crude reaction mixtures. First, however, the various by-products were individually isolated by column chromatography over neutral SilicAR. In order of elution, the by-products isolated were 4,4-difluoroazobenzene, an imidazolinone **3a** discussed in detail below, 1,3,5-tris(4-fluorophenyl)biuret, and 1,3-bis(4-fluorophenyl)urea.

TABLE I

EFFECT OF CO PRESSURE ON THE REACTION OF 4-CHLORONITROBENZENE WITH CO[a]

CO, atm[b]	Time, hr	Conversion of $ArNO_2$, %	Yield of ArNCO, %
20	2	53[c]	7
75	2	97	13
150	2	90	35
300	2	97	46
600	2	30	72
600	4	97	68

[a] Charge: 4-chloronitrobenzene (5 mmol) in 2 ml of CH_3CN solution, NO_2/Pd ratio 5000/1. Run at 250° in 9-ml bomb. [b] At 25°. [c] Insufficient CO is present to react with all the nitrobenzene present.

TABLE II

EFFECT OF REACTION VARIABLES ON ISOCYANATE YIELD[a]

CO, atm[b]	Temp, °C	Time, hr[c]	$ArNO_2$/Pd	Yield of ArNCO, %
100	225	10	10,000	15
100	275	1	10,000	10
300	200	2	200	45
300	250	2	200	46
400	225	15	10,000	44
400	275	2	10,000	50

[a] Charge: 5 mmol of 4-chloronitrobenzene + $PdCl_2$ in 2 ml of CH_3CN solution in 9-ml bomb. [b] At 25°. [c] The time is adjusted to give 100% conversion of nitrobenzene.

(1) W. B. Hardy and R. P. Bennett, *Tetrahedron Lett.*, 961 (1967).

(2) R. P. Bennett and W. B. Hardy, *J. Amer. Chem. Soc.*, **90**, 3295 (1968).

(3) W. W. Prichard, U. S. Patent 3,576,836 to Du Pont; G. F. Ottmann, E. H. Kober, and D. F. Gavin, U. S. Patent 3,523,962 to Olin Matheson; W. B. Hardy and R. P. Bennett, U. S. Patent 3,461,149 to American Cyanamide.

(4) Similar conclusions have been advanced by F. L'Eplattenier, P. Matthys, and F. Calderazzo, *Inorg. Chem.*, **9**, 343 (1970), for the Ru-catalyzed reaction.

All except the imidazolinone were positively identified by comparison with samples prepared independently. Because identification of **3a** was difficult, the structure proof is presented in some detail.

Elemental analysis and high-resolution mass spectroscopy of **3a** gave the empirical formula $C_{20}H_{12}F_3N_3O_2$, or three phenyl nitrenes and two CO's. The infrared spectrum (Figure 1) showed an NH band at 3.12 μ

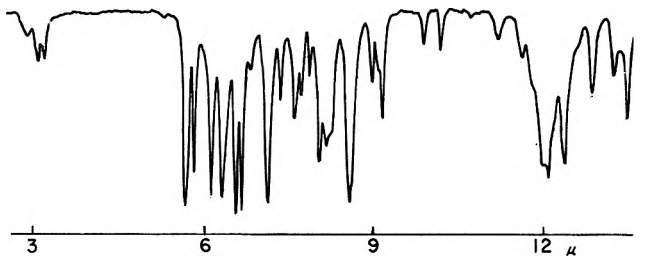


Figure 1.—Infrared spectrum of imidazolinone **3a**.

and unusual carbonyl absorptions at 5.70 and 5.86 μ, which were assigned to an imide linkage. The ultraviolet spectrum showed typical benzenoid absorption at 242 nm (ϵ 32,900) with shoulders at 283 nm (ϵ 6670) and 288 (5630). The most significant feature of the 220-MHz pmr spectrum (Figure 2) was the doublet of doublets (J = 9, 5 Hz) at δ 8.21. The proton-decoupled ^{19}F nmr spectrum in CH_3CN showed three equal-intensity singlets at −112.8, −117.1, and −118.1 ppm.[5] With no proton decoupling, the resonance at −117 ppm was a doublet (J = 5 Hz) of triplets (J = 9 Hz) while the other two were triplets of triplets with the same splittings.

Reaction of **3a** with aqueous or ethanolic base at 80° caused loss of ArNCO rather than hydrolysis.

The infrared imide band was replaced by an amide band at 5.83 μ and the ^{19}F nmr spectrum showed two equal-intensity peaks at −114.3 and −121.6 ppm. The 220-MHz pmr spectrum showed a triplet (J = 9 Hz) and a doublet of doublets (J = 9, 5 Hz), 2 H each, attributed to a phenyl ring with para substituents, one of which is fluorine, and three single-intensity resonances assigned to a trisubstituted benzene ring. The low-field doublet of doublets in **3a** disappeared. The structure of the pyrolysis product, imidazolinone **2a**, is suggested by the general similarity of the high-frequency portion of its infrared spectrum to that of the unfluorinated material **2b** prepared from *N*-phenyl-*o*-phenylenediamine and phosgene, and the ^{19}F nmr spectrum.

On paper, inserting an aryl isocyanate back into imidazolinone **2** generates several alternate structures. Hydrazo compounds are eliminated by the ^{19}F nmr spectrum,[5] leaving **1** and **3** as plausible alternatives.

Chromatography of the by-products from nitrobenzene and CO gave analogous products but in different ratios. The imidazolinone **3b** was present in ~1% yield, while diphenylurea was the major by-product. The imidazolinone **3b** was identical with a sample prepared by $SnCl_4$-promoted condensation of **2b** with phenyl isocyanate. An isomeric product was obtained from the reaction of *N*-phenyl-*o*-phenylenediamine and

(5) F. J. Weigert and W. A. Sheppard; the fluorine nmr studies of the model compounds used to identify the environment of these resonance will be published separately.

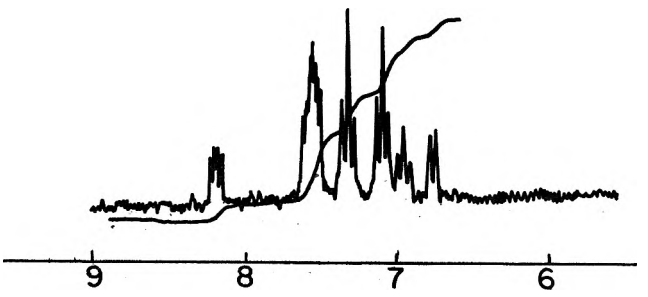
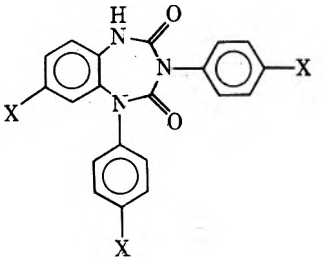
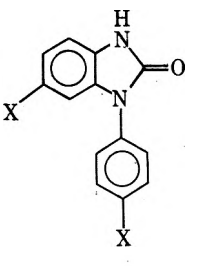


Figure 2.—220-MHz nmr spectrum of imidazolinone **3a**.

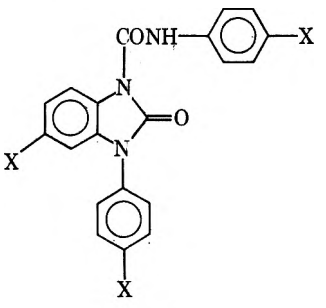
phenyl isocyanate and was assigned the triazepinedione structure **1b**. Imidazolinone **3b** shows a low-



1a, X = F
b, X = H

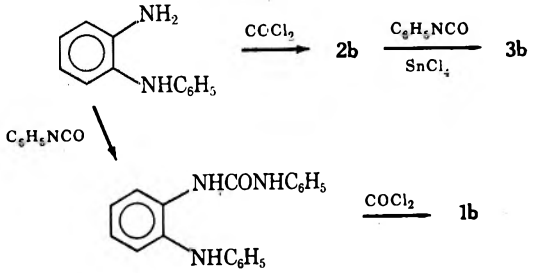


2a, X = F
b, X = H



3a, X = F
b, X = H

field pmr resonance in CH_3CN solution, while triazepinedione **1b** shows no such resonance.



Nitrenes, which are likely intermediates in these reactions,[2,4] are unambiguously produced by the thermolysis of aryl azides.[6] The yield of isocyanate from 4-fluorophenyl azide and CO increases with pressure; however, even at the highest pressure used, significant yield losses to urea and imidazolinone occurred (Table III). The product distributions from both nitrobenzenes and azides show similar pressure variations.

Discussion

Isolation of heptadeuterioaniline from the thermolysis of pentadeuteriophenyl azide suggested that the pro-

(6) P. A. S. Smith and J. H. Hall, *J. Amer. Chem. Soc.*, **84**, 480 (1962).

TABLE III
PRODUCT DISTRIBUTION FROM THE THERMAL DECOMPOSITION OF 4-FLUOROPHENYL AZIDE IN A CO ATMOSPHERE[a]

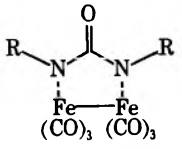
CO pressure, atm[b]	Isocyanate yield (gc), %	By-products yield (nmr), % Azobenzene	Urea	3a
25	0	(7)[c]	(12)[c]	0
50	16			
100	30	10	25	6
200	50	0	10	15
300	60			
400	78	0	8	14

[a] 180°/1 hr, 133 mg azide, 1.5 ml CH_3CN, 0.5 g o-$C_6H_4Cl_2$. [b] Pressure at 25°. [c] Relative yields only; absolute yields very low.

tons attached to the nitrogen came from ring abstraction.[7] In the presence of isocyanate, any aniline

$$C_6D_5N_3 \longrightarrow C_6D_6N \longrightarrow C_6D_5ND_2$$

formed would be converted to urea. Pyrolysis of phenyl azide with iron carbonyl gave a product **4** which



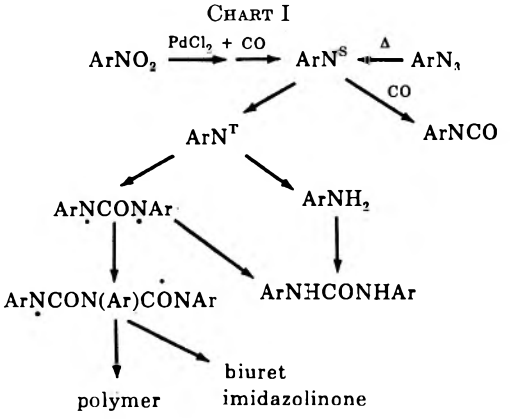
4

formally is the result of trapping the diradical of diphenylurea.[8] Proton abstraction by a similar species could also lead to urea. The biuret may result from the reaction of urea with more isocyanate, or by proton abstraction of a diradical analogous to **4**.

Isocyanate may be formed from singlet nitrene and singlet CO, while a triplet nitrene would abstract hydrogen.[9] Because the nitrene ground state is the triplet,[10] CO must intercept the initially formed excited singlet state; hence the high pressure required for efficient isocyanate formation.

Chart I suggests a mechanism to account for the products of this reaction. Azobenzene may be a precursor to phenyl nitrene, or a product derived from it. Reaction of singlet phenyl nitrene with CO gives isocyanate. If insufficient CO is present, intersystem crossing occurs, giving the triplet which can abstract protons to give aniline or react with isocyanate to give a diradical which can abstract protons to form urea or add another isocyanate to give a second diradical. This diradical can abstract protons to give biuret or cyclize to give imidazolinone **3**. Proton abstraction from the other terminal ring would have led to triazepinedione **1**. Continued reaction of the diradical with isocyanate leads to polymeric species which are always produced.

CHART I



The product distribution from thermal decomposition of substituted aryl azides varies widely with substituent.[6] Similarly, from nitrobenzene and CO, imidazolinone **3** accounts for 10% of the yield from 4-fluoronitrobenzene, less than 1% from nitrobenzene, and none from 4-chloronitrobenzene.

Chart I is drawn from the viewpoint of the organic chemist. Nowhere is the function of the palladium catalyst illustrated; yet it is vital to the success of the reaction. We have no knowledge of the structure of any possible metal-containing intermediates and do not wish to speculate on this phase of the mechanism, in spite of its importance.

Experimental Section

Proton nmr spectra were determined on Varian A-60 and HR-220 instruments, the latter using Fourier transform techniques. Fluorine nmr spectra were determined on a Varian HA-100 using external oscillators for locking and observing sidebands and proton noise decoupling. Ir spectra were determined on a Perkin-Elmer 21, uv spectra on a Cary 14, and mass spectra on a Du Pont CEC-21-110B. Melting points are uncorrected. Gas chromatography was done on a Hewlett-Packard Model 700 operating isothermally at 160° with a 6 ft × 0.25 in. stainless steel column packed with 20% SE-30 (methyl) silicon gum rubber on Chromosorb W. Correction factors for the disc integrator were determined by injecting mixtures with known proportions. Area per cent was directly proportional to mole per cent.

Reactions of Nitrobenzenes and Carbon Monoxide.—In a 10-ml Hastelloy bomb was placed an acetonitrile solution of $(CH_3CN)_2PdCl_2$, nitro compound, and o-dichlorobenzene (internal standard for gc). The bomb was pressured at room temperature with carbon monoxide and heated for the desired period. Pressure was vented and the liquid contents were assayed by gc. Residual oxygen in the bomb was consumed during the reaction forming CO_2 and was not detrimental to the catalytic process.

Reaction of 4-Fluorophenyl Azide and CO.—A solution of 4-$FC_6H_4N_3$, o-$C_6H_4Cl_2$ (internal standard for GC), and C_6H_5F (internal standard for nmr) in CH_3CN was heated in an atmosphere of CO at 180° for 1 hr. The solution was analyzed for isocyanate by gc and by-products by nmr.

Isolation of By-Products from 4-Fluoronitrobenzene and CO.—In a 200-ml Hastelloy bomb was placed 20 g of 4-$FC_6H_4NO_2$, 20 ml of CH_3CN, and 0.1 g of $PdCl_2$. After evacuation, the bomb was pressured to 150 atm with CO and heated at 250° for 2 hr. The bomb was cooled and vented, and the contents were decanted. The volatile fractions consisting of CH_3CN and 4-FC_6H_4NCO were distilled at room temperature and 0.3 mm. The brown residue was dissolved in THF, preadsorbed on 20 g of SilicAR CC-7, and chromatographed. Pentane eluted a small amount of orange solid (~200 mg) identified by ir and ^{19}F nmr as 4,4′-difluoroazobenzene. Benzene–pentane (1:1) eluted 2 g of imidazolinone **3a**. Benzene eluted a small amount of 1,3,5-tris-(4-fluorophenyl)biuret. Continued elution with methylene chloride, ether, acetone, tetrahydrofuran, and methanol produced dark solids which were 1,3-bis(4-fluorophenyl)urea by ir, ^{19}F nmr, and elemental analyses.

1,3,5-Tris(4-fluorophenyl)biuret.—To 2.0 g of 4-fluorophenyl isocyanate in 50 ml of benzene was added 3.0 g of 4-fluoroaniline. A white precipitate of the urea formed immediately. After 15 min at room temperature, 7.8 g of anhydrous stannic chloride was added, forming more precipitate. 4-Flurophenyl isocyanate (2.1 g) was added and the suspension was stirred for 2 hr under

(7) J. H. Hall, J. W. Hill, and J. Fargher, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 8–13, 1968, Paper ORGN 39.

(8) M. Dekker and G. R. Knox, *Chem. Commun.*, 1243 (1967).

(9) J. W. Hall, J. W. Hill, and J. Fargher, *J. Amer. Chem. Soc.*, **90**, 5313 (1968).

(10) E. Wasserman, G. Smolinsky, and W. A. Yager, *ibid.*, **86**, 3166 (1964).

nitrogen. The solid was filtered and addition of petroleum ether (bp 30–60°) gave a second crop. The solid was recrystallized twice from methanol to remove tin salts, giving 3.8 g of biuret as a white solid, mp 175.5–179°. *Anal.* Calcd for $C_{20}H_{14}F_3N_3O_2$: C, 62.4; H, 3.7; N, 11.2. Found: C, 62.1; H, 3.6; N, 10.9. Ir 2.96, 3.16 (NH), 3.25 (=CH), 5.85, 6.02 (C=O), 6.23, 6.45, 6.58, 6.65 (C=C and amide II), ~8 (CF), 11.93, 12.08, 12.36, 12.43 μ (para-disubstituted aromatic); ^{19}F nmr (CH_3CN) −112.8 (1 F), −117.7 (2 F).

7-Fluoro-1-(4-fluorophenyl)-3-(4-fluorophenylcarbamoyl)-2-benzimidazolinone (3a), had mp 201.5–203° (CH_3CN). *Anal.* Calcd for $C_{20}H_{12}F_3N_3O_2$: C, 62.6; H, 3.1; N, 10.9. Found: C, 62.5; H, 3.3; N, 11.1. Uv max (THF) 242 nm (ε 32,800), sh 283 (6570), 288 (5620); ir (KBr) 3.12 (NH), 3.23 (CH), 5.70, 5.86 (C=O), 6.16, 6.35, 6.60, 6.75 (C=C and amide II), 12.07 μ (para aromatic); pmr (DMSO) δ 6.79 (d, d, 1, J = 9, 2 Hz), 6.97 (d, t, 1, J = 2, 9 Hz), 7.12 (t, 2, J = 9 Hz), 7.35 (t, 2, J = 9 Hz), 7.57 (m, 4), 8.21 (d, d, 1, J = 9.5 Hz), 10.73 (broad s, NH); ^{19}F nmr (CH_3CN) δ −112.2 (t, t, 1, J = 5, 9 Hz,) −117.1 (d, t, 1, J = 5, 9 Hz), −118.1 (t, t, 1, J = 5, 9 Hz); mass spectrum (calcd for $C_{20}H_{12}F_3N_3O_2$, 383.0881) 383.0885, (calcd for $C_{13}H_8F_2N_2O$, 246.0604) 246.0608, 217.0556 ($C_{12}H_7F_2N_2$), 137 (C_7H_4FNO).

Pyrolysis of Imidazolinone 3a.—A solution of 200 mg of imidazolinone **3a** and 3 ml of a 10% potassium hydroxide solution was refluxed under nitrogen for 2 hr. On cooling a yellow solid formed and was extracted into ether and dried, the ether was removed on a rotary evaporator, and the product was recrystallized from acetonitrile to give 50 mg of white needles, mp 224–225°. *Anal.* (HRMS). Calcd for $C_{13}H_8F_2N_2O$: mol wt, 246. Found: mol wt, 246 (mass spectrum). Ir 3.13, 3.23, 5.83, 6.18, 6.25, 6.60, 6.69, 8–9, 12.04, 12.51 μ; uv (THF) 293 nm (ε 7960), 250 (6030); pmr (CH_3CN) δ 6.80 (d, d, 1, J = 9, 2 Hz), 6.85 (d, t, 1, J = 2, 9 Hz), 7.08 (d, 1, J = 9 Hz), 7.32 (t, 2, J = 9 Hz), 7.57 (d, d, 2, J = 9, 5 Hz), 8.8 (broad, 1, NH); ^{19}F nmr (CH_3CN) δ −114.3 (1 F), −121.6 (1 F).

1-Phenyl-2-benzimidazolinone was prepared by the reaction of phosgene with *N*-phenyl-*o*-phenylenediamine.[11]

2-Anilinocarbanilide was prepared by the reaction of phenyl isocyanate with *N*-phenyl-*o*-phenylenediamine.[12]

(11) M. L. Oftedahl, R. W. Radue, and M. W. Dietrich, *J. Org. Chem.*, **28**, 578 (1963).

(12) M. C. Kloetzel, S. J. Davis, U. Pandit, C. R. Smith, and H. Nishihara, *J. Med. Pharm. Chem.*, **1**, 197 (1959).

1,3-Diphenyl-1*H*,3*H*,5*H*-1,3,5-benzotriazepine-2,4-dione (1b).—To 100 ml of phosgene-saturated *o*-dichlorobenzene at 10° was added dropwise a solution of 5 g of 2-anilinocarbanilide in 30 ml of THF. After the addition was complete, the solution was warmed to room temperature, and excess phosgene was allowed to escape. Solvent was removed at reduced pressure, leaving a residue which was recrystallized from DMSO–H_2O, giving 1.3 g of triazepinedione as a white solid, mp 197–200°. *Anal.* Calcd for $C_{20}H_{15}N_3O_2$: C, 72.9; H, 4.6; N, 12.8. Found: C, 73.0; H, 4.7; N, 12.9. Ir 5.88, 6.21, 6.26, 6.66, 6.74 μ; nmr (DMSO-d_6–TMS) δ 11.05 (s, NH), 7.52 (s, 8 H), 7.05 (m, 6 H).

1-Phenyl-3-phenylcarbamoyl-2-benzimidazolinone (3b).—A slurry of 4 g of benzimidazolinone **2b**, 2.5 g of phenyl isocyanate, and 5 g of stannic chloride was heated in a test tube under N_2. The initially formed homogeneous melt deposited a solid. The solid was cooled to room temperature, slurried with CH_3OH, and filtered. Chromatography over neutral SilicAR and elution with 1:1 benzene–pentane gave 1 g of imidazolinone, which was recrystallized from CH_3CN, mp 166–168°. *Anal.* Found: C, 72.95; H, 4.60; N, 12.64. Nmr δ 10.6 (s, NH), 8.20 (m, 1 H), 7.62–7.51 (m, 7 H), 7.36 (t, J = 8 Hz, 2 H), 7.26–7.18 (m, 2 H), 7.13 (t, J = 7 Hz, 1 H), 6.99 (m, 1 H); ir 3.11, 3.16, 3.22, 5.75, 5.86, 6.22, 6.37, 6.64, 6.75, 13.20, 14.17 μ.

Reaction of Pentadeuteronitrobenzene with CO.—A solution of 0.7 ml of $C_6D_5NO_2$, 5 mg of $PdCl_2$, and 1 ml of CH_3CN was pressured with 100 atm of CO and heated at 275° for 2 hr. Volatile products were removed by distillation and the residue was sublimed using a Dowtherm bath at 0.05 Torr. The ir spectrum showed significant absorptions at 2495, 2455, and 2390 cm^{-1} (N–D stretch).

Registry No.—**1b**, 38456-60-9; **2a**, 38456-61-0; **2b**, 14813-85-5; **3a**, 38456-63-2; **3b**, 38456-64-3; 4-fluorophenyl azide, 3296-02-4; carbon monoxide, 630-08-0; 4-fluorophenyl isocyanate, 1195-45-5; 4-fluoronitrobenzene, 350-46-9; 1,3,5-tris(4-fluorophenyl)biuret, 38456-65-4; 4-chloronitrobenzene, 100-00-5; 4-chlorophenyl isocyanate, 104-12-1; phenyl isocyanate, 103-71-9.

Acknowledgment.—The author thanks Professor B. L. Trost for valuable discussions.

Reactions of Isocyanides with Activated Acetylenes in Protic Solvents[1]

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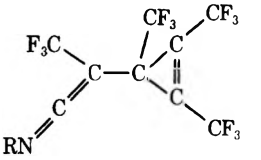
The reaction of isocyanides with activated acetylenes in alcoholic solvents has been shown to produce a mixture of two different 1:1:1 adducts (isocyanide:acetylene:alcohol), an unsaturated imino ester, and a ketenimine. The configurations of the imino esters have been determined and the initial product is always that which results from trans addition. In some cases (methyl propiolate) the initial product is easily isomerized to the more stable isomer. The relative amounts of ketenimine and imino ester that form are dependent on the structures of the acetylene and the isocyanide and to some extent on the nature of the alcohol. In one case, the reaction of *p*-nitrophenyl isocyanide with dimethyl acetylenedicarboxylate in methanol, an ortho ester is obtained. In all cases the results are best interpreted by assuming the initial formation of a 1:1 intermediate (isocyanide:acetylene) with net trans addition to the acetylenic bond.

Previously we demonstrated that isocyanides would react with hexafluorobutyne-2 in aprotic solvents to produce 1:2 adducts of structure **1**.[2]

A few years prior to this work, Meinwald and Aue[3] had produced a similar type of product from the reaction of a nitrene with a normal acetylene. They postulated that their 1:2 product might be produced from an initially formed 1:1 intermediate that could possibly possess predominate carbene or carbonium ion character.



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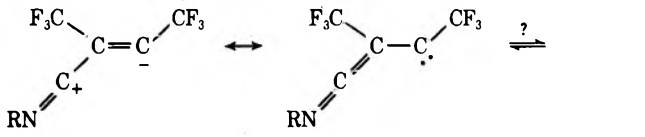
(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971, Abstract ORGN-106.

(2) T. R. Oakes, H. G. David, and F. J. Nagel, *J. Amer. Chem. Soc.*, **91**, 4761 (1969).

(3) J. Meinwald and D. H. Aue, *ibid.*, **88**, 2849 (1966).

In our analogous situation we postulated that our 1:2 adduct was being formed from a 1:1 intermediate (2) that might possess predominate carbene or carban-



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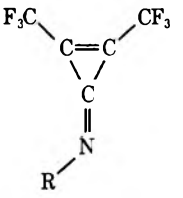
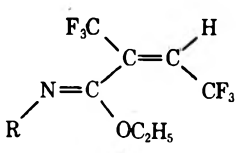


ion character or perhaps even resemble a cyclopropenone imine.

Others[4-6] have postulated similar 1:1 intermediates for the reaction of isocyanides with different activated acetylenes.

In aprotic solvents the products obtained may be 1:2 adducts[2,6] (isocyanide:acetylene), 2:1 adducts,[7] 3:1 adducts,[7] or 2:3 adducts.[4] In all cases it seems reasonable to assume the prior information of a 1:1 intermediate. Previously[2] we had indicated the existence of a 1:1 intermediate by treating isocyanides with hexafluorobutyne-2 in the presence of a protic solvent (ethanol) to form two different 1:1:1 adducts (isocyanide:acetylene:ethanol), an imino ester (3),



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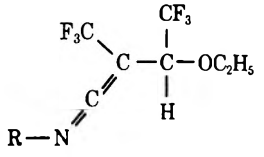

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and a ketenimine (4). Thus, in protic solvents, the 1:1 intermediate could be trapped.

In this work, we have investigated this reaction more fully; we have continued the trapping experiments, we have determined the stereochemistry of the imino esters (3), we have studied the effect of changes of substituents in para-substituted phenyl isocyanides on the composition of the trapped products, and we have also studied the reaction of isocyanides with some other activated acetylenes.

Results and Discussion

To date, the 1:1 intermediate has not been trapped by typical carbene trapping agents other than alcohols. We have attempted to trap the 1:1 intermediate by employing solvent concentrations of various olefins (cyclohexene, dimethyl fumarate, and dimethyl maleate), but the only product obtained in these nonprotic solvents was the original 1:2 adduct 1. Even under conditions of high-dilution addition of hexafluorobutyne-2 to isocyanides in olefin solvents, the only product obtained was 1. The high-dilution reactions generally proceed with much more polymer formation than is obtained by mixing equivalent amounts of isocyanide and hexafluorobutyne-2 in a Parr bottle and the yield of 1 is generally lower, but we have not been able to detect any new low molecular weight compounds. This would argue that the 1:1 intermediate possesses little carbene character. However, others[8] have experienced similar difficulty in trapping oxacarbene intermediates with anything other than alcohols.

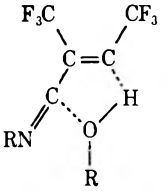
In order to examine the nature of the 1:1 intermediate more fully, we have conducted a substituent study of the reaction of para-substituted phenyl isocyanides with hexafluorobutyne-2 using various alcohols as solvents. Using a variety of substituents we have determined the product ratios of 3 to 4. In alcohol solutions these are the only two products obtained and generally in overall yields of 80–90%.

The relative amounts of the two compounds were determined by integration of the ^{19}F nmr spectrum of the reaction mixture after removal of the solvent. The wide separation of the ^{19}F peaks enabled us to obtain good relative yield data. After the nmr spectrum had been obtained, the mixture was subjected to fractional distillation and spectra and analyses were obtained on the pure compounds. The relative yields are summarized in Table I.

TABLE I
YIELDS OF IMINO ESTERS (3) AND KETENIMINES (4)

Alcohol	Isocyanide	Total yield, %	Ratio of 3:4
Methyl	p-$NO_2C_6H_4$	80	100:0
Methyl	p-ClC_6H_4	73	81:19
Methyl	C_6H_5	94	70:30
Methyl	p-$CH_3C_6H_4$	89	72:28
Methyl	p-$CH_3OC_6H_4$	94	71:29
Ethyl	C_6H_5	80	65:35
Isopropyl	C_6H_5	80	54:46

The data in Table I demonstrate that the reaction is somewhat affected by changes of substituents in the isocyanides. It is interesting to note that electron-withdrawing substituents have a marked effect while electron-donating substituents appear to have no effect on the course of the reaction. The fact that the imino ester possess a trans configuration (*vide infra*), that electron-withdrawing groups favor the formation of the imino ester, and that other normal carbene trapping agents are ineffective in this reaction is consistent with the formation a 1:1 intermediate which is predominantly polar with little or no carbene or cyclopropenone imine character. A single mechanism that accounts for all of the observations is given in Scheme I. The fact that the configuration of the imino ester is exclusively trans would indicate that the addition of alcohol to the intermediate is stepwise or involves more than 1 mol of alcohol. It would exclude a concerted cisoid intermediate of the following type.



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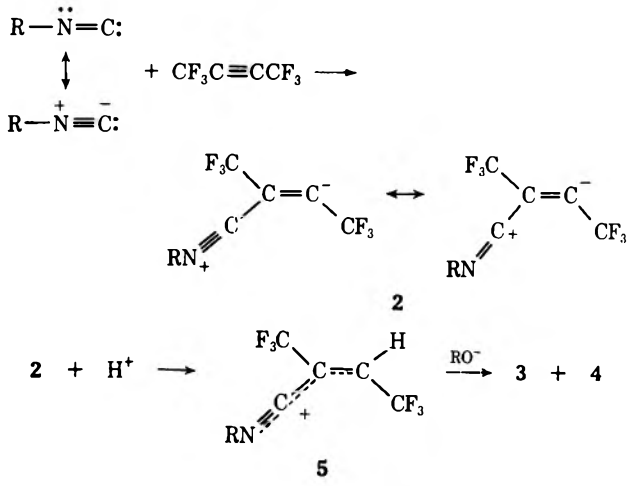
(5) F. Johnson, A. H. Gulbenkian, and W. A. Nasutavicus, *Chem. Commun.*, 608 (1970).

(6) E. Winterfeldt, D. Schumann and H. J. Dillinger, *Chem. Ber.*, **102**, 1656 (1969).

(7) T. Takizawz, N. Obata, Y. Suzuki, and T. Yanagida, *Tetrahedron Lett.*, 3407 (1969).

(8) D. R. Morton, E. Lee-Ruff, R. M. Southam, and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 4349 (1970).

SCHEME I



It would also cast some doubt on the cisoid structure proposed for the 1:1 intermediates,[2,4,5] and upon the intermediacy of a cyclopropenone imine. However, the fact that the imino esters are *exclusively* trans does give us some insight to the stereochemistry of nucleophilic additions to triple bonds in general. These types of additions have been carefully studied by a number of authors. Thus, Truce[9] has developed a "Rule of Trans Nucleophilic Addition." An exception to the rule was noted in the base-catalyzed addition of *p*-toluenethiol to sodium propiolate.[10] Others[11,12] have shown that the reaction of amines with activated acetylenes also involves an exception to the rule. In this last case, the incoming amine is a neutral species and the nitrogen atom begins to develop positive charge in the transition state. It is therefore not unreasonable to expect that the developing negative charge takes a cisoid course. A similar intermediate may be postulated for the reaction of an isocyanide with hexafluorobutyne-2.

It should be stressed that, in any of the above cases where a carbonyl group exists on the acetylene, the vinyl anion may be configurationally unstable or perhaps even linear owing to resonance interaction of the carbonyl group.[13] In the present case, where the electron-withdrawing groups are trifluoromethyl groups, this complication would not be at hand, since such a resonance effect is largely inoperative.

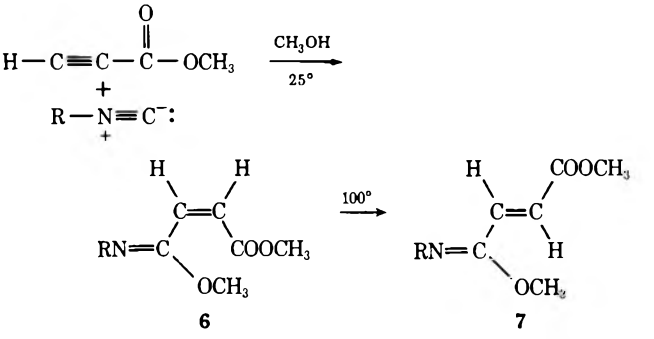
In comparing the attack of an amine to that of an isocyanide on an activated acetylene, it should be noted that both are neutral species and that both incoming groups begin to develop positive charge in the transition state. Thus, a cisoid type intermediate might be anticipated in both cases. However, in the case of the amine a proton is immediately available for concerted transfer while in the case of isocyanide, protonation occurs from the solvent. Thus, the mere development of positive charge on the incoming group does not appear to be sufficient reason for cis addition.

It is possible, of course, that the initial addition does take a cisoid course but that isomerization occurs in some subsequent intermediate or perhaps that the initially formed cis addition product (the imino ester) rearranges to the trans addition product. We have not been able to obtain the imino ester resulting from cis addition either by direct reaction or by attempts at rearranging the obtained imino ester. We have attempted both thermal- and ultraviolet-initiated rearrangement of the trans imino ester but with no success. Thus, we cannot be certain that an initially formed cis addition product does not rearrange to the trans addition product. We do have good indications that this is not the case, however.

We have been able to obtain both the cis and trans addition compounds of methanol and ethanol to hexafluorobutyne-2. As demonstrated by Raunio and Frey,[14] the product that forms is greater than 95% trans when methanol is added to hexafluorobutyne-2, using sodium methoxide as the catalyst. We have shown that this trans compound can then be rearranged to the cis compound by irradiation with ultraviolet light in the presence of acetophenone as the sensitizer. Both cis and trans compounds are quite stable with regard to thermal cis–trans rearrangement. Heating in a sealed tube for 2 hr at 110° caused no rearrangement. Thus compounds similar to the imino esters are thermally stable.

In addition, Saegusa and coworkers[15] have recently reported on the reaction of isocyanides with methyl propiolate in methanol as solvent. By running the reaction in a sealed tube for 24 hr at 110° they obtained the trans imino ester (**7**) exclusively. This would infer a cis addition. We have repeated their work and we have confirmed their results. However, we have discovered that the same reaction will occur at room temperature if the reaction time is extended (4 to 5 days). Under these conditions, we obtain the cis imino ester **6**, which infers a trans addition. Furthermore, the cis imino ester obtained at room temperature can be rearranged to the trans compound by heating at 100° for 24 hr (see Scheme II). Thus,

SCHEME II



it seems likely that the trans imino ester **7** obtained by Saegusa results from an initial trans addition followed by rearrangement.

Even though the cis imino ester **6** will undergo rearrangement when heated at 100° for 24 hr, it is stable enough to be distilled at 70° and only about 50% has rearranged after 10 hr at 100°. Thus, in the reactions of hexafluorobutyne-2, performed at room temperature, it also seems likely that the product obtained

(9) W. E. Truce and J. A. Simms, *J. Amer. Chem. Soc.*, **78**, 2756 (1956).
(10) W. E. Truce and R. F. Heine, *ibid.*, **79**, 5311 (1957).
(11) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965).
(12) E. Winterfeldt and H. Preuss, *Chem. Ber.*, **99**, 450 (1966).
(13) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 234.
(14) E. K. Raunio and T. G. Frey, *J. Org. Chem.*, **36**, 345 (1971).
(15) T. Saegusa, Y. Ito, S. Tomita, H. Kinoshita, and N. Taka-Ishi, *Tetrahedron*, **27**, 27 (1971).

(the imino ester **3**) is the kinetically controlled product and that it did not result from rearrangement of an initially formed cis addition product. With regard to the geometry of the postulated intermediates, there appears to be no reason to invoke a cisoid or cyclopropenone imine type intermediate. Sterically such intermediates appear more stable, but in order to explain the trans addition products either transoid intermediates or a concerted mechanism must be invoked. It may be, of course, that no discrete 1:1 intermediate exists in protic solvents but rather that the reaction between the isocyanide, acetylene, and alcohol is a concerted process and that the steric effect of the two incoming groups is the determining factor. This would be analogous to the mechanism proposed by Winterfeldt[12] for the tertiary amine catalyzed addition of alcohols to activated acetylenes.

The configurational assignments of the cis and trans imino esters from methyl propiolate were made on the basis of their coupling constants. The cis imino ester **6**, formed at room temperature, possesses an AB quartet (assigned to the vinyl protons) centered at $\delta_{TMS}^{CCl_4}$ 6.22 with a coupling constant of 12 Hz, while the product formed by thermal rearrangement or by using Saegusa's conditions has an AB quartet centered at $\delta_{TMS}^{CCl_4}$ 6.84 with a coupling constant of 16 Hz. These coupling constants are consistent with other similar types of alkenes.[16]

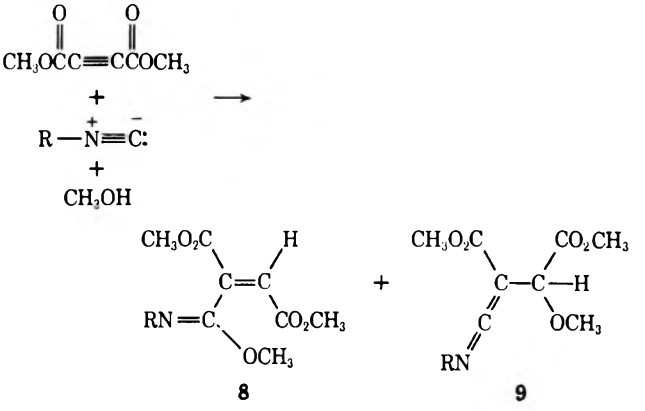
The trans configuration of the imino esters obtained from hexafluorobutyne-2, isocyanides, and alcohols was assigned on the basis of ^{19}F coupling constants.

Raunio and Frey[14] have assigned the configurations to the cis and trans addition products of methanol to hexafluorobutyne-2. For the trans addition product they report no coupling between the two CF_3 groups, while for the cis addition product they report an F_1F_4 coupling constant of 11 Hz. This is consistent with our results. We have also obtained the cis and trans ethanol adducts of hexafluorobutyne-2. In this case, for the trans isomer the F_1F_4 coupling constant is 1.8 Hz while for the cis isomer it is 10 Hz. Others[17] have also reported F_1F_4 coupling constants for similar type compounds and their results agree with ours and with Raunio and Frey. The F_1F_4 coupling constants in the hexafluoroimino esters obtained in this work are 1.5–2.0 Hz. Thus the configuration of the two CF_3 groups is trans.

We have also examined the reaction of isocyanides with dimethyl acetylenedicarboxylate in both the absence and presence of alcohols. In both cases a reaction takes place at room temperature. In the absence of protic solvents (in CH_2Cl_2) the only product isolated is a 2:3 adduct (isocyanide:acetylene) similar to that reported by others.[4] In the presence of methanol a similar reaction takes place as in the case of hexafluorobutyne-2. Again, both imino esters (**8**) and ketenimines (**9**) are obtained (Scheme III).

When R is an aryl group (phenyl, *o*-tolyl, or *p*-nitrophenyl) the only product obtained is the imino ester **8** whereas when R is alkyl (cyclohexyl or *tert*-butyl) both the imino ester **8** and the ketenimine **9** are obtained. In the case of cyclohexyl the ratio of **8**:**9** is about 1:1, whereas in the case of *tert*-butyl isocyanide the ratio is about 1:9. Thus the attack by methoxide may be governed by the steric effect of R in an intermediate similar to **5**. It should be pointed out that the overall yields in this reaction were generally less than in the case of hexafluorobutyne-2. This is partially due to difficulties in distilling these higher boiling materials and partially due to the apparent greater tendency of dimethyl acetylenedicarboxylate to simply undergo an addition reaction with the methanol under these reaction conditions. It is interesting to note that the addition product of methanol to dimethyl acetylenedicarboxylate, which is apparently catalyzed by the isocyanide acting as a base, is predominantly (90%) of the trans configuration, as determined by comparison of the chemical shifts of this compound to that reported by Winterfeldt and Preuss.[12]

SCHEME III



It is assumed that the imino esters obtained from the reaction of isocyanides with dimethyl acetylenedicarboxylate in methanol are trans addition products (**8**). This assumption is based on the formation of the analogous imino esters, formed *via* trans addition, from hexafluorobutyne-2 and from the room-temperature reaction of methylpropiolate. In addition, an interesting product, thought to be an ortho ester, obtained in the case of *p*-nitrophenyl isocyanide helps substantiate the assumed mode of addition to dimethyl acetylenedicarboxylate.

When *p*-nitrophenyl isocyanide is allowed to react with dimethyl acetylenedicarboxylate in methanol for 2 or 3 weeks at room temperature, the product obtained (in 20% yield) after evaporation of the methanol and recrystallization from benzene is a 1:1:2 adduct (isocyanide:acetylene:methanol). The nmr spectrum displays four absorptions of relative area 4:1:3:9. The quartet representing four protons at δ 8.1 is due to the *p*-nitrophenyl protons, the singlet in the vinyl region at 6.70 accounts for one proton, the singlet at 3.80 representing three protons is assigned to a carbomethoxy group, and a singlet at 3.25 representing nine protons is assigned to the ortho ester grouping. A very broad absorption at δ 9.6 accounting for one proton is assigned to a hydrogen-bonded NH proton.

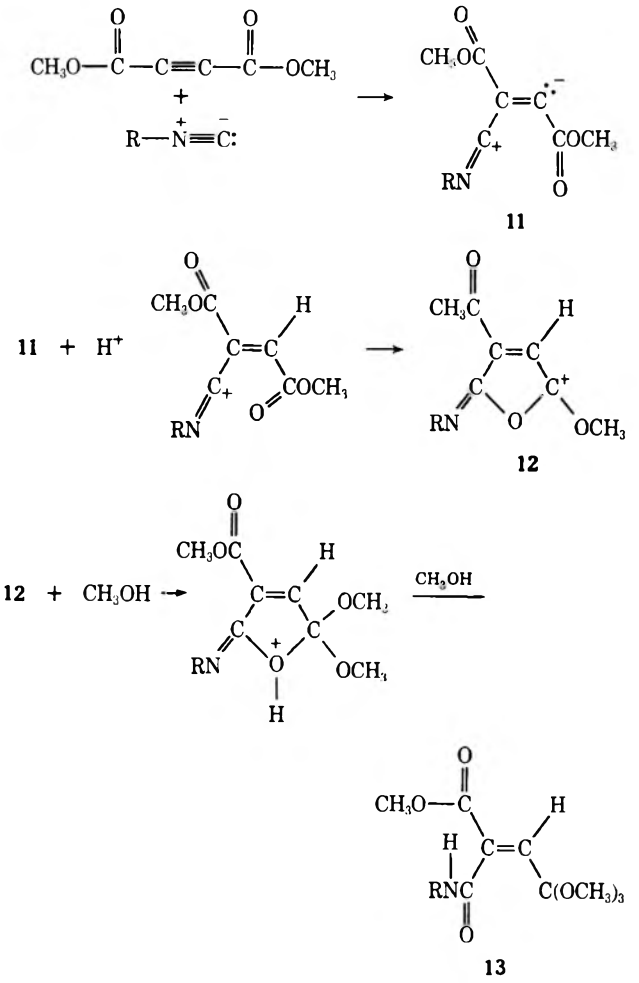
The infrared spectrum displays an NH peak at 3335 cm^{-1} and carbonyl peaks at 1725, 1650, and 1550 cm^{-1}.

A mechanism that accounts for the formation of this compound is given in Scheme IV.

(16) J. W. Emsley, J. Feeney, and L. H. Stucliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, Oxford, 1966, p 739.

(17) Reference 16, p 912.

SCHEME IV



R = p-$NO_2C_6H_4$

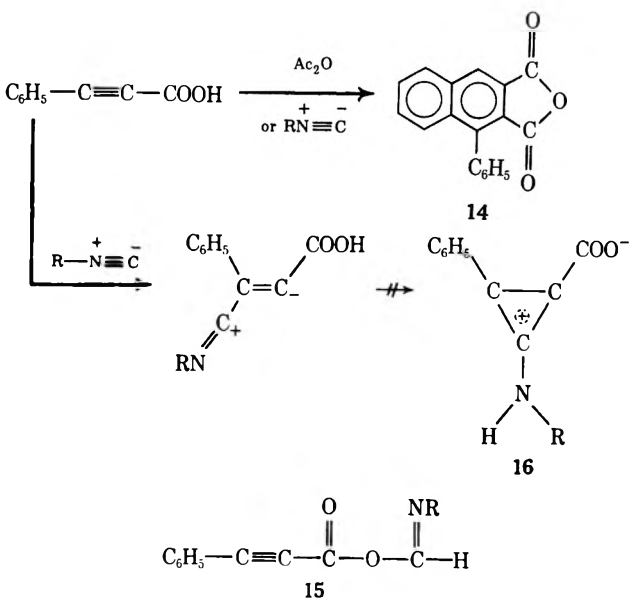
In order to invoke this mechanism, the intermediates involved must result from trans addition.

From all of the above data we feel that the reaction of isocyanides with activated acetylenes in protic solvents involves a trans addition and no evidence exists for the intermediacy of a cisoid intermediate with or without cyclopropenone imine character. Initially we[2] and others[4,5,18] felt that cyclopropenone imines might be formed in these reactions. Apparently the presence of the strong electron-withdrawing groups, that are required to cause the isocyanide to react with the acetylene, sufficiently destabilize the three-membered aromatic system (the cyclopropenone) so as to preclude its formation.

In a final attempt to isolate a cyclopropenone imine type derivative we treated phenylpropiolic acid with various isocyanides, hoping that the isocyanide would react faster with the acetylene function than with the carboxylic acid group, and that proton transfer would result in a stable system (**16**). This was not the case; rather, a naphthoic anhydride derivative resulted (**14**). This same product has been obtained by treating phenylpropiolic acid with acetic anhydride.[19] Thus it is likely that the isocyanide undergoes an α,α addition with the carboxylic acid to form an anhydride-like intermediate (**15**) which then cyclizes to the naphthoic anhydride (Scheme V).

(18) E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.*, **6**, 434 (1967).
(19) A. D. Campbell, *J. Chem. Soc.*, 3659 (1954).

SCHEME V



The formation of naphthoic anhydride derivatives from phenylpropiolic acid and acetic anhydride has been studied extensively.[19] It appears essential that an anhydride be formed first in order that cyclization may occur. The surprising thing in the reaction mediated by isocyanides is that it takes place under such mild conditions.

Experimental Section

The infrared spectra were determined using a Beckman IR-8 spectrophotometer; the nmr spectra were determined with a Varian T-60 equipped with an auxiliary ^{19}F probe or with a Varian 56/60 spectrophotometer; TMS was used as the internal standard for the ^1H spectra while CCl_3F was used for the ^{19}F spectra. The isocyanides were all carefully purified and shown to be free of amines by their nmr spectrum.

Reaction of Isocyanides with Hexafluorobutyne-2 in Methanol.—A 500-ml Parr bottle, with inlet and outlet tubes equipped with $CaCl_2$ drying tubes, in a Dry Ice–acetone bath was charged with 200 ml of alcohol, 0.025 mol of isocyanide, and 10.0 g (0.062 mol) of hexafluorobutyne-2. The bottle was then stoppered and shaken on a Parr apparatus for 2 hr at room temperature. The pressure rapidly rose to 25 psi, but after 2 hr it usually had decreased to about 15 psi. At the end of this time the isocyanide had completely disappeared, as evidenced by ir spectra and lack of odor. The solvent was removed using a rotary evaporator and the crude reaction mixture was analyzed using ir, ^1H nmr, and ^{19}F nmr spectroscopy. Integration of the ^{19}F nmr spectra gave the relative amounts of imino ester and ketenimine. Each reaction was run and analyzed two times or more. At least three integrations of the ^{19}F spectrum were determined for each reaction mixture. The relative yields thus determined are summarized in Table I.

The crude reaction mixture was then fractionally distilled under vacuum to obtain the pure imino ester and ketenimine. These were further examined spectroscopically to conclusively assign the absorptions in the ^{19}F nmr spectra of the mixtures.

The lower boiling fraction, the imino esters, possessed a strong peak in the ir near 1666 cm^{-1} while the high-boiling fraction, the ketenimines, possessed a strong characteristic absorption near 2083 cm^{-1}. The ^1H and ^{19}F chemical shifts are given in Table II. Typical coupling constants are HF_1 = 7.2 Hz for the geminal hydrogen and CF_3 group, HF_4 = 1.8 Hz for the hydrogen cis to the other CF_3 group, and F_1F_4 = 1.8 Hz for the two trans CF_3 groups.

A middle cut of each compound was sent out for analysis. The data are summarized in Table II.

The reaction of phenyl isocyanide with hexafluorobutyne-2 in ethanol and 2-propanol was also examined but analytical samples

TABLE II

PROPERTIES AND ANALYSIS OF IMINO ESTERS (3) AND KETENIMINES (4)

Compd type (registry no.)	Alcohol (registry no.)	Isocyanide (registry no.)	Bp, °C (mm)	Analysis	% C	% H	% N	% F	Proton nmr[a]	^{19}F nmr[b]
3	Methyl	C_6H_5	30–33	Calcd	48.50	3.05	4.71	38.35	3.90 (s, 3), 6.20 (q of	64.4 (d of q, 3)
(38308-64-4)	(67-56-1)	(931-54-4)	(0.25)	Found	48.34	3.18	4.93	38.11	q, 1), 7.0 (m, 5)	65.6 (p, 3)
4	Methyl	C_6H_5	40	Calcd	48.50	3.05	4.71	38.35	3.53 (s, 3), 4.13 (q, 1),	57.9 (s, 3)
(38308-65-5)			(0.25)	Found	49.32	3.52	4.92	38.68	7.30 (s, 5)	79.4 (d, 3)
3	Methyl	p-$CH_3OC_6H_4$	55–58	Calcd	47.72	3.39	4.28	34.83	3.66 (s, 3), 3.86 (s, 3),	65.0 (d of q, 3)
(38308-66-6)		(10349-38-9)	(0.15)	Found	48.42	3.46	4.42	35.42	6.21 (q of q, 1), 6.70 (s, 4)	66.1 (p, 3)
4	Methyl	p-$CH_3OC_6H_4$	76	Calcd	47.72	3.39	4.28	34.83	3.53 (s, 3), 3.75 (s, 3),	58.2 (s, 3)
(38308-67-7)			(0.15)	Found	47.02	3.34	4.73	33.36	4.13 (q, 1), 7.04 (q, 4)	79.6 (d, 3)
3	Methyl	p-$CH_3C_6H_4$	35–36.5	Calcd	50.17	3.56	4.50	36.63	3.25 (s, 3), 3.86 (s, 3),	64.7 (d of q, 3)
(38308-68-8)		(7175-47-5)	(0.15)	Found	50.39	3.82	4.44	35.94	6.16 (q of q, 1), 6.80 (s, 4)	65.8 (p, 3)
4	Methyl	p-$CH_3C_6H_4$	53	Calcd	50.17	3.56	4.50	36.63	3.40 (s, 3), 3.56 (s, 3),	57.9 (s, 3)
(38308-69-9)			(0.15)	Found	50.99	3.91	4.48	34.62	4.13 (q, 1), 7.15 (s, 4)	79.5 (d, 3)
3[c]	Methyl	p-ClC_6H_4	48	Calcd	43.46	2.43	4.22	34.37	3.95 (s, 3), 6.27 (q of	64.7 (d of q, 3)
(38308-70-2)		(1885-81-0)	(0.20)	Found	44.31	2.36	4.35	34.47	q, 1), 7.0 (q, 4)	65.7 (p, 3)
3	Methyl	p-$NO_2C_6H_4$	99–102	Calcd	42.12	2.36	8.19	33.31	4.00 (s, 3), 6.20 (q of	64.7 (d of q, 3)
(38308-71-3)		(1984-23-2)	(mp)	Found	42.40	2.05	8.21	33.73	q, 1), 7.53 (q, 4)	66.1 (p, 3)

[a] The data are given in parts per million (δ) relative to TMS as an internal standard in CCl_4; s = singlet, q = quartet, m = multiplet; the number in parentheses represents the number of protons obtained from integration. [b] The data are given in parts per million relative to CCl_3F as an internal standard in CCl_4; s = singlet, d = doublet, q = quartet, p = pentet. [c] We were not able to obtain an analytical sample of the corresponding ketenimine; however, ir and nmr spectra demonstrated its presence in the original reaction mixture.

were not obtained. The spectral properties of these imino esters and ketenimines are consistent with the assigned structures.

Attempts to isomerize the imino esters, either thermally or with a 450-W Hanovia high-pressure quartz mercury-vapor lamp, were unsuccessful. In contrast, the simple methanol and ethanol adducts of hexafluorobutyne-2, prepared by the method of Haszeldine[20] and shown to be greater than 95% trans by Raunio and Frey,[14] were easily isomerized in the presence of acetophenone to the cis isomer using a 450-W Hanovia lamp. Both of these cis and trans isomers were unaffected upon heating in a sealed tube at 110° for 2 hr.

Methyl *cis*-γ-(*N*-Cyclohexylimino)-γ-methoxycrotonate (6).—To 8.4 g (0.1 mol) of methyl propiolate in 50 ml of methanol was added 10.9 g (0.1 mol) of cyclohexyl isocyanide. The stoppered reaction flask was allowed to stand at 25° for 5 days. The methanol was removed without heating using a rotary evaporator. Distillation of the residue produced a low-boiling fraction, bp 25–35° (0.1 mm), consisting of the cis and trans adducts of methanol to methyl propiolate, and a higher boiling fraction, bp 75–77° (0.1 mm), yield 5.2 g (23%) of 6. The nmr spectrum displayed two doublets ($\delta_{CCl_4}^{TMS}$) for two vinyl protons at 6.0 and 6.42, two singlets at 3.56 and 3.62 for the two methoxy groups, and a broad cyclohexyl absorption centered at 1.4. The infrared spectrum displayed significant peaks at 2930, 2860, 1735, 1685, and 1615 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.16; H, 8.59; N, 6.88.

Methyl *trans*-γ-(*N*-Cyclohexylimino)-γ-methoxycrotonate (7).—This compound could be prepared either by the method of Saegusa[15] or by heating the cis compound (6) in a sealed tube at 110° for 20 hr. The two vinyl doublets now appeared at δ 6.46 and 7.22, the two methoxy singlets at 3.58 and 3.70, and the broad cyclohexyl peak at 1.5. The infrared spectrum displayed significant peaks at 2925, 2850, 1725, 1660, 1615, and 970 cm^{-1}. This last peak was absent in the spectrum of the cis compound.

Reactions of Isocyanides with Dimethyl Acetylenedicarboxylate in Methanol.—To 0.1 mol of the isocyanide in 200 ml of methanol was added 14.2 g (0.1 mol) of dimethyl acetylenedicarboxylate. The alkyl isocyanides were let stand for 2–3 days, while aryl isocyanides required 2–3 weeks for any significant reaction to occur. The methanol was removed using a rotary evaporator and the thick oil was distilled at reduced pressure.

A. Cyclohexyl Isocyanide.—An infrared spectrum of the crude material indicated the presence of both the ketenimine (2050 cm^{-1}) and the imino ester (1675 cm^{-1}). Distillation of the thick oil gave two major cuts. The first cut, bp 95–110° (0.5 mm), possessed a very weak absorption at 2050 cm^{-1} and a medium absorption at 1625 cm^{-1}. For the second cut, bp 115–125° (0.2 mm), the former peak was very strong while the latter was absent. The total yield of both isomers was 50%, each present in about equal amounts as determined by the nmr spectrum of the crude mixture.

Each of the two cuts was redistilled and a center cut was sent out for analysis. The infrared spectrum of the low-boiling distillate (the imino ester 8) displayed significant peaks at 2940, 2860, 1720, 1675, 1625, and 1225 cm^{-1}. The nmr spectrum ($\delta_{CCl_4}^{TMS}$) displayed a singlet (1 H) at 6.90 (vinyl proton), three singlets (9 H) at 3.66, 3.70, and 3.78 (methoxy protons), a broad multiplet (1 H) at 2.9 (C_1 cyclohexyl proton), and a broad multiplet (10 H) at 1.4 (cyclohexyl protons). *Anal.* Calcd for $C_{14}H_{21}NO_5$: C, 59.40; H, 7.43; N, 4.95. Found: C, 59.80; H, 7.38; N, 5.17.

The high-boiling cut, the ketenimine 9, displayed significant peaks in the ir at 2940, 2860, 2050, 1725, 1675, and 1240 cm^{-1}. The nmr spectrum ($\delta_{CCl_4}^{TMS}$) displayed a singlet (1 H) at 4.62 (methine proton), two closely spaced singlets (6 H) at 3.66 and 3.68 (carbomethoxy protons), a singlet (3 H) at 3.33 (methoxy protons), and a broad, diffuse peak (11 H) centered at 1.6 (cyclohexyl protons). *Anal.* Calcd for $C_{14}H_{21}NO_5$: C, 59.40; H, 7.43; N, 4.95. Found: C, 59.39; H, 7.61; N, 5.28.

B. *tert*-Butyl Isocyanide.—The oil was distilled; a large forerun consisting of the addition product of methanol to dimethyl acetylenedicarboxylate (17 g, 65%) and a high-boiling fraction, bp 115–120° (0.3 mm) (5.0 g, 25%), was obtained. The high-boiling fraction possessed a strong ir peak in the ketenimine region (2050 cm^{-1}) and only a small shoulder in the imino ester region (1615 cm^{-1}). The nmr spectrum indicated the presence of about 10% imino ester.

Redistillation produced a pure sample of ketenimine 9. The ir spectrum possessed significant peaks at 2980, 2050, 1725, 1675, and 1250 cm^{-1}. The nmr spectrum ($\delta_{CCl_4}^{TMS}$) displayed a singlet (1 H) at 4.60 (methine proton), a broadened singlet (6 H) at 3.70 (carbomethoxy protons), a singlet (3 H) at 3.33 (methoxy protons), and a singlet (9 H) at 1.40 (*tert*-butyl protons). *Anal.* Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.45. Found: C, 55.46; H, 7.73; N, 4.98.

C. Phenyl Isocyanide.—The thick oil after removal of the methanol showed no absorption in the ketenimine region (2050

(20) R. N. Haszeldine, *J. Chem. Soc.*, 3498 (1952).

cm^{-1}). Distillation gave 5 g (19%) of a thick yellow oil, bp 132–138° (0.25 mm). The ir spectrum displayed significant peaks at 3050 (shoulder), 3000, 2940, 1700, 1650, 1610, 1370, and 1240 cm^{-1}. The nmr spectrum indicated the presence of the imino ester and some impurity (*ca.* 15%) that could not be removed by repeated distillation. The good chemical analysis indicates that the impurity is an isomer of the imino ester (but it is not the ketenimine). The nmr displayed peaks ($\delta_{CCl_4}^{TMS}$) at 7.0 (broad multiplet, 5 H) for the phenyl protons, 6.72 (singlet, 1 H) for the vinyl proton which was superimposed on the phenyl protons, and three singlets at 3.90, 3.70, and 3.64, each representing three protons for the three methoxy groups. *Anal.* Calcd for $C_{14}H_{15}NO_5$: C, 60.60; H, 5.40; N, 5.05. Found: C, 60.12; H, 6.02; N, 5.36.

D. *o*-Tolyl Isocyanide.—After removal of the methanol, the thick oil, which showed no ir absorption in the ketenimine region, was distilled, giving a 60% yield of the imino ester **8**, bp 126–127° (0.25 mm). The ir spectrum displayed significant peaks at 3050 (shoulder), 3000, 2950, 1700, 1650, 1610, 1575, and 1250 cm^{-1}. The nmr spectrum displayed peaks ($\delta_{CCl_4}^{TMS}$) at 6.9 (broad multiplet, 4 H) for the phenyl protons, 6.80 (singlet, 1 H) for the vinyl proton superimposed on the phenyl protons, 3.95, 3.37, and 3.55, all singlets, each representing three protons for the three methoxy groups, and 2.12, a singlet (3 H) for the *o*-methyl group. *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.25; H, 5.50; N, 5.15. Found: C, 61.05; H, 5.75; N, 5.22.

E. *p*-Nitrophenyl Isocyanide. Ortho Ester Formation (13).—To 4.7 g (0.032 mol) of *p*-nitrophenyl isocyanide in 200 ml of methanol was added 4.5 g (0.032 mol) of dimethyl acetylenedicarboxylate. The solution was let stand for 2 weeks and the methanol was removed using a rotary evaporator. The viscous oil was dissolved in 50 ml of benzene and the benzene solution was allowed to evaporate at room temperature. After 2 days crystals had formed; they were collected and recrystallized from benzene, yield 2.2 g (20%), mp 155–159°. The ir spectrum (KBr) displayed significant peaks at 3340, 1725, 1650, 1550, and 1500 cm^{-1}. The nmr spectrum, in deuterioacetone, displayed a quartet at δ 8.10 (4 H, *p*-nitrophenyl protons), a singlet at 6.70 (1 H, vinyl proton), a singlet at 3.80 (3 H, carbomethoxy protons), and a singlet at 3.25 (9 H, methyl ortho ester protons). In addition, a very broad, ill-defined absorption centered at 9.66 integrating for one proton was also present (hydrogen bonded NH). *Anal.* Calcd for $C_{15}H_{18}N_2O_8$: C, 50.84; H, 5.08; N, 7.91; mol wt, 354. Found: C, 50.95; H, 5.10; N, 7.87; mol wt, 343.

F. *p*-Nitrophenyl Isocyanide. Imino Ester Formation (8).—If the above reaction mixture was let stand for only 1 week and the same work-up procedure was used, a small amount (*ca.* 1–2%) of the imino ester **8** could be isolated, mp 94–97°. The ir displayed significant peaks at 2950, 1700, 1670, and 1250 cm^{-1}. The nmr spectrum ($\delta_{CCl_4}^{TMS}$) displayed two doublets (4 H) for the *p*-nitrophenyl protons at 8.10 and 6.84, a singlet (1 H) at 6.75 for the vinyl proton, and three singlets, each representing three protons, at 3.91, 3.80, and 3.75 for the three methoxy groups. *Anal.* Calcd for $C_{14}H_{14}N_2O_7$: C, 52.20; H, 4.35; N, 8.70. Found: C, 52.19; H, 4.47; N, 8.70.

Reaction of Isocyanides with Phenylpropiolic Acid.—Phenylpropiolic acid (1 g) was dissolved in 35 ml of dry benzene and an equimolar amount of an isocyanide (cyclohexyl, *tert*-butyl, benzyl, or *p*-methoxyphenyl) was added. The solution was allowed to stand overnight. (If the benzene was moist, a small amount of the amine salt of phenylpropiolic acid would form owing to hydrolysis of the isocyanide.) Removal of the benzene using a rotary evaporator gave 0.4–0.6 g of pale yellow crystals, mp 255–257°. The ir spectrum displayed two strong peaks at 1820 and 1760 cm^{-1}, the former being weaker than the latter (a cyclic anhydride). A mixture melting point with an authentic sample[21] of 1-phenyl-2,3-naphthoic anhydride gave no depression. The ir spectrum of the product was identical with that of an authentic sample of 1-phenyl-2,3-naphthoic anhydride obtained by refluxing phenylpropiolic acid with acetic anhydride.

Registry No.—**6** (R = cyclohexyl), 38355-41-8; **7** (R = cyclohexyl), 31849-65-7; **8** (R = cyclohexyl), 38308-75-7; **8** (R = phenyl), 38308-76-8; **8** (R = *o*-tolyl), 38308-77-9; **8** (R = *p*-$NO_2C_6H_4$), 38308-78-0; **9** (R = cyclohexyl), 38308-79-1; **9** (R = *t*-Bu), 38308-80-4; **13** (R = *p*-$NO_2C_6H_4$), 38308-81-5; methyl propiolate, 922-67-8; cyclohexyl isocyanide, 931-53-3; dimethyl acetylenedicarboxylate, 762-42-5; *tert*-butyl isocyanide, 7188-38-7; *o*-tolyl isocyanide, 10468-64-1; phenylpropiolic acid, 637-44-5; 1-phenyl-2,3-naphthoic anhydride, 1985-37-1.

(21) F. G. Badder, *J. Chem. Soc.* 1267 (1948).

Methyl- and Ethylnitrosocyanamide. Some Properties and Reactions[1]

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Methylnitrosocyanamide (**3**) and ethylnitrosocyanamide (**4**) were synthesized by aqueous nitrosation of the cyanamides. The ir spectra showed C≡N and N=O bands. The uv spectra indicated resonance structures similar to those of nitrosoureas and nitrosamines. The pmr of **3** and **4** (like those of dialkylnitrosamines) showed N-alkyl nonequivalence attributed to restricted rotation about the N-NO bond. In contrast, the pmr of alkylnitrosoureas showed NH_2 nonequivalence. The mass spectra of **3** and **4** had prominent peaks due to NO^+ and loss of N_2. Compound **4** was more stable to alkali and less stable to acid than ethylnitrosourea. In acid, **3** and **4** gave HNO_2 and the corresponding nitrosoureas (30–61%), perhaps because they are denitrosated to alkylcyanamides, hydrolyzed to alkylureas, and renitrosated. In alkali, **4** gave diazoethane (25%) and cyanate (79%). Nitrosation of methylguanidine proceeded slowly to give **3** (2%), methylnitrosourea (up to 35%), and a third unidentified uv-absorbing product.

Most *N*-nitroso compounds are powerful carcinogens in experimental animals and hence could be involved in the etiology of certain types of human cancer, if they were present in food or were synthesized by acid-catalyzed nitrosation in the stomach.[2] In support of the latter possibility, kinetic studies[3] showed that the acid-catalyzed N-nitrosation of some secondary amines, *N*-alkylureas, and *N*-alkylcarbamates proceeds very readily.

We reported[3d] that nitrosation of methylguanidine (**1**) gave methylnitrosourea (**2**), the new compound methylnitrosocyanamide (**3**), and an unidentified

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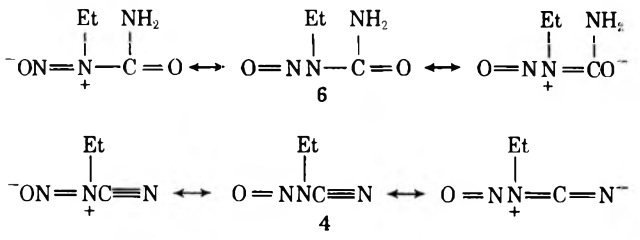
(2) (a) H. Druckrey, R. Preussmann, S. Ivankovic, and D. Schmähl, *Z. Krebsforsch.*, **69**, 103 (1967); (b) P. N. Magee and J. M. Barnes, *Advan. Cancer Res.*, **10**, 163 (1967); (c) J. Sander, *Arch. Hyg. Bakteriol.*, **151**, 22 (1967).

(3) (a) J. Sander, F. Schweinsberg, and H. P. Menz, *Z. Physiol. Chem.*, **349**, 1691 (1968); (b) J. Sander, G. Bürkle, L. Flohe, and B. Aeikens, *Arzneim.-Forsch.*, **21**, 411 (1971); (c) S. S. Mirvish, *J. Nat. Cancer Inst.*, **44**, 633 (1970); (d) S. S. Mirvish, *ibid.*, **46**, 1183 (1971); (e) S. S. Mirvish in "Analysis and Formation of Nitrosamines," International Agency for Research in Cancer, Lyon, France, in press.

third product, but the synthesis of **3** from **1** was given in summary only and its identification was not discussed. Since **1** occurs naturally in meat and fish, and nitrosation of arginine appears to yield analogous products, these reactions present a potential human hazard, though the reaction rates are very much slower than those for the nitrosation of alkylureas.[3d] In this paper we describe the synthesis of **3** and ethylnitrosocyanamide (**4**) from the cyanamides, some properties of **3** and **4**, and the synthesis of **3** from **1**.

Synthesis and Physical Properties of Methyl- and Ethylnitrosocyanamides (3 and 4).—Ethylcyanamide (**5**) was synthesized by treating ethylamine with cyanogen bromide. Nitrosation of **5** gave nitrosocyanamide **4** as shown by elemental analysis, molecular ion of the mass spectrum at *m/e* 99, and ir, uv, and pmr spectra. Strong ir bands at 2230 (C≡N) and 1540 cm^{-1} (N=O) were indicative of the structure. The three weak uv maxima of **4** at 377–406 nm were similar to those shown by ethylnitrosourea (**6**), but were shifted 6 nm hypsochromically. The uv absorption of nitrosourea **6** and nitrosocyanamide **4** is attributed to the resonance structures shown in Scheme I, similar

SCHEME I



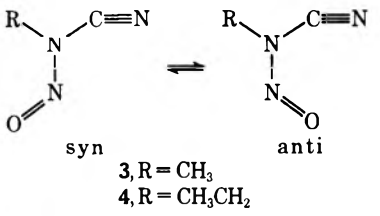
to the explanation of the uv absorption of nitrosamines.[4]

Crude methylcyanamide (**7**) was synthesized from methylamine and cyanogen bromide, and then nitrosated to give **3**. Nitrosocyanamide **3** could not be prepared analytically pure, but was identified by the uv, ir, and pmr spectra, the molecular ion of the high-resolution mass spectrum, and analogy with **4**.

The pmr of nitrosocyanamide **4** at 37° in methylene chloride gave a broad singlet at δ 4.17 attributed to the methylene protons and a poorly resolved triplet centered at 1.41 attributed to the methyl group. At and below 0°, the singlet was split into two quartets centered at δ 4.66 and 3.77 and the triplet was split into two triplets centered at 1.58 and 1.28 (ratio 1:0.84, respectively). At 60°, the pmr showed a single quartet at δ 4.14 and a triplet at 1.42. We attribute this temperature dependence to mobile syn and anti isomers (Scheme II), by analogy with nitrosamines.[5]

The pmr of nitrosocyanamide **3** in methylene chloride showed similar effects. The methyl resonance appeared as a singlet (δ 3.51) at 60°, a broad singlet at 37°, and two singlets at −40° (δ 4.18 and 3.23, ratio 1:2.85, *cf.* 1:0.84 in **4**). In both **3** and **4** we attribute the upfield resonance to the syn isomer (alkyl syn to nitroso), in agreement with the assignments in nitrosamines.[5a] Hence, changing the alkyl group from

SCHEME II

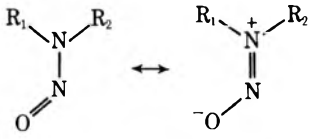


3, R = CH_3
4, R = CH_3CH_2

methyl to ethyl decreases the relative population of syn isomer. This is attributed to steric hindrance by the ethyl group, as in nitrosamines.[5a]

The two conformers of nitrosamines are apparent in the pmr at 36°. Their presence is attributed to restricted rotation about the N–N bond (Scheme III,

SCHEME III

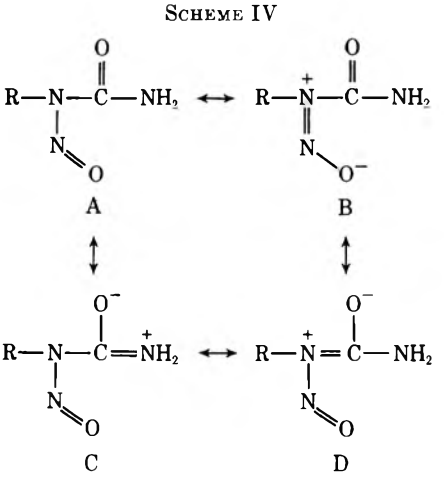


R_1 and R_2 = alkyl).[5a] The inductive effect of the N-alkyl groups would tend to stabilize the dipolar resonance form In nitrosocyanamides **3** and **4** (Scheme III, R_1 = alkyl, R_2 = CN) the electron-withdrawing cyano group would tend to destabilize the dipolar resonance form and hence lower the coalescence temperature.

In contrast, the pmr of nitrosourea **2** in acetone-d_6 showed a sharp methyl peak and that of nitrosourea **6** in acetone-d_6 showed a sharp methylene peak, both of which remained unchanged from 60 to −40°. However, at −40° the protons bound to nitrogen were split into two singlets in both **2** (δ 7.52 and 8.02) and **6** (7.50 and 7.98). This is probably not a solvent effect, since the pmr of **4** showed a similar temperature dependence in acetone-d_6 as in methylene chloride.

In nitrosoureas **2** and **6**, which can be represented by four resonance forms (Scheme IV), the absence of

SCHEME IV



N-alkyl nonequivalence is attributed to the destabilizing of resonance form B (Scheme IV) by the electron-withdrawing amide group, which would lower the barrier to rotation about the N–N bond. The presence of N–H nonequivalence is attributed to restricted

(4) J. T. D'Agostino and H. H. Jaffe, *J. Amer. Chem. Soc.*, **92**, 5160 (1970).

(5) (a) G. J. Karabatsos and R. A. Taller, *ibid.*, **86**, 4373 (1964); (b) W. Lijinsky, L. Keefer, and J. Loo, *Tetrahedron*, **26**, 5137 (1970); (c) J. T. D'Agostino and H. H. Jaffe, *J. Org. Chem.*, **36**, 992 (1971).

rotation about the C–NH_2 bond, owing to the contribution of form C.

The accurate mass measurements for the mass spectral fragmentations of **3** and **4** are given in Table I. Both compounds gave a large *m/e* 30 (NO^+) peak.

TABLE I
ACCURATE MASS MEASUREMENTS

Nominal mass	Determined mass	Ion assignment	Calculated mass
	Methylnitrosocyanamide (**3**, $C_2H_3N_3O$)		
85	85.0277	$C_2H_3N_3O$	85.0276
57	57.0211	C_2H_3NO	57.0214
55	55.0288	$C_2H_3N_2$	55.0296
43	43.0061[a]	CHNO	43.0058
43	43.0182[a]	C_2H_3O	43.0183
41	43.0263	C_2H_3N	41.0265
30	29.9978	NO	29.9980
29	29.0026[b]	CHO	29.0027
29	29.0264[b]	CH_3N	29.0265
	Ethylnitrosocyanamide (**4**, $C_2H_5N_3O$)		
71	71.0361	C_3H_5NO	71.0361
70	69.9998	CN_3O	70.0041
68	68.0360	$C_3H_4N_2$	68.0352
56	56.0134	C_2H_2NO	56.0136
55	55.0290	$C_2H_3N_2$	55.0296
53	53.0133	C_2HN_2	53.0140
41	41.0140	CHN_2	41.0139
40	40.0187	C_2H_2N	40.0177

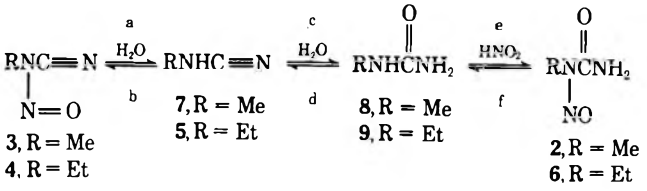
[a] $CHNO/C_2H_3O$ is 1/9. [b] CHO/CH_3N is 1/6.

This fragmentation is common in nitrosamines but is generally of lower intensity.[6] An M − NO peak was observed in **3** but not **4**. A common fragmentation of dialkylnitrosamines is cleavage of one alkyl radical.[6a,f] Loss of an ethyl radical (*m/e* 70) was observed in **4**, but there was no analogous fragmentation in **3**. Interestingly, the mass spectra of **3** and **4** showed prominent peaks resulting from loss of N_2 (*m/e* 57 and 71, respectively). This has been reported in the thermolysis[7] but not the mass spectra of nitrosamines. Most other fragments from **3** and **4** cannot readily be explained by simple cleavages or rearrangements. Loss of 17 (OH)[6] or 31 (NHO),[6f] which are other characteristic fragmentations of nitrosamines, does not occur.

Chemical Properties of Methyl- and Ethylnitrosocyanamides (3 and 4).—Compounds **3** and **4** were unstable, but less so than parent cyanamides **5** and **7**, and were readily extracted by methylene chloride from aqueous solution. Alkaline solutions of **3** and **4** decomposed with a few seconds, as shown by the loss of uv absorption at 370–410 nm. Acidic solutions of **3** and **4** partly decomposed within 10 min at 0° to give HNO_2. The half-lives at 25° of nitrosourea **6** and nitrosocyanamide **4** in various buffers are compared in Table II. Base-induced decomposition of **6** began to occur rapidly at pH 8 (in agreement with previous studies[8]), but **4** remained fairly stable up to pH 10. Acid-induced decomposition of **6** began to proceed rapidly only in 1.0 *N* HCl, but that of **4** occurred rapidly at pH 2.

When **3** was left overnight in cold 3 *N* sulfuric acid, nitrosourea **2** was obtained in 61% yield. Similar treatment of **4** gave nitrosourea **6** in 30% yield. These reactions could occur by direct hydration of the nitrosocyanamides. However, the instability of nitrosocyanamides (Table II) and the formation of HNO_2 in acid suggest that **3** and **4** first lose HNO_2 to give alkylcyanamidees **7** and **5**, which are hydrolyzed to methylurea (**8**) and ethylurea (**9**),[9] and then renitrosated by the HNO_2 liberated in reaction a (Scheme V).

SCHEME V



All these reactions should be reversible; *e.g.*, reactions b and e are those used to synthesize the nitroso derivatives and reaction c is reversible.[9]

This acid-induced decomposition of **3** and **4** to give HNO_2 and (presumably) cyanamides **5** and **7** (reaction a) resembles the acidic decomposition of nitrosoureas (reaction f), which can give quantitative yields of nitrite.[10] In explanation of the greater sensitivity to acid of **4** compared with nitrosourea **6**, the alkyl-substituted nitrogen of **4** should be more basic than that of **6** (*cf.* cyanamide, pK_a 10.3, and urea, pK_a 0.1[11]). This would make **4** more susceptible to protonation of this nitrogen, which presumably initiates the hydrolysis.

Under the highly acidic conditions used, decomposition of **4** (reaction a) would be favored over its formation (reaction b). In contrast, the reverse reaction occurred in our synthesis of **4**, where excess nitrite was used and the pH was 2. The question arises as to why Scheme V proceeds from right to left, *i.e.*, why nitrosation of ureas **8** and **9** is favored over that of cyanamides **5** and **7**. This is not due to a more rapid formation of the nitrosoureas, since cyanamides are nitrosated at least as fast as ureas, as shown in preliminary studies indicating that the kinetic equation for the nitrosation of **4** is similar to that for nitrosation of ureas **8** and **9**.[3d] Instead, the direction of Scheme V is attributed to the more rapid denitrosation of nitrosocyanamides (reaction a) in strong acid as compared with the denitrosation of nitrosoureas (reaction f) (*cf.* Table II). The higher yield of nitrosourea from methyl compound **3** as compared to ethyl compound **4** might be due to the 3.5-fold higher rate constant for the nitrosation of urea **8** compared with urea **9**.[3d]

Alkaline decomposition of **4** in a methanol–ether mixture gave diazoethane in 25% yield, as measured

(6) (a) J. Collin, *Bull. Soc. Roy. Sci. Liege*, **23**, 201 (1954); (b) S. S. Dubov and A. M. Khokhlova, *Zh. Obshch. Khim.*, **34**, 1961 (1964); (c) G. Schroll, R. G. Cooks, P. Klemmensen, and S. O. Lawesson, *Ark. Kemi*, **28**, 413 (1967); (d) S. Billets, H. H. Jaffe, and F. Kaplan, *J. Amer. Chem. Soc.*, **92**, 6964 (1970); (e) J. W. ApSimon and J. D. Cooney, *Can. J. Chem.*, **49**, 1367 (1971); (f) M. J. Saxby, *J. Ass. Offic. Anal. Chem.*, **55**, 9 (1972).

(7) W. Rickatson and T. S. Stevens, *J. Chem. Soc. D*, 3960 (1963).

(8) E. R. Garrett, S. Goto, and J. F. Stubbins, *J. Pharm. Sci.*, **54**, 119 (1965).

(9) (a) M. J. Sullivan and M. L. Kilpatrick, *J. Amer. Chem. Soc.*, **67**, 1815 (1945); (b) T. Mukaiyama, S. Ohishi, and H. Takamura, *Bull. Chem. Soc. Jap.*, **27**, 416 (1954).

(10) (a) A. Forist, *Anal. Chem.*, **36**, 1338 (1964); (b) R. Preussmann in "Analysis and Formation of Nitrosamines," International Agency for Research in Cancer, Lyon, France, in press.

(11) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965.

TABLE II

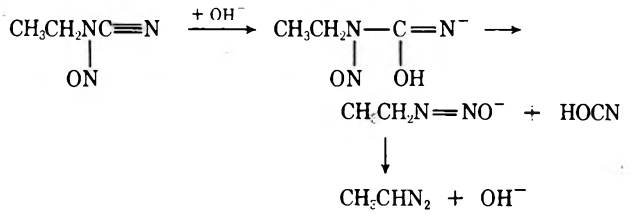
HALF-LIVES AT 25° OF ETHYLNITROSOUREA (6) AND ETHYLNITROSOCYANAMIDE (4), GIVEN IN HOURS

Buffer	1.0 *N* HCl	0.1 *N* HCl	pH 2	pH 3	pH 4	pH 5	pH 6	pH 7	pH 8	pH 9	pH 10	0.1 *N* NaOH
Compound 6	1.7	>50	>50	>50	>50	>50	22	2.6	0.45	0.022	0.008	0.002
Compound 4	<0.002	0.07	0.28	1.6	7.8	20	46	37	25	12	1.2	0.004

by distillation of the diazoethane into a benzoic acid solution and estimation of ethyl benzoate. Alkaline decomposition of **4** in aqueous solution gave a 79% yield of cyanate. Under similar conditions, nitrosourea **6** gave a 45% yield of diazoethane and a 66% yield of cyanate (*cf.* ref 12).

To explain the greater stability toward base of nitrosocyanamides as compared with nitrosoureas, we note that the first step in the base-induced decomposition of nitrosoureas may be abstraction of H^+ from the amide NH_2.[12] In the base-induced decomposition of nitrosocyanamides, such a step is impossible and a less facile mechanism must be operating. One possibility is attack of OH^- on the carbon atom of the cyanide group, analogous to mechanisms proposed for the acid-catalyzed hydrolysis of cyanamides[9] and (perhaps wrongly[12]) for the alkaline decomposition of nitrosoureas[8] (Scheme VI).

SCHEME VI

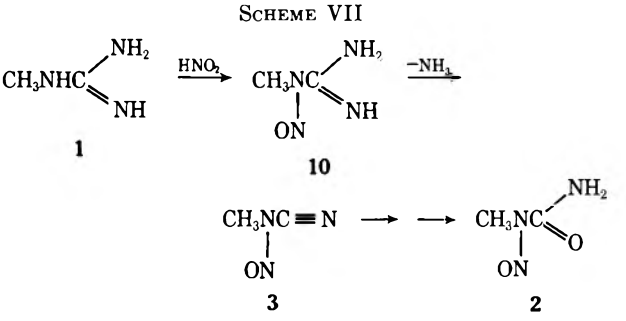


Formation of Methylnitrosocyanamide (3) from Methylguanidine (1).—When 0.05 *M* guanidine **1** was treated with 0.2 *M* nitrite at pH 1 and 25°, methylene chloride extracts of the reaction mixture contained both nitrosocyanamide **3** and nitrosourea **2**. Under these conditions, the yield of **3** rose to 2% of **1** at 3 hr and then declined, and the yield of **2** continued rising to 7% of **1** at 10 hr.[3d] Under highly acidic conditions, the yield of **2** was 35% and **3** was not detected.[3d] The identity of **3** prepared from **1** with **3** prepared from cyanamide **7** was demonstrated by the similar uv, ir, and pmr spectra and similar reaction in acid to give HNO_2 and nitrosourea **2**.

The aqueous solution after nitrosation of guanidine **1** contained a third product which was not extractable by methylene chloride and showed uv max (acetone) 382, 397, and 415 nm. The uv spectrum changed reversibly on adding triethylamine to an acetone solution, or in aqueous solutions above pH 8, to give a substance with uv max (acetone) 370 (inflection), 381, and 397 nm. The product, which has not been purified, was unstable in strong acid (when it yielded HNO_2) and alkali. It could be the unknown *N*-methyl-*N*-nitrosoguanidine (**10**).

We speculate (Scheme VII) that acid-catalyzed nitrosation of **1** first gives nitrosoguanidine **10**. Then **10** could lose ammonia to give **3**, which would be slowly converted to **2** as in Scheme V. Related reactions have been reported for nitrosoguanidine,[13,14] *N*-alkyl-*N'*-nitrosoguanidines,[14] *N*-alkyl-*N'*-nitroguanidines,[15] and *N*-alkyl-*N*-nitroso-*N'*-nitroguanidines.[16] Nitrosation of creatine and creatinine gave nitrososarcosine and a C-nitroso derivative, respectively.[17]

SCHEME VII



In Vivo **Effects.**—Nitrosocyanamide **4** was highly toxic to rats, with an acute LD_{50} of 15 mg/kg body weight when injected intraperitoneally in tricaprolein solution.[18] We are now testing the effect of long-term feeding of **4** to rats.

Experimental Section

N-Nitroso compounds were kept at or below 0° where possible, never heated above 25°, and treated with care because of their actual or potential carcinogenic activity.[2] Solutions in methylene chloride were dried over sodium sulfate and evaporated at 25 mm. Infrared (ir) spectra were determined on a Beckman IR-18 spectrophotometer. Proton magnetic resonance (pmr) spectra were determined on a Varian HA-100 spectrometer equipped with a Model V-4343 variable temperature accessory. Mass spectra were determined on an AEI Model MS-9 mass spectrometer. Exact mass measurements were determined at a resolving power of 14,000. Melting points are corrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Ethylcyanamide (5) (Modified from Literature[9b]).—A solution of 40 g (445 mmol) of ethylamine in 150 ml of CH_2Cl_2 was cooled to −10 to −20° in a flask fitted with a separating funnel and drying tube. A solution of 30.4 g (286 mmol) of cyanogen bromide in 180 ml of CH_2Cl_2 was added over 1 hr, and the mixture was stirred at −10 to −20° for another hour and filtered. To retard polymerization, the filtrate was just acidified (as shown by adding drops to wet indicator paper) with 97% formic acid, when two phases formed. The bottom phase was evaporated to give 16.15 g (81%) of crude **5** as a colorless, viscous oil. The product was stored overnight under N_2 at −15° and then nitrosated.

A small sample of **5** was distilled at 54–56° (0.3 mm) [lit.[9b] bp 94–95° (4 mm)]. The distillate was less stable than the crude product and solidified after 2–3 days at −15°. Freshly distilled **5** showed little uv absorption; ir (CCl_4) 3220 (NH), 2980 (CH), and 2230 cm^{-1} (C≡N) [undistilled material also showed ir peaks at 1720 (C=N of ? dimer) and 1610 cm^{-1} (NH of ? dimer)];

(12) (a) W. M. Jones, D. L. Muck, and T. K. Tandy, *J. Amer. Chem. Soc.*, **88**, 68 (1966); (b) W. Kirmse and G. Wächterhäuser, *Justus Liebigs Ann. Chem.*, **707**, 44 (1967).

(13) W. D. Bancroft and B. C. Belden, *J. Phys. Chem.*, **35**, 2684 (1931).

(14) T. L. Davis and E. N. Rosenquist, *J. Amer. Chem. Soc.*, **59**, 2112 (1937).

(15) T. L. Davis and R. C. Elderfield, *ibid.*, **55**, 731 (1933).

(16) (a) A. F. McKay, W. L. Orr, G. W. Taylor, M. N. Buchanan, and J. F. Crooker, *Can. J. Chem.*, **28B**, 683 (1950); (b) S. R. Harris, *J. Amer. Chem. Soc.*, **80**, 2302 (1958); (c) P. D. Lawley, and C. J. Thatcher, *Biochem. J.*, **116**, 693 (1970).

(17) M. C. Archer, S. D. Clark, J. E. Thilly, and S. R. Tannenbaum, *Science*, **174**, 1341 (1971).

(18) H. Garcia, private communication.

pmr at 0° ($CDCl_3$) δ 1.17 (t, 3, J = 7 Hz, CH_3), 3.03 (q, 2, J = 7 Hz, CH_2), 5.4–5.9 (broad, 1, NH); mass spectrum (70 eV, gallium inlet system) m/e (rel intensity) 70 (42), 55 (100), 53 (20), 43 (26), 42 (36), 41 (25), 40 (18), 30 (26), 29 (57), 28 (69), 27 (74), 26 (24).

Ethylnitrosocyanamide (4).—Crude cyanamide **5** (16.1 g, 231 mmol) was dissolved in 500 ml of $HClO_4$–0.05 M sodium citrate buffer at pH 2. To this was added a freshly prepared solution of 34.5 g (500 mmol) of $NaNO_2$ in 250 ml of water acidified to pH 2 with $HClO_4$. After 1 hr at 25° without stirring, another similar solution of HNO_2 was added. After another hour the mixture was extracted with 4 × 150 ml of CH_2Cl_2. The extract was dried and evaporated to give 11.3 g of greenish-brown oil. This was distilled at 22° (0.4 mm) and the distillate was collected in a tube cooled with Dry Ice–ethanol. The first fraction (2.4 g) contained solvent, but the second fraction, 7.6 g of brownish-yellow lachrymatory oil, was pure **4** (33%). This was always handled in a hood, and was stable when stored at −15° under N_2: d^{25}_4 1.0444; uv max (CH_2Cl_2) 256 nm (ε 3410), 362 (inflection, 72), 377 (116), 390 (156), and 406 (135); uv max (water) 257 nm (ε 3640), 376 (104), 388 (126), and 402 (100); ir (CCl_4) 2980 and 2940 (CH), 2230 (C≡N), 1540 (N=O), and 925 cm^{-1} (NNO); pmr ($CDCl_3$) δ 1.41 (m, 3, CH_3) and 4.17 (very broad, 2, CH_2); mass spectrum (70 eV, direct inlet system) m/e (rel intensity) 99 (6), 70 (47), 68 (31), 67 (19), 56 (10), 55 (82), 53 (52), 43 (30), 42 (34), 41 (34), 40 (24), 30 (100), 29 (53), 28 (100), 27 (78), 26 (25).

Anal. Calcd for $C_3H_5N_3O$: C, 36.4; H, 5.1; N, 42.4. Found: C, 36.5; H, 5.2; N, 42.1.

Ethylnitrosourea (6).[3d]—This showed uv max (CH_2Cl_2) 237 nm (ε 7100), 382 (79), 396 (121), and 414 (111) (*cf.* ref 3d); pmr ($CDCl_3$) δ 1.00 (t, 3, J = 7.5 Hz, CH_3) and 3.83 (q, 2, J = 7.5 Hz, CH_2).

Methylnitrosocyanamide (3) from Methylcyanamide (7).—Methylamine and cyanogen bromide were allowed to react as for the synthesis of **5**, to give **7** as an impure oil:[9b] ir (CH_2Cl_2) 3400 (NH), 3000 (CH), 2250 and 2230 (C≡N of monomer and ? dimer), 1740 (C=N of ? dimer), and 1670 cm^{-1} (NH of ? dimer). Compound **7** could not be distilled owing to its ready polymerization[9b] and was nitrosated directly by the method used to synthesize **4**. The resulting solution of **3** in CH_2Cl_2 was distilled at 20° (0.4 mm) to give a volatile, lachrymatory oil, which was redistilled. The middle fraction of the final distillate was nearly pure **3**: uv max (CH_2Cl_2) 253 nm (ε 3240), 373 (121), 385 (164), 401 (145); ir (CCl_4) 3080 and 2960 (CH), 2250 (C≡N), 1540 (N=O), and 910 cm^{-1} (NNO); pmr ($CDCl_3$) δ 3.39 (s, CH_3); mass spectrum (70 eV, direct inlet system) m/e (rel intensity) 85 (100), 57 (20), 56 (8), 55 (6), 47 (7), 43 (9), 41 (8), 30 (60), 29 (12). The accurate mass of the molecular ion, obtained by introducing the sample through an unheated gas manifold, was 85.0277 (calcd for $C_2H_3N_3O$, 85.0276); by this method of introduction CH_2Cl_2 (m/e 88, 86, and 84) was also detected. The elemental analysis of a sample subjected to 1-mm vacuum to remove CH_2Cl_2 was within 0.2% of the theoretical value for C and H, but was 1% low for N. The CH_2Cl_2–pH 5 buffer partition coefficient was 17:1 at 25°, as determined at 385 nm (ε in pH 5 buffer 135).

Methylnitrosourea (3).[3d]—This showed pmr ($CDCl_3$) δ 3.14 (s, CH_3).

Acidic Decomposition of Methyl- and Ethylnitrosocyanamide (3 and 4).—A solution of 135 mg of **3** in 80 ml of ice-cold 3 N H_2SO_4 was left for 10 min at 0° and then extracted with CH_2Cl_2. The extract had uv maxima at 358, 372, and 386 nm indicative of HNO_2.[3d] Similar acidic solutions of 199 mg of **3** were left overnight at 4° and then extracted with 6 × 50 ml of CH_2Cl_2. Evaporation of the extract gave 147 mg of impure **2** (61%, mp 111–113°), which was recrystallized twice from CH_2Cl_2–hexane (1:1)[3d] to give crystals, mp 125°, not depressed on admixture with pure **2** (lit.[3d] mp 126°), uv (CH_2Cl_2), and pmr ($CDCl_3$) spectra as for pure **2**. Compound **4** (192 mg) was treated similarly to give 67 mg (30%) of **6**, mp 99°, not depressed on admixture with pure **6** (mp 99–100°[3d]), uv (CH_2Cl_2) and pmr ($CDCl_3$) as for pure **6**.

Alkaline Decomposition of Ethylnitrosocyanamide (4) (Based on Literature[19]).—A mixture of 209 mg (2.11 mmol) of **4** in 10 ml of ether and 10 ml of 10% KOH in methanol was stirred at 0° in a hood until A at 390 nm reached a minimum of *ca.* 0.300 (*ca.* 1 hr). The ether was then distilled into 15 ml of ice-cold ether containing benzoic acid (1.0 mmol) to give 31 ml of solution A. In 5 ml of solution A, unreacted benzoic acid was back-titrated with 0.1 N NaOH after adding 5 ml of water, 2.5 ml of ethanol, and phenolphthalein. The results showed that 0.52 mmol of benzoic acid (25% from **4**) had reacted with the diazoethane formed from **4**. After the titration, the ether solution contained ethyl benzoate corresponding to 23% from **4**, as estimated by A at 272 nm.

The remainder of ether solution A was extracted with 6 × 25 ml of saturated Na_2CO_3 solution and 3 × 25 ml of water, and dried over Na_2SO_4 to give solution B. An aliquot of solution B was evaporated to dryness, dissolved in absolute ethanol, and subjected to glc on 15% Chromosorb W at 125°. A single peak was observed, with correct retention time for ethyl benzoate and peak height corresponding to 19% yield from **4**. Another aliquot of solution B showed (after evaporation) ir (CCl_4) identical with that of pure ethyl benzoate. A similar experiment with nitrosourea **6** gave a 45% yield of ethyl benzoate, as estimated by back-titration of unreacted benzoic acid.

To demonstrate the formation of cyanate, a solution of 100 mg of **4** in 20 ml of 0.04 N NaOH was left for 10 min at 25° (solution C.) This was analyzed for cyanate using the blue copper nitrate–pyridine complex,[20] which showed the correct absorption spectrum (max 680 nm). An aliquot of solution C was evaporated to dryness (0.1 mm, 25°). The residue showed ir (Nujol mull) 2220 (s), 1290 (w), and 1200 (w), as given by authentic NaCNO.[21] Cyanate was also estimated after similar decomposition of 100 mg of nitrosourea **6**.

Methylnitrosocyanamide (3) from Methylguanidine (1).—A solution of 3.65 g of methylguanidine sulfate [recrystallized from ethanol–H_2O (6:1), mp 243–244°, 30 mmol of **1**], 13.8 (200 mmol) of $NaNO_2$, and 8.8 g (50 mmol) of trisodium citrate·$2H_2O$ in 1 l. of water was acidified with $HClO_4$ to pH 1 (pH meter), allowed to react at 25° for 2 hr, and extracted with 5 × 200 ml of CH_2Cl_2. The dried extract was evaporated to give 1.2 g of crude **3**, which was distilled twice as before, to give 150 mg of distillate. The uv (CH_2Cl_2), ir (CCl_4), and pmr ($CDCl_3$) spectra were identical with those of **3** synthesized from **7**. The uv absorption disappeared rapidly in alkali. A once-distilled sample (202 mg, 2.48 mmol) of **3** synthesized from **1** was dissolved in 120 ml of ice-cold 3.0 N H_2SO_3 and its decomposition was examined as before. The products were HNO_2 (shown by the uv spectrum) and 148 mg of impure nitrosourea **2** (58%, 1.43 mmol), mp 108–110°. This was recrystallized from CH_2Cl_2–hexane (1:1) to give 48 mg of **2**, mp 118°, not depressed when mixed with pure **2** (lit.[3d] mp 126°), uv (CH_2Cl_2) and pmr ($CDCl_3$) the same as for pure **2**.

Registry No.—**1**, 471-29-4; **3**, 33808-17-6; **4**, 38434-77-4; **5**, 38434-78-5; **6**, 759-73-9; **7**, 4674-68-4.

(19) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1951, p 844.

(20) E. L. Martin and J. McClelland, *Anal. Chem.*, **23**, 1519 (1951).

(21) C. R. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, p 345.

Condensation–Cyclization Reactions of Electron-Deficient Aromatics. VI. Isomeric Bridgehead and Nitronate Substituted Bicyclic Nitropropene Nitronates[1]

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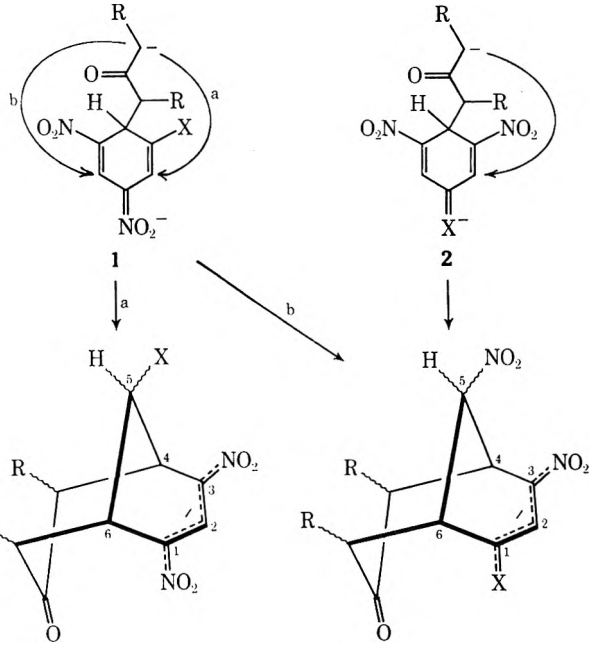
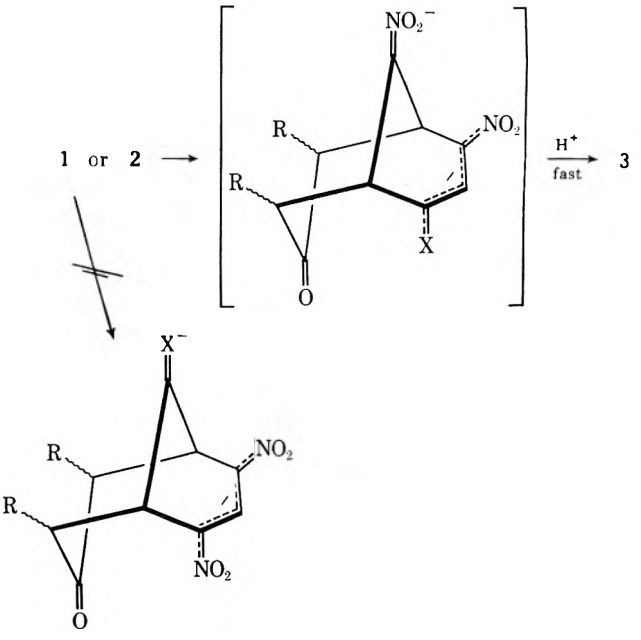
The reaction of 1-substituted 2,4,6-trinitrobenzenes with 1,3-dicarbomethoxyacetone has been shown to yield bridgehead-substituted and 2-substituted 3-nitropropene nitronates. The relationship of these isomeric products to the cyclohexadienate σ complexes formed from the reaction of simple nucleophiles with these aromatic precursors is discussed. Various mechanistic routes to products are considered, and the absence of isomers in certain cases is explained. Mechanistic aspects of the reactions of 1-substituted 3,5-dinitrobenzenes are also discussed.

Previous work on condensation–cyclization reactions of electron-deficient benzenes with ketones and keto esters has been concerned with systems in which three electron-withdrawing substituents on the aromatic ring are symmetrically disposed.[1] All those systems we have studied thus far have been 1-X-3,5-dinitrobenzenes where X = NO_2,[1] CN,[1] CO_2CH_3,[1] and COR.[2] Two possible products, **3** and **4**, could result from this type of aromatic, since the cyclization presumably could occur through either of the isomeric σ complexes **1** or **2**.[3] Only **3** was formed, however.[1,2] This result



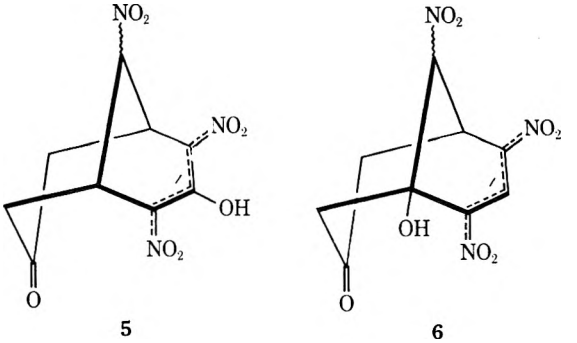
can be rationalized in two ways. The activated complex for the slow step in the cyclization process resembles that doubly charged conjugate base of the product produced by proton abstraction from C-5,[3] and the conjugate base of **3** should be much more stable than that of **4**. This stability could result in a lower energy path for cyclization leading to **3**, rather than **4** (X = CN, CO_2CH_3, or COR).

Alternately, it is possible that the only σ complex precursor to bicyclic product is **2**, which may be kinetically favored over **1**. Cyclization of **2** can only yield **3**. This latter possibility is supported by the recent



work of Crampton[4] and others,[5] which provides evidence for kinetically favored σ complexes formed by nucleophilic acetonate attack para to the X substituent (X = Cl[5] and CO_2CH_3[4]). It would require that cyclization be much more rapid than reversion of **2** to **1**, however.

We noted with interest the recent report of the bicyclic nitropropene nitronate **5**, prepared from picric acid and acetone,[6] which forms in preference to **6**.



With the objective of probing further the electronic structure of the nitropropene nitronate function,[7] and

(1) Previous papers: M. J. Strauss, T. C. Jensen, H. Schran, and K. O'Conner, *J. Org. Chem.*, **35**, 383 (1970); H. Schran and M. J. Strauss, *ibid.*, **36**, 856 (1971); M. J. Strauss and S. P. B. Taylor, *ibid.*, **36**, 3059 (1971); M. J. Strauss, S. P. B. Taylor, and H. Shindo, *ibid.*, **37**, 3658 (1972).

(2) M. J. Strauss and S. P. B. Taylor, unpublished work.

(3) M. J. Strauss and H. Schran, *Tetrahedron Lett.*, 2349 (1971).

(4) M. R. Crampton and H. A. Khan, *J. Chem. Soc., Perkin Trans. 2*, 733 (1972).

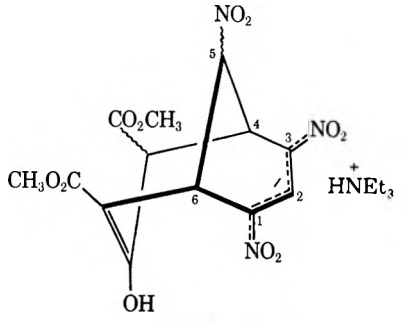
(5) M. Kimura, N. Obi, and M. Kawazoi, *Chem. Pharm. Bull.*, **20**, 452 (1972).

(6) T. Kabeya, K. Kohashi, Y. Ohkura, and T. Momose, *ibid.*, **19**, 645 (1971).

(7) M. J. Strauss and E. Weltin, *Tetrahedron Lett.*, 629 (1971).

in order to expand the scope of reactions of electron-deficient aromatics to yield both bridgehead- and nitronate-substituted bicyclics, we have investigated the reactions of 1-X-2,4,6-trinitro systems where X is inductively electron withdrawing and electron donating. It was anticipated that the inductive effect of X might influence the course of the reaction for preferential formation of bridgehead-substituted or nitronate-substituted products.

The bridging ketonic substrate used in the present study was 1,3-dicarbomethoxyacetone, which rapidly yields **7** when treated with 1,3,5-trinitrobenzene in the presence of triethylamine.[8] Three possible products, **8**, **9**, and **10**, might result from the reaction of 1-X-2,4,6-trinitrobenzenes with 1,3-dicarbomethoxyacetone. The reactions of 2,4,6-trinitrotoluene (TNT), methyl 2,4,6-trinitrobenzoate (MTNB), and *N*-(2-nitrophenyl)picramide (NPP) are now considered.



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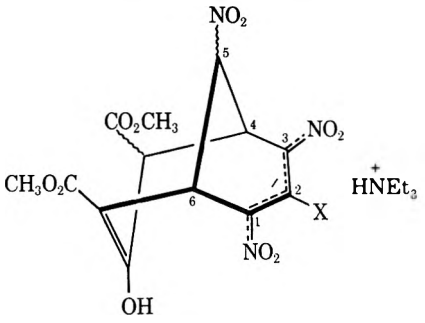
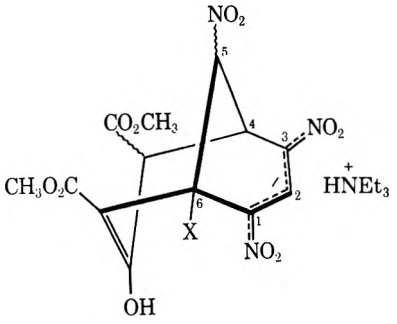
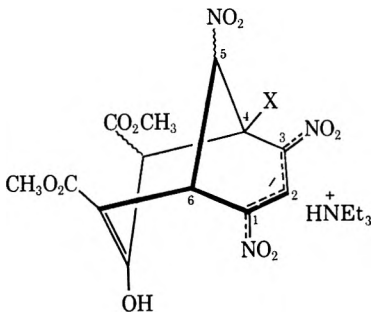


8a, X = CH_3
b, X = CO_2CH_3
c, X = $NHC_6H_4NO_2$

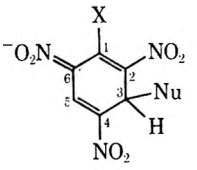


9a, X = CH_3
b, X = CO_2CH_3
c, X = $NHC_6H_4NO_2$

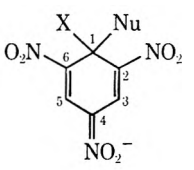


10a, X = CH_3
b, X = CO_2CH_3
c, X = $NHC_6H_4NO_2$

The reaction of TNT with nucleophiles has been the subject of extensive investigation by several research groups during the past 17 years.[9] It has become clear that a variety of different interactions can occur, including charge-transfer complexation, radical ion formation, proton abstraction, and σ complexation. With strongly basic nucleophiles such as hydroxide and alkoxide, the main processes occurring appear to be α-hydrogen abstraction and radical ion formation.[9a,b,d,g,h,k,l] With weaker bases such as cyanide, only σ complexation occurs to yield **11** (X = CH_3, Nu = CN).[9d,e] TNT σ complexes like **11** [Nu = C_2H_5O or 2,4,6-$(NO_2)_3C_6H_2CH_2$, X = CH_3] have been reported to form in small concentration in strongly basic solutions of TNT, however.[9k,l]



11



12

Interestingly, with 2,4,6-trinitrobenzaldehyde addition occurs at C-1 to yield **12** (X = CHO, Nu = CN).[9d,e] This change in mode of addition with change in substrate structure is of considerable interest, since cyclization of carbanionic σ complexes (*vide supra*) like **12** (Nu = RCH_2COCH_2) can only yield bridgehead-substituted products analogous to **9** (and **10**). On the other hand, structures like **11** could yield products analogous to **8** or **9** (and **10**). The preference for **11** or **12** also bears directly on the much discussed problem of isomeric addition in 2,4,6-trinitroanisole and related electron-deficient aromatics.[10]

Since addition to C-1 of TNT has not yet been observed, whereas C-3 addition of both cyanide and TNT anion has been reported,[9] it is quite probable that the reaction of TNT with 1,3-dicarbomethoxyacetone in the presence of triethylamine will yield the C-3 adduct **11** [X = CH_3, Nu = $CH(CO_2CH_3)COCH_2CO_2CH_3$]. The cyclization step must then involve intramolecular attack at C-1 to yield **9a** or **10a**, or at C-5 to yield **8a**.

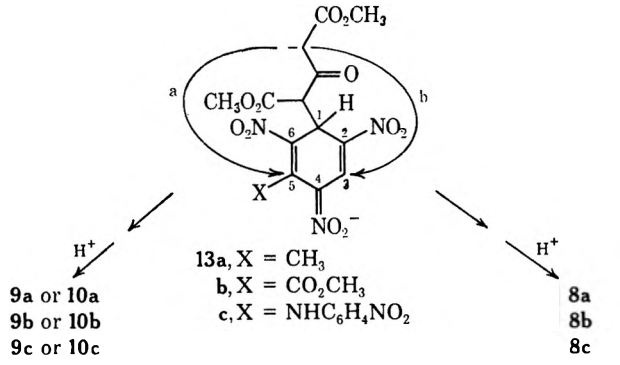
(8) M. J. Strauss and S. P. B. Taylor, *J. Org. Chem.*, **38**, 856 (1973).

(9) (a) E. F. Caldin and G. Long, *Proc. Roy. Soc., Ser. A*, **228**, 263 (1955); (b) J. A. Blake, M. J. B. Evans, and K. E. Russell, *Can. J. Chem.*, **44**, 119 (1966); (c) K. G. Shipp and L. A. Kaplan, *J. Org. Chem.*, **31**, 857 (1966); (d) E. Buncel, A. R. Norris, and W. Proudlock, *Can. J. Chem.*, **46**, 2759 (1968); (e) A. R. Norris, *ibid.*, **47**, 2895 (1969); (f) *ibid.*, **45**, 175 (1967); (g) R. E. Miller and W. F. K. Wynne Jones, *J. Chem. Soc.*, 2375 (1959); (h) K. Bowden and R. Stewart, *Tetrahedron*, **21**, 261 (1965); (i) S. S. Gitis and A. Ya. Kaminskii, *Zh. Org. Khim.*, **2**, 1811 (1966); (j) S. S. Gitis and T. Krosovskii, *J. Gen. Chem. USSR*, **29**, 2612 (1959); (k) E. Buncel, A. R. Norris, K. E. Russell, and R. Tucker, *J. Amer. Chem. Soc.*, **94**, 1646 (1972); (l) C. Bernasconi, *J. Org. Chem.*, **36**, 1671 (1971).

(10) (a) J. H. Fendler, E. J. Fendler, and C. E. Griffin, *J. Org. Chem.*, **34**, 689 (1969); (b) E. F. Fendler, J. H. Fendler, N. L. Arthur, and C. E. Griffin, *ibid.*, **37**, 812 (1972); (c) M. I. Foreman and R. Foster, *Can. J. Chem.*, **47**, 729 (1969); (d) F. Terrier and M. Simonnin, *Bull. Soc. Chim. Fr.*, **2**, 677 (1971); (e) F. Terrier, F. Millot, and P. Letellier, *ibid.*, **5**, 1743 (1970); (f) R. Schaal, F. Terrier, J. Halle, and A. Chatrousee, *Tetrahedron Lett.*, 1393 (1970); (g) F. Terrier, F. Millot, and M. Simonnin, *ibid.*, 2933 (1971); (h) C. Bernasconi, *J. Amer. Chem. Soc.*, **93**, 6975 (1971).

Addition of excess triethylamine to a saturated solution of TNT in 5 ml of 1,3-dicarbomethoxyacetone yields a dark red solution which turns dark orange on standing. Addition of anhydrous diethyl ether results in a brown-orange precipitate. After work-up and recrystallization from ethanol–ether solution, large orange crystals of product are obtained which analyze correctly for a 1:1:1 adduct of TNT, ketone, and amine. The pmr spectrum of this product (see Experimental Section) is similar to that reported previously for the analogous 1,3,5-trinitrobenzene adduct,[1] with one significant difference. The C-2 nitropropene nitronate proton which is expected to appear at $\sim\delta$ 8.5 is absent. This observation and the quartet observed for the C-5 proton are consistent only with structure **8a**. The methyl group appears at δ 2.46, 0.28 ppm upfield from that in the precursor TNT. The intermediacy of **12** [Nu = $CH(CO_2CH_3)COCH_2CO_2CH_3$, X = CH_3], at least on the reaction coordinate leading to product, is ruled out by the structure of **8a**.

Based on an analogy to tertiary and secondary carbanion stability, it might be supposed that **8a** would be less stable than **9a** or **10a**. This is not necessarily so, however, since most of the charge on **8**, **9**, or **10** resides on the oxygens of the nitro groups, and the carbon framework of the anion might in fact be slightly positive.[7,11] If this were the case, **8a** might be more stable than **9a** or **10a**. It is likely that the reaction pathway is not controlled by the thermodynamic stability of the possible products **8** or **9** and **10** in any case, but is kinetically controlled by the relative stability of the precursor intermediate **11** [X = CH_3, Nu = $CH(CO_2CH_3)COCH_2CO_2CH_3$] and the complexes for the alternate routes of cyclization of **11** through **13a**. The preference for cyclization of **13**



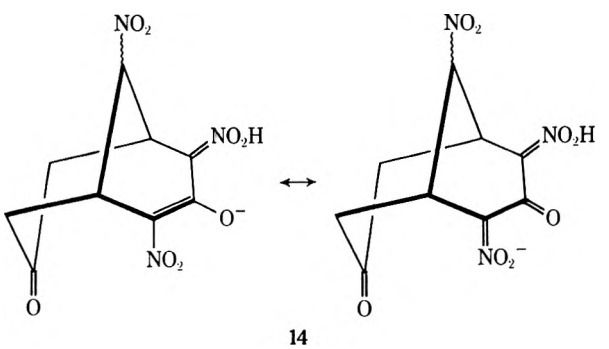
via path b remains, even when X is inductively electron withdrawing as in **13b**, although to a lesser extent (*vide infra*). The electronic effect of X does not cause a profound change in the course of the reaction. The preference for path b is thus likely to be steric in origin and probably results from noncoplanarity of the ring and nitro group ortho to both X and the side chain in **13**. Such noncoplanarity would favor attack by path b, where the nitro group developing additional charge is well conjugated with the site of anionic attack. Such an argument is in accord with that presented to explain why path b is favored over path a in the cyclization of **1** to **3**, rather than **4**. *It appears that the charge-stabilizing ability of the ring substituent developing charge in the cyclization step is most likely a major directive influence in intramolecular cyclizations of anionic σ complexes.*

The reaction of methyl 2,4,6-trinitrobenzoate (MTNB) with 1,3-dicarbomethoxyacetone in the presence of triethylamine gave two products, each analyzing correctly for a 1:1:1 adduct of amine, ketone, and MTNB. These were observed to crystallize separately from the reaction mixture during work-up (see Experimental Section). The product formed in larger quantity (*ca.* 80%) had a pmr spectrum characterizing **8b**; the nitronate proton resonance expected for **9b** or **10b** is absent. The other product isolated in smaller yield (*ca.* 20%) showed a singlet pmr absorption at δ 8.25, expected for a C-2 nitropropene nitronate proton,[1] and only *one* bridgehead proton, centered at δ 5.20 as a doublet ($J \cong 2.5$ cps). The latter proton is coupled to the C-5 bridging proton at δ 4.80, which also appears as a doublet ($J \cong 2.5$ cps). The proton α to CO_2CH_3 does *not* appear as a doublet, as in all the other 1,3-dicarbomethoxyacetone adducts studied, but as a singlet. This latter observation, as well as the above spectral results, provides substantial evidence for structure **10b**. The observation of this bridgehead-substituted product, even in minor amounts, would seem to support the idea that the greater electrophilic character of C-5 in **13b**, relative to **13a**, may moderate the preference for cyclization by path b in the former case.

It is interesting to note that, with *N*-(2-nitrophenyl)-picramide (NPP), the only product which could be detected and isolated was **8c**. This is not unexpected, since the *m*-nitrophenyl group is quite large, and should favor cyclization at C-3 in **13c**.

It is peculiar that the visible spectra of all the 2-substituted nitropropene nitronates prepared by us have visible maxima at about the same wavelength as unsubstituted compounds (from 446 to 499 nm in MeOH), whereas the only other previously reported 2-substituted structure, **5**, has a visible maximum at 398 nm.[6] This latter absorption is similar to that which we have previously found for nitropropene nitronic *acids*, and this suggests that the proposed structure for **5** may be incorrect. The pmr data reported by Momose, *et al.*, for **5** are completely consistent with **14**, a nitronic acid generated by hydroxylic proton

5 ⟶



14

transfer to an adjacent nitronate function of **5**, if proton transfer between nitronate and nitronic acid functions is rapid compared to the pmr time scale.

Experimental Section

All melting points are uncorrected. Ir and visible spectra were recorded with PE Models 21 and 402 spectrophotometers, re-

(11) H. Hosoya, S. Hosoya, and S. Nagakura, *Theor. Chim. Acta*, **12**, 117 (1968).

spectively. Pmr spectra were recorded on JEOL MH-100 and C-60 HL spectrometers, and chemical shifts are reported with respect to internal TMS. Elemental analyses were performed by G. I. Robertson Laboratory, Florham Park, N. J.

Preparation of 8a.—To a solution of 2.0 g (0.0093 mol) of TNT dissolved in a minimum amount of 1,3-dicarbomethoxyacetone at 25° was added about 3 ml of triethylamine. After standing at room temperature for 10 hr, the reaction mixture was washed with anhydrous ether to remove the unreacted ketone. After several 100-ml washings the oily residue finally solidified to an orange powder, which when recrystallized from a 1:4 ether–ethanol mixture yielded cubic crystals of **8a**: mp 116–117°; λ_{max} (MeOH) 446 nm; ir (KBr) 1730, 1662, 1610, 1555, 1490, 1450 cm^{-1}; pmr ($DCCl_3$) δ 1.36 [t, 9 H, $^+HN(CH_2CH_3)_3$], 2.46 (s, 3 H, CH_3), 3.18 [q, 6 H, $^+HN(CH_2CH_3)_3$], 3.75 and 3.85 (each a singlet, 3 H each, CO_2CH_3), 4.15 (d, 1 H, $CHCO_2CH_3$), 4.42 (q, 1 H, $CHNO_2$), 5.30 (d, 2 H, bridgehead protons), 11.08 [br, 2 H, $HN(CH_2CH_3)_3$ and OH]. A pmr spectrum of the crude product showed the absence of **9a**.

Anal. Calcd for $C_{20}H_{30}N_4O_{11}$: C, 47.81; H, 6.02; N, 11.15. Found: C, 48.04; H, 6.31; N, 11.09.

Preparation of 8b and 10b.—To a solution of 2.0 g (0.0074 mol) of methyl 2,4,6-trinitrobenzoate dissolved in a minimum amount of 1,3-dicarbomethoxyacetone at 50° was added 2 ml of tetrahydrofuran and 3 ml of triethylamine. After 4 hr at 25° the reaction mixture was washed with 75-ml portions of anhydrous ether. The resulting oil was dissolved in 35 ml of hot methanol and 90 ml of ether was added. After standing for 2 days at 25°, crystals were deposited on the bottom of the flask. Examination of these with a stereomicroscope showed two distinct crystalline forms. The crystals formed in larger quantity (*ca.* 80%) were a dull orange, while a smaller quantity of bright red-orange crystals were also formed (*ca.* 20%). These crystals were separated manually under the microscope, and each was recrystallized from ether–methanol solution. The product formed in the largest amount was **8b**, the remaining amount being **10b**. There was essentially no product left in the mother liquor.

8b had mp 142–143° and was hygroscopic; λ_{max} (MeOH) 499 nm; ir (KBr) 1742, 1725, 1665, 1610, 1555 cm^{-1}; pmr ($CDCl_3$) δ 1.35 [t, 9 H, $^+HN(CH_2CH_3)_3$], 3.15 [q, 6 H, $^+HN(CH_2CH_3)_3$], 3.80 (s, 3 H, CO_2CH_3), 3.85 (s, 6 H, two CO_2CH_3), 3.82 (d, 1 H, $CHCO_2CH_3$), 4.5 (q, 1 H, $CHNO_2$), 5.26 and 5.46 (two q, bridgehead protons), 12.1 [br, 2 H, $^+HN(CH_2CH_3)_3$ and OH].

Anal. Calcd for $C_{21}H_{30}N_4O_{13}$: C, 46.16; H, 5.53; N, 10.25. Found: C, 45.68; H, 5.76; N, 9.99.

10b had mp 142–143°; λ_{max} (MeOH) 497 nm; ir (KBr) 1755, 1740, 1650, 1610, 1555 cm^{-1}; pmr ($CDCl_3$) δ 1.35 [t, 9 H, $^+HN(CH_2CH_3)_3$], 3.15 [q, 6 H, $^+HN(CH_2CH_3)_3$], 3.70 (s, 3 H, CO_2CH_3), 3.85 (s, 6 H, two CO_2CH_3), 4.80 (s, 1 H, $CHCO_2CH_3$), 5.2 (d, 1 H, $CHNO_2$), 5.38 (br d, 1 H, bridgehead), 8.75 (s, 1 H, nitropropene nitronate), 12.1 [br, 2 H, $^+HN(CH_2CH_3)_3$ and OH].

Anal. Calcd for $C_{21}H_{30}N_4O_{13}$: C, 46.16; H, 5.53; N, 10.25. Found: C, 46.96; H, 6.19; N, 9.42

Preparation of 8c.—A solution of 2 g (0.008 mol) of *N*-(2-nitrophenyl)picramide and 3 ml of triethylamine in the minimum amount of 1,3-dicarbomethoxyacetone necessary for dissolution was allowed to stand at room temperature for 4 hr. After washing the resulting reaction mixture with two 125-ml portions of ether an oily residue was obtained, which when recrystallized from a methanol–ether solution yielded orange crystals of **8c**: mp 155°; λ_{max} (CH_3OH) 458 nm; ir (KBr) 1740, 1660, 1610, 1535 cm^{-1}; pmr ($CDCl_3$) δ 1.10 [t, 9 H, $^+HN(CH_2CH_3)_3$], 2.85 [q, 6 H, $^+HN(CH_2CH_3)_3$], 3.70 and 3.78 (two s, 3 H each, two CO_2CH_3), 4.1 (d, 1 H, $CHCO_2CH_3$), 4.3 (q, 1 H, $CHNO_2$), 5.15 and 5.50 (two q, 2 H, bridgehead), 7.2–7.8 (m, 4 H, *m*-$NO_2C_6H_4$), 12.4 [broad s, 2 H, $^+HN(CH_2CH_3)_3$ and OH].

Anal. Calcd for $C_{25}H_{32}N_6O_{13}$: C, 48.10; H, 5.18; N, 13.48. Found: C, 47.93; H, 5.31; N, 13.34.

Registry No.—**8a**, 38218-79-0; **8b**, 38355-40-7; **8c**, 38218-80-3; **10b**, 38413-80-8; TNT, 118-96-7; MTNB, 15012-38-1; NPP, 38229-29-7; 1,3-dicarbomethoxyacetone, 1830-54-2.

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Photochemical Transformations of Small Ring Heterocyclic Compounds. XLVIII. Further Studies on the Photocycloaddition and Photodimerization Reactions of Arylazirines[1]

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Further evidence for the mechanism of the photodimerization of arylazirines was obtained by irradiating a mixture of phenyl- and diphenylazirine. The formation of a mixture of *endo*- and *exo*-2,4,5-triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene is rationalized in terms of 1,3-dipolar addition of the nitrile ylide derived from diphenylazirine onto the C–N double bond of phenylazirine. Irradiation of methyl- and dimethylphenylazirine in an inert solvent gave 1,3-diazabicyclo[3.1.0]hex-3-enes as primary photoproducts. The initial photodimers undergo subsequent photoreaction. The products formed depend on the substituent groups, the time of irradiation, and the particular solvent employed. The photocycloaddition of arylazirines has been found to proceed with a wide variety of dipolarophiles and provides a synthetic route into systems otherwise difficult to prepare.

In earlier papers we have shown that arylazirines undergo photocycloaddition with electron-deficient olefins to give Δ^1-pyrroline derivatives.[1,5] The formation of the adducts was interpreted as proceeding by way of irreversible ring opening of the azirine ring to form a nitrile ylide intermediate, which was subsequently trapped by a suitable dipolarophile. Arylazirines are also known to undergo photodimerization to 1,3-diazabicyclo[3.1.0]hex-3-enes.[6,7] The formation of these dimers was rationalized in terms of 1,3-dipolar addition of the initially generated nitrile ylide onto a ground-state azirine molecule. This conclusion was reached by a study of the variation of the quantum

(1) Part XLVII: A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *J. Amer. Chem. Soc.*, **95**, 1954 (1973). Part XLVI: *ibid.*, **95**, 1945 (1973).

(2) Alfred P. Sloan Foundation Fellow, 1968–1972; National Institutes of Health Special Postdoctoral Fellow, 1972–1973.

(3) NDEA Title IV Fellow, 1969–1971.

(4) NSF Science Faculty Fellow, 1970–1971; Virginia Military Institute Faculty Fellow, 1971–1973.

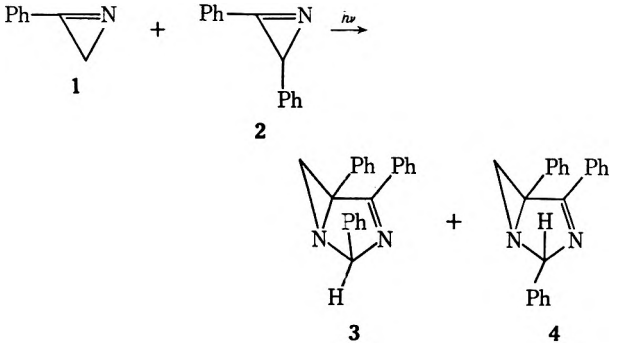
(5) A. Padwa and J. Smolanoff, *J. Amer. Chem. Soc.*, **93**, 548 (1971).

(6) A. Padwa, S. Clough, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *ibid.*, **94**, 1395 (1972).

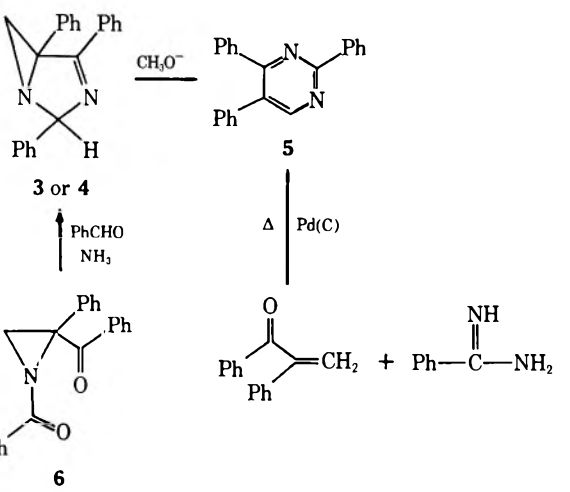
(7) N. Gakis, M. Marky, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55**, 748 (1972).

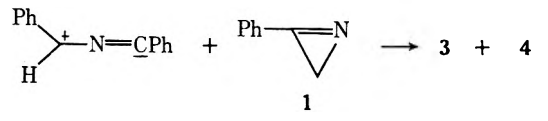
yield for cycloadduct formation as a function of the concentration of added dipolarophile.[6] According to this mechanistic scheme, it should be possible to generate a nitrile ylide from one arylazirine and intercept it with the C–N double bond of another azirine molecule. The present paper describes a reaction of this type which provides additional support for the mechanism of dimerization. To learn more about the effect of substituents in the azirine system, we also chose to study the photodimerization of methyl- and dimethylphenylazirine. An additional objective of this study was to examine the photobehavior of arylazirines with dipolarophiles other than electron-deficient olefins, and we herein report on such reactions. This process provides a synthetic route into systems otherwise difficult to prepare.

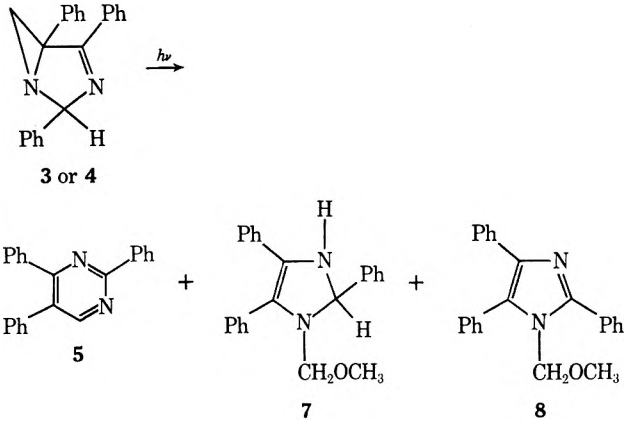
Coirradiation of Phenyl- and Diphenylazirine.—Further evidence for the mechanism of the photodimerization of arylazirines was derived by irradiating an equimolar mixture of 2-phenyl- and 2,3-diphenylazirine (1 and 2). At 3130 Å, the extinction coefficient for diphenylazirine is about 20 times that of phenylazirine, so that *ca.* 95% of the light is absorbed by diphenylazirine in the above experiment. Under these conditions a mixture of two 1:1 adducts was isolated. These were separated by liquid–liquid partition chromatography and identified as *endo*- and *exo*-2,4,5-triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene (**3** and **4**) on the basis of the evidence presented below.



The component of shortest retention time, **3** (20% of the 1:1 adducts), mp 176–177°, had the following nmr spectrum ($CDCl_3$, 100 MHz): aromatic protons at τ 2.70 (15 H, m) and singlets at 8.26 (1 H), 7.42 (1 H), and 3.32 (1 H). The second component (**4**, 20%), mp 85–87°, displayed an nmr spectrum (100 MHz) consisting of singlets at τ 7.98 (1 H), 6.92 (1 H), and 4.06 (1 H), and a multiplet centered at 2.75 (15 H). Upon treatment with sodium methoxide in methanol, **3** (and/or **4**) afforded 2,4,5-triphenylpyrimidine (**5**), mp 110–111°.[8] Compound **5** was prepared independently by the reaction of α-phenylacrylophenone with benzamidine followed by oxidation over palladium on charcoal. The above structural assignments were further confirmed by an independent synthesis of **3** and **4** from 1,2-dibenzoyl-2-phenylaziridine (**6**), benzaldehyde, and ammonia. The formation of **3** and **4** can be most economically rationalized in terms of 1,3-dipolar addition of the initially generated nitrile ylide onto phenylazirine. On further irradiation (in cyclohexane), **3** and **4** are converted to triphenylpyrimidine (**5**) in low yield. When the irradiation of **3** (or **4**) was carried out in methanol, two new compounds were formed in addition to **5** (5%). These structures have been assigned as *N*-methoxymethyl-2,4,5-triphenyl-2,3-dihydroimidazole (**7**) and *N*-methoxymethyl-2,4,5-triphenylimidazole (**8**). Treatment of **8** with aqueous acid afforded triphenylimidazole. The formation of **7** and **8** can be attributed to the addition of methanol to the azomethine ylide[9,10] formed on irradiation of **3** (or **4**).







Photodimerization Reactions of Methyl- and Dimethylphenylazirines.—As part of a study of the effect of substituents on the photoreactions of arylazirines, we have examined the photochemistry of 3-methyl-(**9**) and 3,3-dimethyl-2-phenylazirine (**10**). When 3-methyl-2-phenylazirine (**9**) was irradiated in cyclohexane, a 3:1 mixture of diazabicyclohexenes **11** and **12** was obtained in 45% yield. The structure of the dimers rests firmly on spectroscopic and chemical evidence. Thus, these substances were shown by their elemental analyses and mass spectra to be dimeric. The nmr spectrum of the major dimer **11** ($CDCl_3$) showed two

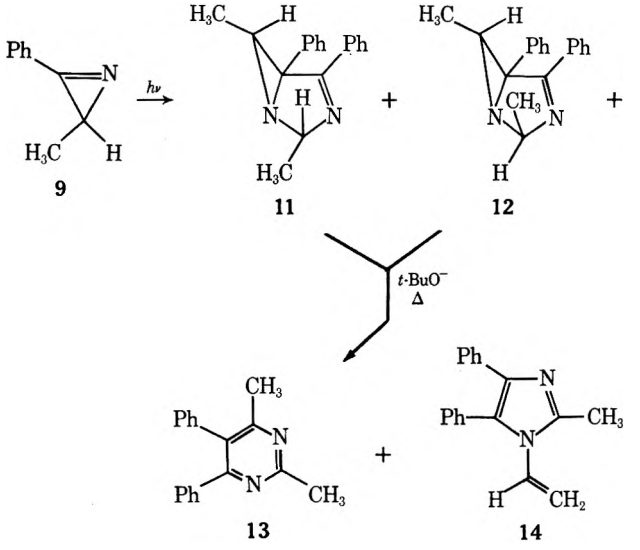
(8) H. Heine, R. Weese, R. Cooper, and A. Durbetaki, *J. Org. Chem.*, **32**, 2708 (1967). These authors were the first to report the base-catalyzed oxidative rearrangement of 1,3-diazabicyclo[3.1.0]hex-3-enes to substituted pyrimidines.

(9) A. Padwa and E. Glazer, *Chem. Commun.*, 838 (1971); A. Padwa and E. Glazer, *J. Amer. Chem. Soc.*, **94**, 7788 (1972).

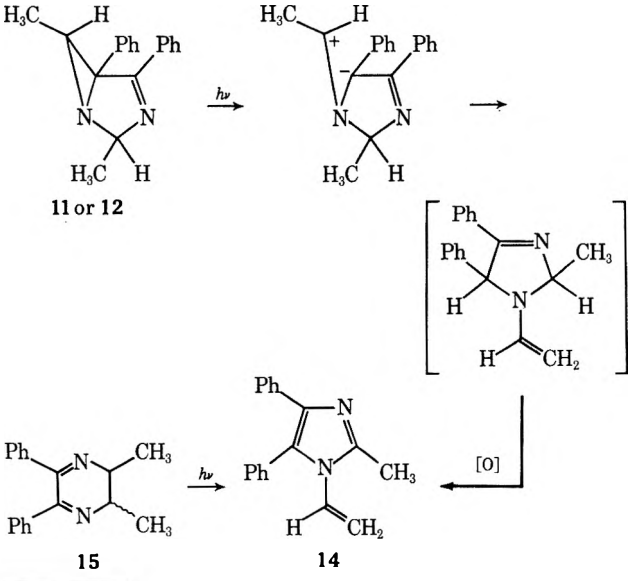
(10) T. DoMinh and A. M. Trozzolo, *ibid.*, **94**, 4046 (1972); **92**, 6997 (1970).

methyl doublets at τ 8.72 (J = 5.0 Hz) and 8.40 (J = 6.5 Hz), two single hydrogen quartets at 8.03 (J = 5.0 Hz) and 5.02 (J = 6.5 Hz), and a multiplet centered at 2.60 (10 H). The minor isomer **12** showed methyl doublets at τ 8.73 (J = 6.0 Hz) and 8.45 (J = 6.0 Hz), single hydrogen quartets at 7.86 (J = 6.0 Hz) and 4.34 (J = 6.0 Hz), and a multiplet centered at 2.60 (10 H). Chemical confirmation of these structures was obtained by treating **11** (and/or **12**) with potassium *tert*-butoxide in refluxing toluene to give 2,4-dimethyl-5,6-diphenylpyrimidine (**13**) (85%), mp 105–106°.

In addition to dimers **11** and **12**, pyrimidine **13** (8%) and *N*-vinyl-3-methyl-4,5-diphenylimidazole (**14**) (12%), mp 83–84°, nmr ($CDCl_3$) τ 7.46 (3 H, s), 5.04 (1 H, d, J = 16.0 Hz), 5.01 (1 H, d, J = 10 Hz), 3.51 (1 H, dd, J = 16 and 10 Hz), 2.56–3.00 (10 H, m), were also isolated from the irradiation of **9**. Imidazole **14** was independently synthesized by irradiating 2,3-dihydro-2,3-dimethyl-5,6-diphenylpyrazine (**15**) in



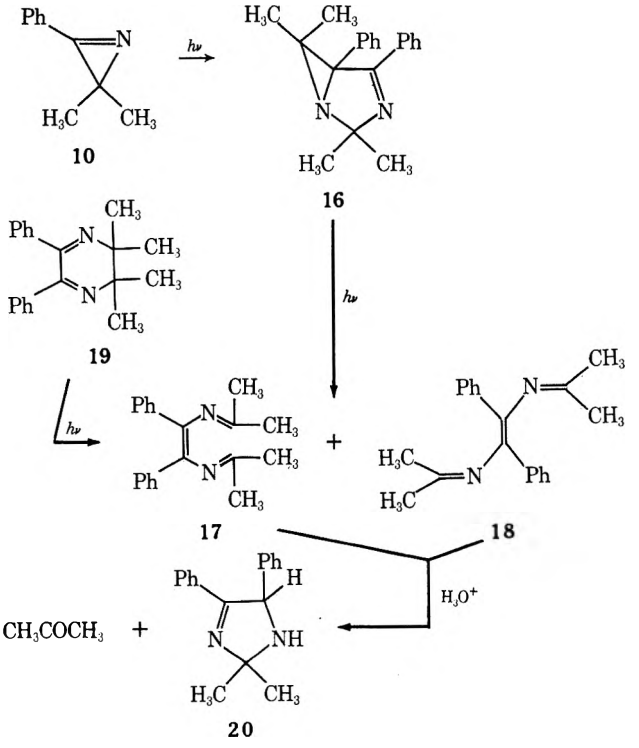
cyclohexane according to the procedure of Beak and Miesel.[11] These workers have shown that 2,3-dihydropyrazines rearrange to imidazoles upon photolysis. Suspicion that compounds **13** and **14** are secondary photoproducts was confirmed by the finding that the photolysis of **11** (and/or **12**) in cyclohexane afforded



(11) P. Beak and J. L. Miesel, *J. Amer. Chem. Soc.*, **89**, 2375 (1967).

pyrimidine **13** and imidazole **14**. The photoconversion of **11** (or **12**) into **14** may be formulated as proceeding *via* an azomethine ylide, formed by cleavage of the aziridine C–C bond. Proton transfer followed by oxidation of the transient *N*-vinylimidazoline readily accounts for the formation of **14**. The isolation of pyrimidine **13** from the photolysis of **11** (or **12**) can be attributed to cleavage of the aziridine C–N bond followed by loss of hydrogen.

To determine the influence of two methyl substituents on the photodimerization reaction, the photochemistry of 3,3-dimethyl-2-phenylazirine (**10**) was examined. It was felt that, by blocking the remaining position of the azirine ring, the expected diazabicyclic dimer would not be capable of imidazole or pyrimidine formation by the prescribed pathway. Either increased photochemical stability or formation of other valence tautomers[11,12] of the dimer might be expected. Irradiation of **10** for 6 hr in pentane using 2537-Å light gave a complex mixture of photoproducts. By carrying out the irradiation for short periods of time (2 hr), 4,5-diphenyl-2,2,6,6-tetramethyl-1,3-diazabicyclo[3.1.0]hex-3-ene (**16**), mp 71–72°, was obtained in good yield (45%). Irradiation of **10** for 3.5 hr gave **16** as well as two new substances (**17** and **18**). The same two compounds were also obtained from the irradiation of **16** or from the irradiation of 2,3-diphenyl-5,5,6,6-tetramethyldihydropyrazine (**19**). These new photoproducts were separated by fractional crystallization and were identified as *cis*- (**17**) and *trans*-2,7-dimethyl-4,5-diphenyl-3,6-diazaocta-2,4,6-triene (**18**). Both isomers were transformed into 2,2-dimethyl-4,5-diphenyl-3-imidazoline (**20**) and acetone

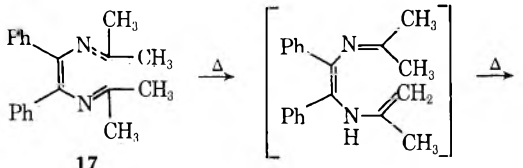


when treated with methanol containing a trace of acid. This observation provides substantial support for the mechanism of imidazoline formation from the irradia-

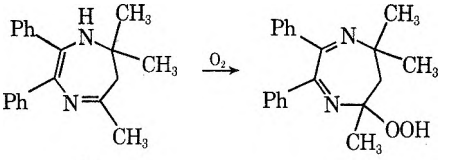
(12) D. R. Arnold, V. Y. Abraitys, and D. McLeod, Jr., *Can. J. Chem.*, **49**, 923 (1971).

tion of dihydropyrazines as suggested by Beak and Miesel.[11]

When *cis*-enediimine **17** was allowed to stand in the dark at room temperature in a degassed chloroform solution, it was smoothly converted into 2,3-diphenyl-5,7,7-trimethyl-1,4-diazacyclohepta-2,4-diene (**21**) (90%), mp 117–119°. This compound was easily characterized by its nmr spectrum, which showed singlets at τ 9.54 (6 H), 7.70 (3 H), 7.48 (2 H), and 7.30 (1 H, NH). The latter three singlets disappeared within 30 min at 80° on D_2O exchange. The formation of product **21** from *cis*-enediimine **17** can be interpreted in terms of a 1,3-hydrogen shift to give **22** as a transient intermediate which could then lead to **21** by enamine addition across the double bond. Although nmr studies have failed to give evidence for the presence of **22**, it is not unreasonable to suppose that this species is present in such small amounts that it cannot be detected spectroscopically. The passage of **17** to **22** is undoubtedly assisted by the driving force arising from relief of methyl group crowding.



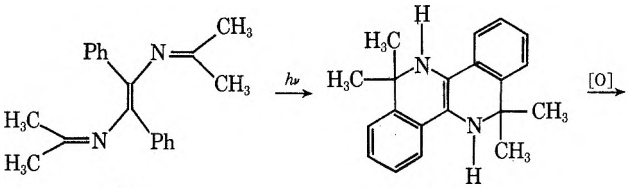
17 **22**



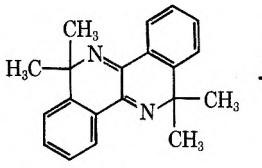
21 **23**

On standing for an additional period of time in an aerated chloroform solution at 25°, **21** underwent smooth conversion to hydroperoxide **23**, mp 142–143°, nmr (pyridine) τ 8.60 (3 H, s), 8.39 (3 H, s), 8.30 (3 H, s), 7.34 (1 H, d, J = 15.0 Hz), and 6.78 (1 H, d, J = 15.0 Hz). This structure was supported by the observation that **23** liberated iodine from an acidified potassium iodide solution. The formation of hydroperoxides from the reaction of enamines and certain Schiff bases with molecular oxygen has been reported in the literature[13–16] and provides good chemical analogy for the above transformation.

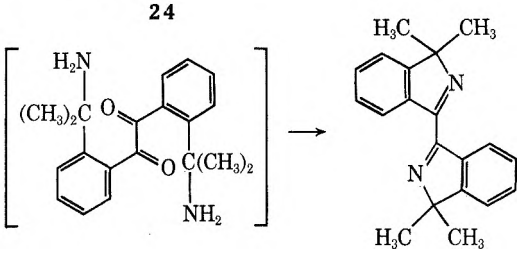
Irradiation of dimethylphenylazirine **10** for 5 hr gave a mixture of **16**, **17**, **18**, and a new photoproduct, **24**. Compound **24** was shown to be a secondary photoproduct derived from enediimine **18**. Its structure is assigned as 6,12-dihydro-6,6,12,12-tetramethyl-5,11-diazachrysene (**24**), mp 189–190°, nmr ($CDCl_3$) τ 8.36 (12 H, s) and 1.5–2.6 (8 H, m). Diazachrysene **24** was transformed into isoindole **25**, mp 203–204°, on treatment with aqueous acid. The formation of **24** from **18** is analogous to the photocyclization of stilbenes to phenanthrenes.[17] We have, in fact, been able to detect the presence of **26** as a transient intermediate



18 **26**



24



25

in the reaction mixture. This material is subsequently oxidized to **24** on work-up.

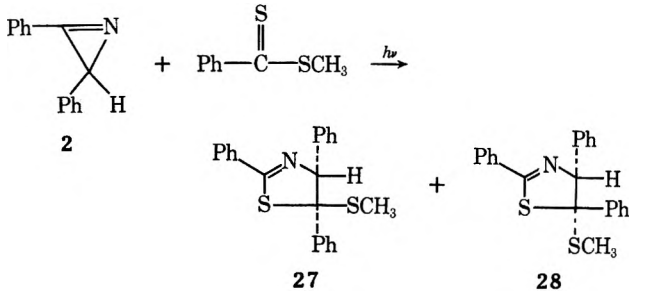
The above results indicate that the photodimerization of arylazirines to 1,3-diazabicyclo[3.1.0]hex-3-enes is a general reaction which is independent of the nature of the substituent groups attached to the C atom of the azirine ring.[18] The primary photoproducts have been found to undergo subsequent reaction on further irradiation. Our results indicate that the secondary photoproducts formed from the irradiation of the diazabicyclohexenes depend on the substituent groups, the time of irradiation, and the particular solvent employed.

Cycloaddition of Arylazirines with Hetero Multiple Double Bonds.—As was pointed out earlier, photochemically generated nitrile ylides can be trapped with electron-deficient carbon–carbon multiple bonds and, in their absence, with the carbon–nitrogen double bond of unreacted azirine. We felt that the photoaddition of arylazirines would not be restricted to just electron-deficient double bonds, but would also occur with other dipolarophiles. Huisgen has recently demonstrated that nitrile ylides, generated by ground-state reactions, undergo cycloaddition with a wide variety of hetero-multiple bonds.[20] The results outlined below demonstrate that the photoaddition of azirines proceeds with a number of dipolarophiles and provides a convenient route for the synthesis of a variety of five-membered heterocyclic rings.[21]

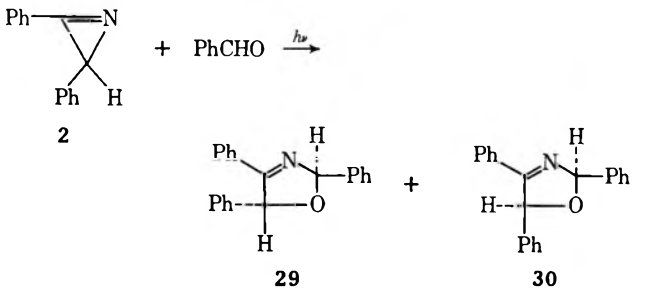
Irradiation of 2,3-diphenylazirine (**2**) in benzene with an internal water-cooled mercury arc lamp in the presence of an equimolar amount of methyl dithiobenzoate[22] produced a mixture of two Δ^2-thiazolines,

(13) C. L. Stevens and R. J. Gasser, *J. Amer. Chem. Soc.*, **79**, 6057 (1957).
(14) B. Witkop and J. B. Patrick, *ibid.*, **75**, 4476 (1953).
(15) B. Witkop and H. M. Kissman, *ibid.*, **75**, 1975 (1953).
(16) R. Criegee and G. Lohans, *Chem. Ber.*, **84**, 219 (1951).
(17) For a review, see F. R. Stermitz in "Organic Photochemistry," Vol. I, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1967, p 247.
(18) Similar results have been observed by Schmid and coworkers.[7,19]
(19) B. Jackson, N. Gakis, M. Marky, H. J. Hansen, W. von Philipsborn, and H. Schmid, *Helv. Chim. Acta*, **55**, 916 (1972).
(20) R. Huisgen, H. Stangl, H. J. Sturm, R. Raab, and K. Bunge, *Chem. Ber.*, **105**, 1258 (1972); K. Bunge, R. Huisgen, R. Raab, and H. Stangl, *ibid.*, **105**, 1279 (1972); K. Bunge, R. Huisgen, R. Raab, and H. J. Sturm, *ibid.*, **105**, 1307 (1972); R. Huisgen, R. Sustmann, and K. Bunge, *ibid.*, **105**, 1324 (1972).
(21) Similar results have recently been reported by B. Jackson, M. Marky, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55**, 919 (1972).
(22) E. J. Hedgley and H. G. Fletcher, *J. Org. Chem.*, **30**, 1282 (1965).

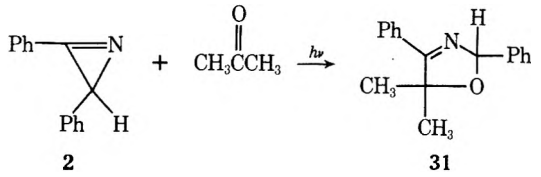
27 (mp 116–117°) and 28 (mp 125–126°). Nmr analysis of the crude photolysate indicated that 28 was the major adduct (28:27 = 1.5:1.0) by comparison of the methyl singlets at τ 7.86 (27) and 8.10 (28).



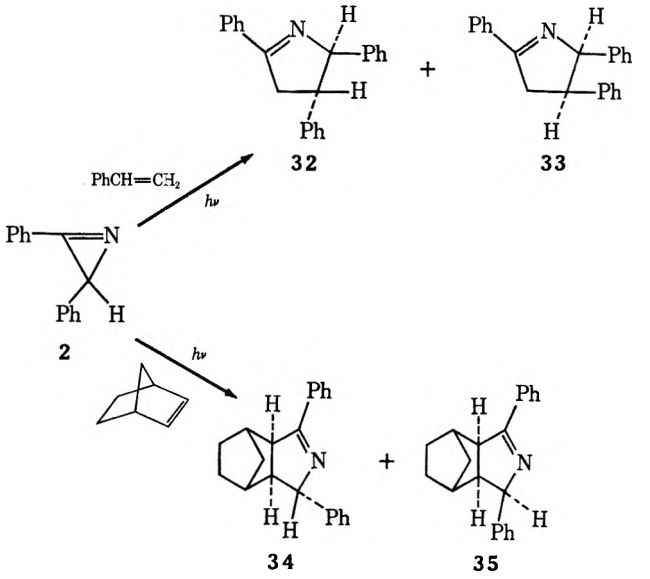
Similar irradiation of a solution of 2 in benzene which contained an excess of benzaldehyde proceeded to give two Δ^3-oxazolines 29 (mp 107–108°) and 30 (mp 30–31°). The ratio of the two cycloadducts (29:30 = 1:2) was determined by nmr analysis of the doublets associated with proton H_5 [τ 3.72 (29) and 3.87 (30)] in the crude photolysate. Very recently Schmid and coworkers have also reported that arylazirines undergo photochemical cycloaddition with aldehydes to give Δ^3-oxazolines.[23]



The photocycloaddition of diphenylazirine with acetone was not as facile as that encountered with benzaldehyde. When a benzene solution of diphenylazirine was irradiated with a moderate excess of acetone (3 *M*), no photoadduct was obtained; instead tetraphenylpyrazine was produced on extended irradiation.[6] However, when a large excess of acetone was used, a single cycloadduct was isolated in moderate yield. On the basis of its spectral data this material is assigned as 2,4-diphenyl-5,5-dimethyl-Δ^3-oxazoline (31). The low-field position of proton H_2 (τ 3.43) supports this orientation of addition.[20]



Photolysis of a solution of 2 and excess styrene gave Δ^1-pyrrolines 32 and 33. Comparison of the signals of proton H_5, which appeared at τ 4.42 (33) and 4.71 (32), indicated that 32 was the major component of the mixture (32:33 = 1.5:1.0). The less reactive dipolarophile norbornene also formed a mixture of two adducts with diphenylazirine. Irradiation of a solution of diphenylazirine with norbornene gave a 1:1 mixture of tricyclic Δ^1-pyrrolines 34 and 35. The nmr spectra of 34 and 35 were essentially identical



with those of the adducts obtained from the reaction of *N*-(*p*-nitrobenzyl)benzimidoyl chloride with triethylamine and norbornene.[20]

Experimental Section[24]

Coirradiation of 2-Phenylazirine with 2,3-Diphenylazirine at 3130 Å.—A series of eight Pyrex test tubes, each containing 100 mg of 2,3-diphenylazirine and 70 mg of 2-phenylazirine in 45 ml of benzene, was irradiated with a 450-W Hanovia lamp. The light was filtered by circulation of a solution containing 46 g of nickel sulfate hexahydrate and 14 g of cobaltous sulfate heptahydrate in 100 ml of water through the inner jacket.[25] This solution permitted the following wavelength distribution to pass through: 6% 2967 Å, 20% 3025 Å, 62% 3130 Å, 10% 3340 Å. After 14 hr, the tubes were combined and the solvent was removed under reduced pressure. The crude oil was subjected to scanning liquid–liquid partition chromatography. The first peak in the chromatogram (23 mg) was identified as tetraphenylpyrazine. The second fraction contained 224 mg (20%) of *endo*-2,4,5-triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene (3): mp 176–177°; ir (KBr) 6.19, 6.35, 6.70, 9.30, 13.25, 14.45 μ; uv (95% ethanol) 247 nm (ϵ 11,400); nmr ($CDCl_3$, 100 MHz) τ 8.26 (1 H, s), 7.42 (1 H, s), 3.32 (1 H, s), and 2.20–2.76 (15 H, m); *m/e* 310 (M^+), 206, 193, 179, 166, 104 (base), 103, 91, 89, and 77.

Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03. Found: C, 84.82; H, 5.81; N, 9.06.

The third fraction contained 297 mg (20%) of a clear yellow oil which was purified by preparative thick layer chromatography to give *exo*-2,4,5-triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene (4) as a white, crystalline solid: mp 85–87°; ir (KBr) 6.28, 6.38, 6.70, 6.92, and 7.20 μ; uv (95% ethanol) 248 nm (ϵ 15,200); nmr ($CDCl_3$, 100 MHz) τ 7.98 (1 H, s), 6.92 (1 H, s), 4.06 (1 H, s), and 2.2–2.8 (15 H, m); *m/e* 310 (M^+), 206, 193, 179, 165, 104, 103, 91, 89, and 77.

Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03. Found: C, 84.54; H, 5.88; N, 9.07.

Treatment of *endo*- and *exo*-2,4,5-Triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene with Sodium Methoxide.—Confirmation of the structures of diazabicyclohexenes 3 and 4 was obtained by their base-catalyzed rearrangement of 2,4,5-triphenylpyrimidine (5).

(23) H. Giezendanner, M. Marky, B. Jackson, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55**, 745 (1972).

(24) All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by Scandinavian Laboratory, Herlev, Denmark. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 60 MHz with a Varian Associates high-resolution spectrometer and at 100 MHz using a Jeol-MH-100 spectrometer.

(25) P. J. Wagner and G. S. Hammond, *J. Amer. Chem. Soc.*, **88**, 1245 (1966).

A solution of 75 mg of *endo*- (or *exo*-) bicyclohexene (**3** or **4**) in 10 ml of a freshly prepared 0.13 *N* sodium methoxide–methanol solution was heated at reflux for 10 hr. Removal of the solvent gave a yellow solid, which was thoroughly washed with water. This solid was identified as 3,6-dihydro-2,4,5-triphenylpyrimidine, mp 89–98°, nmr ($CDCl_3$) τ 5.44 (2 H, s), 5.12 (1 H, broad s), 2.20–3.00 (15 H, m).

A mixture of the above dihydropyrimidine and 5% palladium on charcoal in benzene was heated at reflux for 1 hr. The catalyst was separated by filtration and the solvent was removed *in vacuo* to give 2,4,5-triphenylpyrimidine (**5**) (60 mg, 80%) as a crystalline solid: mp 110–111°; ir (KBr) 6.45, 6.60, 7.10, 7.32, 8.55, 9.35, 9.80, 14.45 μ; nmr ($CDCl_3$) τ 2.40–3.00 (15 H, m), 1.34 (1 H, s); uv (95% ethanol) 263 nm (ϵ 30,400); *m/e* 308 (M^+, base), 102, and 77.

Anal. Calcd for $C_{22}H_{16}N_2$: C, 85.69; H, 5.23; N, 9.09. Found: C, 85.42; H, 5.36; N, 8.88.

Pyrimidine **5** was further confirmed by an independent synthesis. A mixture of 5.0 g of α-phenylacrylophenone[26] and 2.63 g of benzamidine hydrochloride in 50 ml of 95% ethanol was stirred at room temperature. To the above mixture was added a solution containing 1.34 g of potassium hydroxide in 50 ml of 95% ethanol. The resulting solution was heated at reflux for 1.5 hr. The yellow solid which remained was oxidized by heating in benzene in the presence of palladium on charcoal. Removal of the catalyst followed by concentration of the solvent gave white crystals (90%), mp 110–111°. The infrared spectrum of this material was identical in all respects with that of a sample of **5** obtained from the base-catalyzed rearrangement of **3** (or **4**). A mixture melting point was undepressed at 110–111°.

Synthesis of *exo*- and *endo*-2,4,5-Triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene.—The structure of the mixed photodimer **3** or **4** was further confirmed by an unequivocal synthesis. A solution containing 5.0 g of 1,2-dibenzoyl-2-phenylaziridine[6] (**6**), 0.8 g of ammonium bromide, and 15 ml of benzaldehyde in 100 ml of ethanol was saturated with ammonia. The solution was allowed to stand at room temperature for 6 days, at which time a crystalline precipitate had formed. Fractional crystallization of the crude solid gave *endo*- (**3**) and *exo*-2,4,5-triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene (**4**). The infrared and nmr spectra of both compounds prepared in this fashion were identical in all respects with those of the materials isolated from the coirradiation of mono- and diphenylazirines.

Irradiation of 2,4,5-Triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene.—A solution containing 700 mg of diazabicyclohexene **3** (or **4**) in 500 ml of absolute methanol was irradiated under a nitrogen atmosphere through a Corex filter for 8 hr. The solvent was removed under reduced pressure and the residual oil was subjected to liquid–liquid partition chromatography. The first peak in the chromatogram was identified as 2,4,5-triphenylpyrimidine (**5**) (15%). The second fraction was a white, crystalline solid, mp 148–149°, whose structure is assigned as *N*-methoxymethyl-2,4,5-triphenyl-2,3-dihydroimidazole (**7**) (9%) on the basis of the following data: ir (KBr) 6.19, 6.89, 7.20, 7.30, 9.24, 10.31, 10.80, 12.05, 12.98, 13.22, 13.79, 13.95, 14.40 μ; nmr ($CDCl_3$, 100 MHz) τ 6.68 (3 H, s), 4.44 (2 H, s), 2.81 (1 H, s), and 1.2–2.6 (15 H, m). The third component in the reaction mixture was identified as *N*-methoxymethyl-2,4,5-triphenylimidazole (**8**) (19%): mp 112–113°; ir (KBr) 6.45, 6.60, 7.10, 8.55, 9.74, 12.08, 13.09, 13.35, 13.80 μ; nmr ($CDCl_3$) τ 6.44 (3 H, s), 4.64 (2 H, s), and 2.0–3.0 (15 H, m). Treatment of imidazole **8** with mild acid or by chromatographing over silica gel gave 2,4,5-triphenylimidazole, thereby providing additional support for the above structural assignments.

Photodimerization of 3-Methyl-2-phenylazirine (9).—A solution containing 2.0 g of methylphenylazirine (**9**) in 500 ml of cyclohexane was irradiated with a 550-W Hanovia lamp using a Pyrex filter for 11 hr. The solvent was removed under reduced pressure, giving a crude oil containing two significant components. The mixture was separated by thick layer chromatography. The major component amounted to 600 mg (30%) of a crystalline solid, mp 95–96°, whose structure is assigned as *exo*-2,6-dimethyl-4,5-diphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene (**11**) on the basis of the following data: ir (KBr) 3.40, 6.26, 6.94, 7.58, 7.70, 9.19, 9.32, 9.84, 12.84, 13.12, and 14.40 μ; uv (cyclohexane) 230 nm (ϵ 12,300); nmr ($CDCl_3$, 100 MHz) τ 8.72 (3 H, d, J = 5.0 Hz), 8.40 (3 H, d, J = 6.5 Hz), 8.03 (1 H, q, J = 5.0 Hz), 5.02 (1 H, q, J = 6.5 Hz), 2.30–2.90 (10 H, m); *m/e* 262 (M^+), 104 (base), and 77.

Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.40; H, 6.92; N, 10.68. Found: C, 82.21; H, 6.88; N, 10.62.

The minor component (10%) present in the reaction mixture was contaminated with the major dimer (**11**) and all attempts to crystallize this material failed. The structure of this component is assigned as *endo*-2,6-dimethyl-4,5-diphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene (**12**) on the basis of its nmr spectrum and chemical behavior: nmr ($CDCl_3$, 100 MHz) τ 8.73 (3 H, d, J = 6.0 Hz), 8.45 (3 H, d, J = 6.0 Hz), 7.86 (1 H, q, J = 6 Hz), 4.34 (1 H, q, J = 6 Hz), 2.30–2.90 (10 H, m).

Base-Catalyzed Isomerization of 2,6-Dimethyl-4,5-diphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene.—Chemical confirmation of the structures of **11** and **12** was obtained by their base-catalyzed rearrangement to 2,4-dimethyl-5,6-diphenylpyrimidine (**13**). A mixture of 80 mg of **11** and/or **12**) and 200 mg of potassium *tert*-butoxide was heated at reflux in a 5:1 mixture of toluene and xylene for 3.5 hr. The reaction mixture was washed with water and taken up in ether. The ethereal solution was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crystalline solid that formed (68 mg, 85%), mp 105–106°, was assigned the structure of 2,4-dimethyl-5,6-diphenylpyrimidine (**13**): ir (KBr) 6.59, 7.14, 8.50, 9.94, 11.69, 13.18, 14.31 μ; uv (cyclohexane) 273 nm (ϵ 10,300) and 225 (18,700); nmr ($CDCl_3$, 100 MHz) τ 7.65 (3 H, s), 7.23 (3 H, s), 2.60–3.10 (10 H, m); *m/e* 260 (M^+).

Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.05; H, 6.17; N, 10.72.

Irradiation of 2,6-Dimethyl-4,5-diphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene.—A solution containing 518 mg of diazabicyclohexene **11** (or **12**) in 125 ml of cyclohexane was irradiated under a nitrogen atmosphere using a 450-W Hanovia lamp equipped with a Pyrex filter for 4.5 hr. Concentration of the solution *in vacuo* left a crude mixture of compounds which was separated by thick layer chromatography. One of the many components present was identified as 2,4-dimethyl-5,6-diphenylpyrimidine (**13**) (8%). Another band contained 18 mg (3%) of a crystalline solid, mp 83–84°, whose structure is assigned as *N*-vinyl-4,5-diphenyl-3-methylimidazole (**14**) on the basis of the following data: ir (KBr) 6.05, 7.15, 10.21, 10.87, 12.85, 13.14, 14.40 μ; nmr ($CDCl_3$, 100 MHz) τ 7.46 (3 H, s), 5.04 (1 H, d, J = 16 Hz), 5.01 (1 H, d, J = 10 Hz), 3.51 (1 H, dd, J = 16 and 10 Hz), 2.56–3.0 (10 H, m); *m/e* 260 (M^+).

Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 82.85; H, 6.36; N, 10.76.

Structure **14** was further confirmed by an independent synthesis. A solution containing 460 mg of 2,3-dihydro-2,3-dimethyl-5,6-diphenylpyrazine (**15**)[11] in 125 ml of cyclohexane was irradiated with a 450-W lamp equipped with a Pyrex filter for 1 hr. Concentration of the solution *in vacuo* left a pale yellow oil, which was subjected to thick layer chromatography. One of the bands of the thick layer plate was identified as *N*-vinyl-4,5-diphenyl-3-methylimidazole (**14**) (19%). The infrared and nmr spectra of this compound were identical in every detail with those of a sample of **14** obtained from the irradiation of **11**.

When the irradiation of diazabicyclohexene **11** was carried out in absolute ethanol, the only products identified were pyrimidine **13** and 4,5-diphenyl-1-(1-ethoxyethyl)-2-methylimidazole.[11] Under these conditions there was no detectable signs of vinylimidazole **14**.

Photodimerization of 3,3-Dimethyl-2-phenylazirine (10).—A solution containing 2.2 g of dimethylphenylazirine **10** in 20 ml of pentane was irradiated at 2537 Å using a Rayonet "merry-go-round" apparatus for 160 min. Thick layer chromatography of the residue gave 700 mg (45% based on reacted starting material) of a crystalline dimer, mp 71–72°, whose structure is assigned as 4,5-diphenyl-2,2,6,6-tetramethyl-1,3-diazabicyclo[3.1.0]hex-3-ene (**16**) on the basis of the following data: ir (KBr) 6.24, 6.92, 7.40, 8.22, 13.16, 14.42 μ; uv (cyclohexane) 232 nm (ϵ 13,400); nmr ($CDCl_3$, 100 MHz) τ 8.78 (3 H, s), 8.55 (3 H, s), 8.41 (3 H, s), 8.32 (3 H, s), 2.4–2.9 (10 H, m); *m/e* 290 (M^+).

Anal. Calcd for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.59; H, 7.60; N, 9.63.

Irradiation of 4,5-Diphenyl-2,2,6,6-tetramethyl-1,3-diazabicyclo[3.1.0]hex-3-ene (16).—A solution of 50 mg of diazabicyclohexene **16** in 1 ml of pentane was irradiated at 2537 Å for 105 min. An nmr spectrum of the crude reaction mixture in benzene indicated the presence of two major components. The same two components could also be obtained from an extended irradiation

(26) L. Mehr, E. J. Becker, and P. E. Spoerri, *J. Amer. Chem. Soc.*, **77**, 984 (1955).

of dimethylphenylazirine. The minor component of the mixture (40%) was isolated by thick layer chromatography using ethyl acetate as the eluent and was assigned the structure of *trans*-2,7-dimethyl-4,5-diphenyl-3,6-diazaocta-2,4,6-triene (**18**), mp 165–166°, on the basis of the following data: ir (KBr) 6.04, 6.74, 6.95, 7.35, 8.14, 12.93, 14.30 μ; uv (cyclohexane) 320 nm (ϵ 11,300) and 230 (12,000); nmr ($CDCl_3$, 100 MHz) τ 8.38 (6 H, s), 8.06 (6 H, s), 2.4–2.8 (10 H, m); *m/e* 290 (M^+).

Anal. Calcd for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64, N, 9.65. Found: C, 82.48; H, 7.68; N, 9.65.

Chemical confirmation of this structure was obtained from some acid hydrolysis experiments. A solution containing 44 mg of **18** in 5 ml of 50% aqueous hydrochloric acid was refluxed for 24 hr. The aqueous system was extracted with chloroform, washed with water, and dried over magnesium sulfate. Removal of the solvent gave a white solid, mp 91–93°, whose structure was identified as benzil by comparison with an authentic sample.

A solution of 30 mg of enediimine **18** in 4 ml of methanol containing 1 drop of dilute hydrochloric acid was allowed to stand at room temperature for several hours. The reaction mixture was made basic with 10% sodium hydroxide and extracted with 10 ml of ether. The ether was dried over magnesium sulfate and the solvent was evaporated under reduced pressure to give a single compound whose structure was shown to be 2,2-dimethyl-4,5-diphenyl-3-imidazoline (**20**):[11] ir (KBr) 6.00, 6.20, 6.40, 6.75, 6.98 μ; nmr ($CDCl_3$) τ 8.52 (3 H, s), 8.39 (3 H, s), 7.44 (1 H, broad s), 4.52 (1 H, s), 2.3–2.8 (10 H, m). Upon standing in the open for several days, imidazoline **20** was quantitatively oxidized to 2,2-dimethyl-4,5-diphenylisoimidazole, mp 75–77° (lit. mp 76–78°).[27]

When the irradiation of diazabicyclohexene **16** was carried out in methanol, a nearly quantitative yield of 2,2-dimethyl-4,5-diphenyl-3-imidazoline (**20**) was obtained.

***cis*-2,7-Dimethyl-4,5-diphenyl-3,6-diazaocta-2,4,6-triene (17).**—The major component (50%) formed from the photolysis of diazabicyclohexene **16** was separated from *trans*-enediimine **18** by fractional crystallization from anhydrous ether, mp 82–95°. An nmr spectrum of the purest crop obtained revealed the presence of **18** as a persistent impurity (*ca.* 8%). The structure of the major product is assigned as *cis*-2,7-dimethyl-4,5-diphenyl-3,6-diazaocta-2,4,6-triene (**17**) on the basis of the following data: ir (KBr) 6.05, 6.70, 6.93, 7.33, 8.05, 9.28, 11.25, 12.85, 14.30 μ; uv (cyclohexane) 228 nm (ϵ 15,400) and 312 (10,700); nmr ($CDCl_3$, 100 MHz) τ 8.04 (6 H, s), 8.17 (6 H, s), 2.5–3.9 (10 H, m); *m/e* 290 (M^+), 275, 235 (base), 194, 165, and 104.

cis-Enediimine **17** was rapidly converted to an isomeric compound when it was allowed to stand in deuteriochloroform at room temperature for 50 min. This same compound could also be obtained quantitatively when **17** was heated in benzene at 65° for 45 min. The structure of this compound is assigned as 2,3-diphenyl-5,7,7-trimethyl-1,4-diazacyclohepta-2,4-diene (**21**): mp 114–119°; ir (KBr) 2.98, 3.40, 6.10, 6.25, 6.70, 6.92, 9.32, 10.68, 13.12, 14.30 μ; uv (cyclohexane) 252 nm (ϵ 7700) and 357 (6400); *m/e* 290 (M^+), 288, 275, 234, 194, 172, 165, 105, 104, 77; nmr ($CDCl_3$) τ 8.54 (6 H, s), 7.70 (3 H, s), 7.48 (2 H, s), 7.30 (1 H, broad s), 2.3–3.0 (10 H, m). When **21** was treated with deuterium oxide (containing a catalytic amount of hydroxide ion) at 80° for 0.5 hr, the singlets at τ 7.48, 7.70, and 7.30 were washed out. Replacing the deuterium oxide with water and heating for 4 hr caused the return of these peaks.

When diazacycloheptadiene **21** was allowed to stand in chloroform in an open atmosphere, it was gradually converted into still another new compound. This same material could be prepared in quantitative yield by bubbling oxygen through a chloroform solution of **21**. The white crystalline solid obtained, mp 142–143°, was assigned the structure of 2,3-diphenyl-5-hydroperoxy-5,7,7-trimethyl-1,4-diazacyclohepta-1,3-diene (**23**) on the basis of the following data: ir (KBr) 3.21, 3.45, 6.13, 6.20, 6.91, 8.42, 8.91 μ; uv (methanol) 228 nm (ϵ 12,700) and 259 (8100); *m/e* 288, 287, 162, 122, 105, 103, and 77; partial nmr (100 MHz, pyridine) τ 8.60 (3 H, s), 8.39, (3 H, s), 8.30 (3 H, s), 7.34 (1 H, d, J = 15 Hz), 6.78 (1 H, d, J = 15 Hz).

Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.11; H, 6.85; N, 8.55.

Further support for the structure of hydroperoxide **23** was obtained by the observation that **23** liberated iodine from an acidified methanol solution containing potassium iodide.

(27) M. Weiss, *J. Amer. Chem. Soc.*, **74**, 5193 (1952).

The structure of *cis*-enediimine **17** was further verified by the acid-catalyzed hydrolysis of **17** to imidazoline **20** using the same procedure as was described above for *trans*-enediimine **18**. *cis*- and *trans*-enediimines **17** and **18** were also found to be interconverted photochemically.

Irradiation of 2,3-Diphenyl-5,5,6,6-tetramethyldihydropyrazine (19).—A solution of 50 mg of diphenyltetramethyldihydropyrazine **19** in 1.5 ml of pentane was irradiated in a quartz nmr tube with 2537-Å light for 1 hr. Removal of the solvent followed by immediate analysis by nmr ($CDCl_3$) indicated the presence of a mixture of *cis*- and *trans*-2,7-dimethyl-4,5-diphenyl-3,6-diazaocta-2,4,6-triene (**17** and **18**) (ratio 5:4). On standing in the nmr tubes, *cis*-enediimine **17** was converted into **21** and **23**.

Irradiation of *trans*-2,7-Dimethyl-4,5-diphenyl-3,6-diazaocta-2,4,6-triene (18).—A solution containing 226 mg of *trans*-enediimine **18** in 15 ml of absolute methanol was irradiated at 2537 Å for 12 hr. Analysis of the reaction mixture by glpc (5 ft × 0.25 in. column of 5% SE-30 on Chromosorb W) at 205° indicated a trace of 2,2-dimethyl-4,5-diphenylimidazole (3%) and a second photoproduct (53%) which was assigned as 6,12-dihydro-6,6,12,12-tetramethyl-5,11-diazachrysene (**24**). Compound **24** was obtained as a crystalline material, mp 189–190°, by crystallization of the reaction residue from acetone: ir (KBr) 6.27, 7.86, 8.55, 13.10 μ; uv (methanol) 225 nm (ϵ 30,200), 230 sh (29,000), 268 (22,900), 291 (15,700), 302 (14,800), and 365 (400); nmr ($CDCl_3$, 100 MHz) τ 8.33 (12 H, s), 2.40–2.68 (6 H, m), 1.50–1.64 (2 H, m); *m/e* 288 (M^+), 273 (base), and 258.

Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.29; H, 6.99; N, 9.71. Found: C, 83.13; H, 7.03; N, 9.60.

Nmr analysis of the crude reaction mixture indicated that **24** was not a primary photochemical product but rather was derived by subsequent oxidation of a transient intermediate. This species presumably corresponds to 5,6,11,12-tetrahydro-6,6,12,12-tetramethyl-5,11-diazachrysene (**26**), nmr ($CDCl_3$, 100 MHz) τ 8.62 (12 H, s), 7.50 (2 H, broad s), 1.5–2.70 (8 H, m).

Acid-Catalyzed Rearrangement of 6,12-Dihydro-6,6,12,12-tetramethyl-5,11-diazachrysene (24).—To a 46-mg sample of **24** in 5 ml of methanol was added 2 ml of a 50% aqueous hydrochloric acid solution. The mixture was heated at reflux for 3 hr, made basic with 10% sodium hydroxide, and extracted with two 15-ml portions of ether. The extracts were washed twice with water, dried over magnesium sulfate, and concentrated to yield a crude solid. Recrystallization from acetone gave 25 mg (55%) of a white solid, mp 203–204°, which had the following spectral properties: ir (KBr) 6.26, 6.56, 6.88, 7.89, 8.18, 8.58, 10.72, 13.00, 13.67 μ; uv (cyclohexane) 223 nm (19,100), 259 (10,300), 287 sh (5300), and 293 (3700); nmr ($CDCl_3$, 100 MHz) τ 8.38 (12 H, s), 2.3–2.6 (6 H, m), 1.3–1.5 (2 H, m); *m/e* 288 (M^+), 273 (base), 258, and 129.

Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.29; H, 6.99; N, 9.71. Found: C, 83.01; H, 6.91; N, 9.64.

On the basis of the above data this compound is assigned the structure of 3,3′-bis(1,1-dimethyl-1*H*-isoindole) (**25**).

Photoaddition of Methyl Dithiobenzoate with Diphenylazirine.—A solution of 0.3 g of diphenylazirine and 0.26 g of methyl dithiobenzoate in 150 ml of benzene was irradiated for 3 hr through a Pyrex filter sleeve. Analysis of the mixture by nmr showed that it contained two components (**27** and **28**, ratio 1:1.5). Chromatography of the residue on 27 g of silica gel using a 2:1 benzene–cyclohexane mixture gave 85 mg (18%) of *trans*-5-methylmercapto-2,4,5-triphenyl-Δ^2-thiazoline (**28**): mp 125–126°; ir (KBr) 6.25 μ (C=N); nmr τ 1.96–2.87 (m, 15 H), 4.28 (s, 1 H), and 8.10 (s, 1 H); *m/e* 313, 210, and 193. The second component isolated from the chromatography amounted to 65 mg (13%) of *cis*-5-methylmercapto-2,4,5-triphenyl-Δ^2-thiazoline (**27**): mp 116–117°; ir (KBr) 6.27 μ (C=N); nmr τ 1.95–3.20 (m, 15 H), 4.13 (s, 1 H), and 7.86 (s, 1 H); *m/e* 313, 210, and 193.

Photoaddition of Benzaldehyde with Diphenylazirine.—A solution of 0.3 g of diphenylazirine and 0.38 g of benzaldehyde in 150 ml of benzene was irradiated for 2 hr through a Pyrex filter. The crude residue showed the presence of two components by nmr analysis. The minor component (11%) was separated by liquid–liquid partition chromatography[28] and was assigned as *trans*-2,4,5-triphenyl-Δ^3-oxazoline (**29**): mp 107–108°; ir (KBr) 6.12 (C=N), 9.46, and 9.70 μ; nmr ($CDCl_3$) τ 2.17–2.82 (m 15 H), 3.02 (d, 1 H, J = 5.3 Hz), and 3.72 (d, 1 H, J = 5.3 Hz); uv (cyclohexane) 247 and 288 nm (ϵ 17,500 and 540). The

(28) A. Padwa and L. Hamilton, *ibid.*, **89**, 102 (1967).

major component (20%) from the irradiation was identified as *cis*-2,4,5-triphenyl-Δ^3-oxazoline (**30**): mp 30–31°; ir (neat film) 6.18 (C=N), 9.40, and 9.76 μ; nmr ($CDCl_3$) τ 2.22–2.87 (m, 15 H), 3.15 (d, 1 H, J = 4.7 Hz), and 3.87 (d, 1 H, J = 4.7 Hz).

Photoaddition of Acetone with Diphenylazirine.—A solution of 0.3 g of diphenylazirine in 150 ml of a 2:1 benzene–acetone mixture was irradiated for 1.5 hr under a nitrogen atmosphere using a 550-W Hanovia lamp equipped with a Pyrex filter. Removal of the solvent left a dark oil which was purified by preparative thick layer chromatography using a 2:1 benzene–cyclohexane mixture. The major component isolated from the preparative thick layer plate amounted to 130 mg (39%) of a colorless oil whose structure is assigned as 2,4-diphenyl-5,5-dimethyl-Δ^3-oxazoline (**31**) on the basis of the following data: m/e 251 (parent) and 193 (P − acetone); ir (neat film) 6.14 (C=N), 9.1, and 9.65 μ (CO); nmr τ 8.35 (s, 6 H), 3.43 (s, 1 H), 2.10–3.10 (m, 10 H). The low-field position of proton H_2 supports this orientation of addition.

Photoaddition of Styrene with Diphenylazirine.—A solution of 0.5 g of diphenylazirine and 0.5 g of styrene in 500 ml of benzene was irradiated for 22 hr under a nitrogen atmosphere using a 450-W Hanovia lamp equipped with a Pyrex filter. The nmr spectrum of the crude reaction mixture revealed the presence of two major photoadducts in a ratio of 1.5:1 (combined yield 50%). The two components could not be separated by chromatography on all columns tried. Characterization was accomplished by nmr spectroscopy. The major adduct showed a doublet at τ 4.71 while the minor component had a doublet at τ 4.42 (1 H). The remaining portion of the spectrum was essentially identical with the spectrum of the adducts obtained from the reaction of *N*-(*p*-nitrobenzyl)benzimidoyl chloride with triethylamine and styrene.[20]

Photoaddition of Norbornene with Diphenylazirine.—A solution containing 579 mg of diphenylazirine and 5.8 g of norbornene in 500 ml of benzene was irradiated for 22 hr through a Pyrex filter using a 450-W Hanovia immersion lamp. Removal of the solvent and excess norbornene under reduced pressure left a yellow oil. The crude reaction mixture contained two major photoadducts as evidenced by vpc analysis (combined yield 36%). The mixture could be partially separated by liquid–liquid partition chromatography. The trans tricyclic-Δ^1-pyrroline (**34**) was a crystalline solid: mp 141–143°; ir (KBr) 6.15 μ (C=N); nmr ($CDCl_3$) τ 8.6 (6 H, m), 7.9 (1 H, m), 7.68 (2 H, m), 6.7 (1 H, m), 5.3 (1 H, m), and 2.0–3.0 (10 H, m); uv (95% ethanol) 246 nm (ϵ 10,700); m/e 287 (base), 246, 193, 168, 130, 105, 91, and 77. The *cis*-Δ^1-pyrroline (**35**) could not be completely separated from the trans isomer. The nmr spectra of both **34** and **35** were essentially identical with the spectra of the adducts obtained by Huisgen from the reaction of *N*-(*p*-nitrobenzyl)benzimidoyl chloride with triethylamine and norbornene.[20]

Registry No.—**3**, 37428-95-8; **4**, 37428-96-9; **5**, 37428-97-0; **7**, 37428-98-1; **8**, 37428-99-2; **9**, 16205-14-4; **10**, 14491-02-2; **11**, 36879-68-2; **12**, 36879-69-3; **13**, 38202-09-4; **14**, 38202-10-7; **16**, 38202-11-8; **17**, 38215-47-3; **18**, 38215-48-4; **20**, 16340-36-6; **21**, 38202-13-0; **23**, 38202-14-1; **24**, 38202-15-2; **25**, 38202-16-3; **27**, 38215-49-5; **28**, 38215-50-8; **29**, 36879-78-4; **30**, 36879-77-3; **31**, 38202-17-4; **34**, 38215-53-1; **35**, 38215-54-2; 2-phenylazirine, 7654-06-0; 2,3-diphenylazirine, 16483-98-0; 3,6-dihydro-2,4,5-triphenylpyrimidine, 38202-18-5; methyl dithiobenzoate, 2168-78-7; benzaldehyde, 100-52-7; acetone, 67-64-1; norbornene, 498-66-8.

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The Preparation and Photolytic Decomposition of Tetrabromodiazocyclopentadiene[1]

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Tetrabromodiazocyclopentadiene (**3**) was prepared in a 45% yield from hexabromocyclopentadiene. Photolysis of **3** in a variety of olefins produced spiro[2.4]heptadienes in good yields. The products were heat and light sensitive and several were isolated as viscous liquids. Products due to insertion into C–H bonds were not detected by nmr analysis of the crude reaction mixtures. Photolysis in *trans*-4-methyl-2-pentene produced only the trans addition product, while photolysis in *cis*-4-methyl-2-pentene produced a mixture of the trans (55%) and the cis adducts (45%). It is concluded that the carbene adds to olefins while in the triplet spin state.

The photolytic decomposition of diazocyclopentadiene is known to yield a carbene which has a triplet ground state,[2] but which reacts in solution while in the singlet state.[3,4] In fact, the carbene is so reactive that attempts to produce the triplet state in solution by collisional deactivation were unsuccessful.[4]

We studied the decomposition of tetrachlorodiazocyclopentadiene and found that the carbene also reacted primarily while in the singlet state.[5,6] However, the presence of the four chlorine atoms allowed facile study of the triplet state by collisional deactivation with hexafluorobenzene.[6,7]

Tetrabromodiazocyclopentadiene (**3**) had been previously prepared,[8] but its decomposition to the carbene had not been studied. We thought that it would be of interest to study what effect four large bromine atoms would have on the reactions of the carbene. Thus, we now wish to report a new synthesis of **3** and a study of its photolytic decomposition in the presence of olefins.

Synthesis of Tetrabromodiazocyclopentadiene (3).—In 1963, a small amount of **3** was prepared in 15% yield from cyclopentadiene.[8] We devised an alternate synthesis to avoid the preparation of large quantities of diazocyclopentadiene, which has reportedly undergone

(1) Taken in part from the Ph.D. Thesis of K. J. Sienkowski, Purdue University, 1972. Acknowledgment is made to the Stauffer Chemical Co. and the Viol Memorial Fellowship Fund for partial support of this research.

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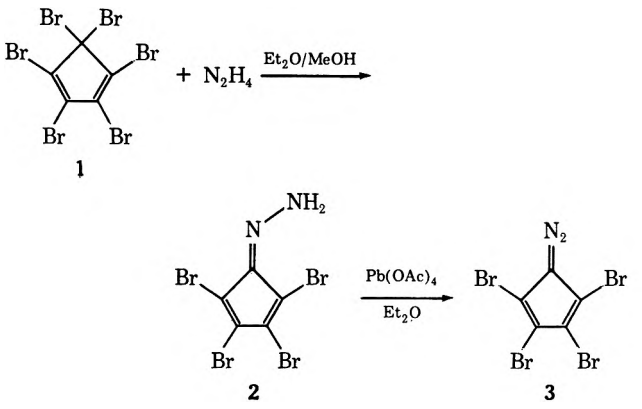
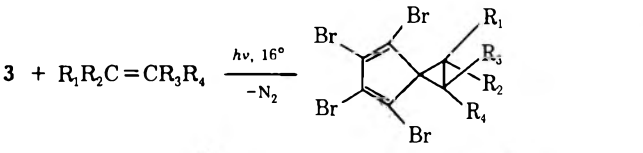
explosive decomposition.[9-11] **3** was successfully prepared in 45% yield in two steps from hexabromocyclopentadiene (**1**).[12,13] The nucleophilic addition of hydrazine to **1** produced tetrabromocyclopentadienone hydrazone (**2**) in 50% yield. This is only the second reported nucleophilic attack on **1**.[14] **2** is a fluffy, reddish-brown solid which be easily dehydrogenated with lead tetraacetate to produce **3** in greater than 80% yield.



3 is a very stable, orange solid which can be stored indefinitely in the dark at room temperature, but which can be decomposed readily when photolyzed. The infrared spectrum was identical with that reported by Cram, displaying intense diazo absorptions at 4.75 and 4.82 μ.[8]

Synthesis and Identification of 1,2,3,4-Tetrabromospiro[2,4]heptadienes.—The photolysis of **3** in a variety of olefins at 16° liberated nitrogen and produced the expected spirocyclopropanes (**4a-h**) in good yields.



4a, R_1 = H; R_2 = R_3 = R_4 = CH_3
b, R_1 = R_2 = R_3 = H; R_4 = n-C_4H_9
c, R_1 = R_2 = R_3 = H; R_4 = t-C_4H_9
d, R_1 = R_2 = R_3 = H; R_4 = CH_2Cl
e, R_1 = R_2 = R_3 = H; R_4 = C_6H_5
f, R_1 = R_2 = R_3 = H; R_4 = C_2H_3
g, R_1 = R_2 = H; R_3 = CH_3; R_4 = C_6H_5
h, R_1 = R_3 = H; R_2R_4 = $-(CH_2)_4-$

The crude reaction mixtures were carefully studied by nmr, with special attention to the vinylic region, to ensure that any insertion products would be detected. However, no insertion product for any of the olefins was observed.[15]

In general, the crude materials were quite viscous and heat-sensitive liquids, thus preventing their purification by distillation or gas chromatography. However, purification was readily effected by column chromatography on either Florisil or Florisil PR.

Structures **4a-h** were assigned on the basis of spectral data and elemental analyses. The mass spectra and elemental analyses showed that the products were 1:1 carbene-olefin adducts. All products had molecular ions which were observed as symmetrical five-peak clusters corresponding to the presence of four bromine atoms.[16] The adducts generally fragmented in one of two ways. Some lost bromine atoms consecutively to give peaks at M − 80, M − 160, M − 240, and M − 320. Others, which had an unsubstituted cyclopropyl carbon, fragmented to give a $C_6H_2Br_4\cdot^+$ species at m/e 390.

The infrared spectrum of all adducts shows the –BrC=CBr– stretch at *ca.* 6.48 μ,[13,14] and the cyclopropyl ring at *ca.* 9.6 μ.[5,6,17] The nmr spectra feature absorptions similar to but shifted slightly downfield from the absorptions of model compounds obtained using diazo- and tetrachlorodiazocyclopentadiene with the same olefins.[3-6,18]

Although the cyclopropyl protons of spirocyclopropanes absorb between δ 0.80 and 0.25,[19-22] those of **4a-h** absorb between δ 2.0 and 3.0. This shift to lower fields is a general feature of spiro[2.4]heptadienes.[3,5,6,7,23] It has been suggested that this shift is due to delocalization of the electrons of the C–C bonds of the cyclopropanes into the proximate π system.[22]

Stereospecificity of the Addition Reaction.—A study was instituted to determine the stereospecificity of the addition of tetrabromocyclopentadienylidene (**5**) to olefins and thereby gain information regarding the spin state of the reacting carbene. Skell postulated that a singlet carbene would add in a single, concerted step, while a triplet would add in a two-step process which could destroy the stereochemical integrity of the product.[24-26] This diagnostic test for spin states has received widespread acceptance.[4,7,27-33]

Photolysis of **3** in *trans*-4-methyl-2-pentene produced a golden liquid in 89% yield which was identified by spectral means as *trans*-1,2,3,4-tetrabromo-6-methyl-7-isopropylspiro[2.4]hepta-1,3-diene (**6**). The nmr spectrum of **6** shows a complex multiplet centered at δ 2.2 which was assigned to the cyclopropyl protons and the isopropyl carbinyl proton. The cyclopropyl methyl group appears as a doublet at δ 1.55 (J = 6 Hz), while the isopropyl methyl groups were nonequivalent and

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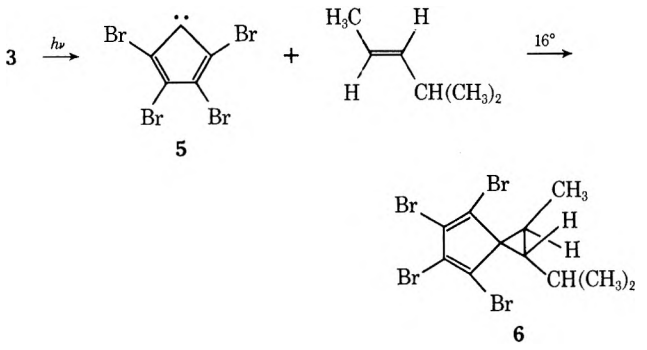
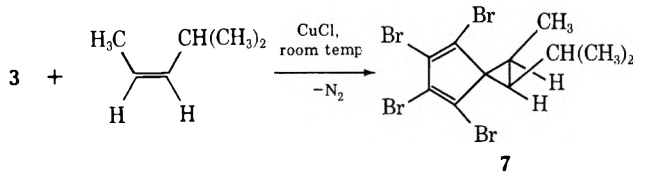


5

6

appear as two doublets at δ 0.79 (J = 6 Hz) and 1.11 (J = 6 Hz). The area ratios of the signals were correct for the assigned structure. The trans configuration for **6** was proven by preparing a sample of pure *cis*-1,2,3,4-tetrabromo-6-methyl-7-isopropylspiro[2.4]-hepta-1,3-diene (**7**) as described below and comparing



7

the nmr spectra of both **6** and **7**. The differences in the spectra showed conclusively that the photolysis of **3** in *trans*-4-methyl-2-pentene gave only the trans product.

The photolytic addition of **5** to the double bond of *cis*-4-methyl-2-pentene proceeded nonstereospecifically, as shown by an nmr spectrum (60% **6** and 40% **7**). However, a pure sample of **7** was obtained by the following alternate procedure. Cuprous chloride catalyzed the stereospecific addition of **3** to *cis*-4-methyl-2-pentene to produce pure **7** in 51% yield. This method of cyclopropane synthesis has been shown to produce stereospecific products.[7,34]

The nmr spectrum of **7** shows four areas of absorption which were quite similar to the absorptions of **6**. The doublets at δ 0.87 (J = 6.5 Hz) and 1.08 (J = 6.5 Hz) were assigned to the isopropyl methyl groups. A doublet at δ 1.58 (J = 6.5 Hz) was attributed to the cyclopropyl methyl group, and a complex absorption centered at δ 2.3 was assigned to the three methine protons.

McBee,[5] Jones,[7] and von E. Doering[35] have all noted the photoinstability of certain cyclopropanes. Under the photolytic conditions employed, **6** was stable while **7** completely isomerized to **6** after 1 hr. In order to prevent isomerization of **7** during the study of the stereospecificity of addition, filters were employed which prevented transmission of light below 350 nm.[36] Ultraviolet spectra shows that **7** did not absorb light above 340 nm while **3** absorbs out to 370 nm.

Using filtered light, **3** was again photolyzed in *cis*-4-methyl-2-pentene for 1 hr. Investigation of the products by nmr revealed the presence of both **6** (55%) and **7** (45%). In addition, the excess olefin was analyzed (glc) and shown to be 94.7% *cis*- and 5.3% *trans*-4-methyl-2-pentene.[39]

A possible, though unlikely, explanation for the observed nonstereospecificity of addition was that a high degree of discrimination by **5** for *trans*- rather than *cis*-4-methyl-2-pentene could give up to 55% **6**. However, when **3** was photolyzed in a mixture of *cis*- and *trans*-4-methyl-2-pentene (60:40) using filtered light, 32% of **7** was observed in the product. If the carbene discriminated to a large extent, less than 10% **7** would be produced. Therefore, the presence of 5% trans olefin observed after the photolysis does not account for the gross nonstereospecificity which was observed.

Photosensitization by **3** was also negated as a possible cause for the nonstereospecificity of the addition by irradiating equimolar amounts of **3** and **7** for 1 hr using filtered light. An nmr spectrum of the product showed that **7** was recovered unchanged.

The results of the stereospecificity study coupled with the reluctance of **5** to insert into C–H bonds[14,31] indicate that the properties of **5** can be best described as arising from the triplet state. However, being cognizant of several cautionary notes in the literature which have warned that both spin states must be observed in order to attach a high degree of certainty to a spin-state determination,[31,40] we attempted to observe chemically the singlet state of **5**. Jones and Rettig successfully accomplished such an experiment with fluorenylidene by scavenging the large triplet component with a diene, thus allowing the singlet component to become the major reacting species with *cis*-2-butene and to give stereospecific addition.[7] However, when **3** was photolyzed using filtered light in a 9:1 molar ratio of 1,3-butadiene to *cis*-4-methyl-2-pentene, the ratio of **6** to **7** was unchanged. Thus, we were unable to observe reaction due to the singlet state of **5**.

Intersystem crossing must occur quite readily for **5**. Several factors might influence the singlet to triplet conversion, such as resonance stabilization,[4] steric hindrance,[41] or a "heavy atom" effect.[42] The steric requirements of **5** are quite large compared to those of cyclopentadienylidene and tetrachlorocyclopentadienylidene, as was shown by its failure to add to the double bond of 2,3-dimethyl-2-butene.[16] This steric problem of **5** might allow many nonreactive collisions to occur,and thus give the carbene time to undergo intersystem crossing. In addition, heavy atoms are known to enhance the probability of spin-forbidden transitions through coupling of spin and orbital angular momenta. The basic requirement for the "heavy atom" effect is that the π electrons undergoing the transition spend a small amount of time on the heavy atom. This process could occur in **5** and account for the facile intersystem crossing.

This work provides chemical evidence for the formation of triplet tetrabromocyclopentadienylidene. The interesting chemical differences between cyclopentadienylidene and tetrabromocyclopentadienylidene which we have pointed out may provide the first instance of a "heavy atom" effect in carbene chemistry.

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Experimental Section

Procedure and Equipment.—All melting points are uncorrected Elemental analyses were determined by Dr. C. S. Yeh and her staff at Purdue University. Nuclear magnetic resonance spectra were determined using a Varian A-60A nmr spectrometer. Carbon tetrachloride was used as the solvent (unless otherwise noted) employing tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 221 infrared spectrophotometer. Ultraviolet spectra were recorded on a Bausch and Lomb Spectronic 505 spectrophotometer or a Cary 15 using spectrophotometric grade *n*-hexane. Mass spectra were determined on a Hitachi Perkin-Elmer HU-6D high-resolution mass spectrometer. Reported *m/e* values are for the monoisotopic (Br = 79) peak. Gas chromatographic analyses of the olefins were conducted using a 12 ft × 0.25 in. stainless steel column packed with 20% silver nitrate–benzyl cyanide on 60/80 mesh Chromosorb P. The light source used in the photolyses was a 400-W General Electric H400 A33-1 mercury lamp powered by a Jefferson 237-421 mercury lamp ballast transformer. Styrene and α-methylstyrene were of commercial grade and were distilled immediately before use. All other olefins were also commercial grade, but were used without further purification. The solvents utilized in column elution chromatography were distilled prior to use.

Hexabromocyclopentadiene (1).—This compound was prepared using several modifications of Straus' procedure.[12]

Tetrabromocyclopentadienone Hydrazone (2).—1 (54.0 g, 0.1 mol) was dissolved in 800 ml of anhydrous ethyl ether. The solution was immersed in an ice bath throughout the course of the reaction. Anhydrous hydrazine (4.8 g, 0.15 mol) was poured into 200 ml of anhydrous ethyl ether, and methanol was added until the hydrazine dissolved. The hydrazine solution was then added dropwise to the magnetically stirred solution of 1. As the reaction proceeded, the yellow ethereal solution turned red-brown and a precipitate formed. After complete addition, the solution was filtered and evaporated to dryness. A large, fritted glass Büchner funnel was three-fourths filled with silica gel using hexane as solvent. An oversized piece of filter paper was fitted on top, and the large mass of solid was taken up in hexane as completely as possible and filtered through the silica gel. 1 (37.6 g, 0.069 mol) was recovered from the eluent. The hydrazone 2 (6.6 g, 54% yield) was insoluble in the hexane and was recovered from the top of the filter paper. This material was used without further purification. A sample purified by recrystallization from carbon tetrachloride gave pure 2: mp 145° dec; ir (KBr) 2.95, 3.07, 3.15, 6.22, 6.44 (s), 6.56, 6.82, 7.92, 8.22, 8.30, 9.80, 13.05, 14.90 μ; uv max (methanol) 343 nm (log ε 4.33); *m/e* 406 (molecular ion, base ion), 377 (loss of N_2H), 327 (loss of Br), 297 (loss of BrN_2H).

Anal. Calcd for $C_5H_2Br_4N_2$: C, 14.65; H, 0.49; Br, 78.01; N, 6.84. Found: C, 14.72; H, 0.71; Br, 78.13; N, 6.94.

Tetrabromodiazocyclopentadiene (3).—Lead tetraacetate[43] (30 g, 67.6 mmol) was suspended in 500 ml of anhydrous ethyl ether containing magnesium sulfate (10 g). 2 (9.3 g, 22.6 mmol) was dissolved in anhydrous ethyl ether and added dropwise to the magnetically stirred lead tetraacetate solution over a 45-min period. After complete addition, stirring was continued for an additional 45 min. The solution was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in hexane and filtered through silica gel. Evaporation of the yellow fraction and recrystallization from hexane gave 7.5 g (81.3% yield) of 3: mp 132° dec; ir (CCl_4) 4.75 (s), 4.82 (s), 6.70 (m), 6.98 (w), 7.10 (w), 7.25 (s), 7.56 (w), 8.10 (s), 9.58 μ (w); *m/e* 404 (molecular ion), 376 (base ion, loss of N_2); uv max (hexane) 310 nm (log ε 4.24), 318 (shoulder, 4.21).

Anal. Calcd for $C_5Br_4N_2$: C, 14.73; Br, 78.40; N, 6.87. Found: C, 14.92; Br, 78.70; N, 6.70.

1,2,3,4-Tetrabromo-6,6,7-trimethylspiro[2.4]hepta-1,3-diene (4a).—A solution of 3 (4.08 g, 10 mmol) in 2-methyl-2-butene (100 ml) was photolyzed for 17 hr at 16°. The crude oil which was obtained upon removal of the excess solvent was chromatographed on Florisil PR. Hexane eluted a light yellow oil which could not be induced to crystallize. Chromatography again on Florisil PR gave 3.55 g (79% yield) of pure 4a: ir (neat) 6.48 (s), 9.60 μ (m); nmr δ 2.61 (1, q, J = 6.5 Hz, cyclopropyl), 1.67 (6, s, C-6 methyl groups), 1.55 (3, d, J = 6.5 Hz, C-7 methyl); *m/e* 446 (molecular ion), 366 (base ion, loss of HBr).

(43) 2,3,4,5-Tetrachlorocyclopentadienone hydrazone was readily oxidized to tetrachlorodiazocyclopentadiene using mercuric oxide or silver oxide.[5,6] However, 2 was inert to these reagents.

Anal. Calcd for $C_{10}H_{10}Br_4$: C, 26.70; H, 2.24; Br, 71.06. Found: C, 26.76; H, 2.33; Br, 70.99.

Preparation of Other Spiro[2.4]heptadienes.—These were prepared as described for 4a except that 50 ml of the olefin was generally used and the photolyses were from 1 to 3 hr. All purifications were effected by column elution chromatography using Florisil or Florisil PR as the support and eluting with hexane.

1,2,3,4-Tetrabromo-6-*n*-butylspiro[2.4]hepta-1,3-diene (4b).—The yield of viscous liquid identified as 4b was 97%: nmr δ 0.88 (3.2, m), 1.26 (4.3, m), 1.93 (5.0, m); ir (neat) 6.47 (s), 9.61 μ (m); *m/e* 460 (molecular ion), 390 (base ion, loss of C_5H_{10}).

Anal. Calcd for $C_{11}H_{12}Br_4$: C, 28.48; H, 2.61. Found: C, 29.26; H, 2.66.

1,2,3,4-Tetrabromo-6-*tert*-butylspiro[2.4]hepta-1,3-diene (4c).—Recrystallization from hexane gave a 95% yield of 4c: mp 66–66.5°; ir (CCl_4) 3.35 (m), 6.44 (m), 8.11 (s), 8.23 (s), 9.21 (m), 9.60 (m), 10.22 (s), 11.65 μ (m); nmr δ 1.12 (3.04, s, *tert*-butyl), 2.1 (1.0, m, cyclopropyl); *m/e* 460 (molecular ion), 390 (base ion, loss of C_5H_{10}); uv max (hexane) 253 nm (log ε 3.90), 286 (3.55).

Anal. Calcd for $C_{11}H_{12}Br_4$: C, 28.48; H, 2.61; Br, 68.91. Found: C, 28.64; H, 2.79; Br, 68.71.

1,2,3,4-Tetrabromo-6-chloromethylspiro[2.4]hepta-1,3-diene (4d).—Recrystallization from methanol gave a 95% yield of 4d: mp 76–77.5°; ir (KBr) 6.47 (s), 8.25 (s), 8.32 (s), 9.20 (m), 9.85 (m), 10.30 (s), 11.55 (s), 14.33 μ (s); nmr δ 4.02 (2, m, methylene), 2.57 (1.1, quintet, cyclopropyl methine), 1.97 (1.9, m, cyclopropyl methylene); *m/e* 452 (molecular ion), 390 (base ion, loss of C_2H_3Cl); uv max (hexane) 249 nm (log ε 3.85), 290 (3.54).

Anal. Calcd for $C_8H_5Br_4Cl$: C, 21.06; H, 1.10; Br, 70.07; Cl, 7.77. Found: C, 21.24; H, 0.90; Br, 70.10; Cl, 7.67.

1,2,3,4-Tetrabromo-6-phenylspiro[2.4]hepta-1,3-diene (4e).—4e was isolated as a viscous, yellow liquid: ir (neat) 6.48 (m), 6.70 (s), 6.90 (s), 8.30 (s), 9.70 (m), 10.10 (s), 10.26 (s), 11.08 (s), 13.10 (s), 14.40 μ (s); nmr ($CDCl_3$) δ 7.15 (5.0, s, aromatic), 3.46 (1, t, benzyl), 2.17 (2 m, methylene); *m/e* 480 (molecular ion), 242 (base ion, loss of HBr_3).

Anal. Calcd for $C_{13}H_8Br_4$: C, 32.27; H, 1.67. Found: C, 33.00; H, 1.60.

1,2,3,4-Tetrabromo-6-vinylspiro[2.4]hepta-1,3-diene (4f).—Recrystallization from methanol provided an 87% yield of 4f: mp 63–64°; nmr δ 2.02 (2, d, J = 9 Hz, methylene), 2.81 (1, q, cyclopropyl methine), 5.26 (2, m, vinyl), 6.23 (1, m, vinyl); *m/e* 429 (molecular ion), 271 (base ion, loss of Br_2).

Anal. Calcd for $C_9H_5Br_4$: C, 24.92; H, 1.39; Br, 73.69. Found: C, 24.64; H, 1.19; Br, 74.40.

1,2,3,4-Tetrabromo-6-methyl-6-phenylspiro[2.4]hepta-1,3-diene (4g).—Recrystallization from hexane afforded an 87% yield of 4g: mp 134–135°; ir (CCl_4) 6.51 (s), 6.71 (s), 6.94 (s), 8.19 (s), 9.56 (m), 9.78 (w), 13.20 (s), 14.40 μ (s); nmr ($CDCl_3$) δ 1.98 (2.9, s, methyl), 2.44 (2, q, J = 5.5 Hz, cyclopropyl), 7.38 (5.1, s, aromatic); *m/e* 494 (molecular ion), 415 (base ion, loss of Br).

Anal. Calcd for $C_{14}H_{10}Br_4$: C, 33.77; H, 2.02; Br, 64.20. Found: C, 33.93; H, 2.25; Br, 63.86.

Norcarane-7-spiro-5′-(1′,2′,3′,4′-tetrabromocyclopenta-1′,3′-diene) (4h).—Recrystallization from methanol provided a 56% yield of 4h: mp 99–99.5°; ir (CCl_4) 3.39 (s), 3.47 (s), 6.48 (s), 6.92 (s), 8.1 (s), 8.51 (m), 9.7 (w), 10.2 μ (s); nmr δ 2.5–1.5 (broad complex absorption).

Anal. Calcd for $C_{11}H_{10}Br_4$: C, 28.60; H, 2.18; Br, 69.21. Found: C, 28.76; H, 2.37; Br, 68.98.

***trans*-1,2,3,4-Tetrabromo-6-methyl-7-isopropylspiro[2.4]hepta-1,3-diene (6).**—6 was isolated as a viscous liquid in 89% yield: nmr δ 0.79 (1, d, J = 6 Hz, isopropyl methyl), 1.11 (1, d, J = 6 Hz, isopropyl methyl), 1.55 (1, d, J = 6 Hz, cyclopropyl methyl), 2.2 (1, m, methine).

***cis*-1,2,3,4-Tetrabromo-6-methyl-7-isopropylspiro[2.4]hepta-1,3-diene (7).**—To a solution of 3 (1.0 g, 2.45 mmol) in 25 ml of *cis*-4-methyl-2-pentene was added 0.2 g of cuprous chloride. Evolution of N_2 occurred slowly from the magnetically stirred solution. After 39.5 hr at room temperature, the olefin was distilled off and was shown to be pure *cis*-4-methyl-2-pentene (glc). The dark mass was chromatographed on Florisil PR using cyclohexane and gave 0.58 g of a light, viscous liquid (51% yield) identified as 7: nmr δ 0.87 (d, J = 6.5 Hz), 1.08 (d, J = 6.5 Hz) 1.58 (d, J = 6.5 Hz), 2.3 (m); uv max (hexane) 254 nm (log ε 3.97), 286 (3.61).

Photolysis of 3 in *cis*-4-Methyl-2-pentene.—*cis*-4-Methyl-2-pentene (50 ml, 99.5% cis) containing 3 (1.9 g, 4.65 mmol) was deoxygenated for 20 min by bubbling dry nitrogen through the

solution. The olefin was checked at this point and it was found that no isomerization had yet occurred (glc). The olefin (at 16°) was not able to dissolve the entire quantity of **3**. Both the amount of nitrogen released and the olefin composition were monitored during the photolysis. The photolysis was stopped after 75 ml of nitrogen had evolved, indicating that *ca.* three-fourths of **3** had decomposed. The olefin composition at this point was 92.6% *cis*- and 7.4% *trans*-4-methyl-2-pentene. The isolated material, having a total weight of 1.9 g, consisted of crystals (**3**) and an oil. Nmr analysis of the product mixture showed that both **6** (57%) and **7** (43%) were formed.

Irradiation of 6 in Cyclohexane.—A solution of **6** (50 mg) in cyclohexane was brought to 16° and irradiated for 8 hr. The excess cyclohexane was removed under reduced pressure and the remaining oil was analyzed by nmr. Compound **6** remained unchanged. **7** was not observed under these conditions.

Irradiation of 7 in Cyclohexane.—A solution of **7** (50 mg) in cyclohexane (50 ml) was brought to 16° in a Pyrex tube and irradiated for 1 hr. The excess solvent was stripped off, leaving an oil which was analyzed by nmr. Nearly complete isomerization to **6** was found. A small peak due to **7** was visible (<5%).

Irradiation of 7 in Cyclohexane Using Filtered Light.—A solution of **7** (0.15 g, 0.325 mmol) in 100 ml of cyclohexane was irradiated for 1 hr at 16° using filtered light. The filters employed were 5 cm of $CuSO_4 \cdot 5H_2O$ in H_2O (100 g/l.)[37] and 1 cm of 2,7-dimethyldiaza-3,6-cycloheptadiene-1,6-perchlorate in H_2O (0.1 g/100 ml).[37,38] These filters cut off all light below 350 nm. All of the apparatus which remained above the aqueous copper sulfate solution was covered with aluminum foil to prevent unfiltered light from striking the solution. Analysis of the product isolated showed that pure **7** was unchanged.

Photolysis of 3 in *cis*-4-Methyl-2-pentene Using Filtering Solutions.—*cis*-4-Methyl-2-pentene (50 ml) containing **3** (1.0 g, 2.45 mmol) was irradiated for 1 hr at 16° employing both filtering solutions as previously described. The starting olefin was stripped off and was found to be 94.7% *cis*- and 5.3% *trans*-4-methyl-2-pentene (glc). Analysis of the dark oil product showed that both **6** (55%) and **7** (45%) were present (nmr analysis using peak heights of the cyclopropyl methyl absorptions).

Photolysis of 3 in a Mixture of *cis*- and *trans*-4-Methyl-2-pentene.—A mixture of *cis*- and *trans*-4-methyl-2-pentene (*ca.* 60:40) containing **3** (0.5 g, 1.22 mmol) was irradiated at 16° for 1.5 hr using filtered light. Stripping off to the excess olefins left an oil in which **6** and **7** were observed in the ratio of 68:32, respectively.

Attempted Photosensitized Isomerization of 7 by 3.—A solution containing **3** (0.44 g, 1.08 mmol) and **7** (0.50 g, 1.08 mmol) in cyclohexane (100 ml) was photolyzed at 16° for 1 hr employing filtered light. After the cyclohexane was stripped off, nmr analysis of the product showed that **7** was unchanged by the conditions employed.

Photolysis of 3 in *cis*-4-Methyl-2-pentene Containing 90 Mol % 1,3-Butadiene.—*cis*-4-Methyl-2-pentene (3.46 g, 41.1 mmol) containing **3** (1.0 g, 2.45 mmol) and 1,3-butadiene (20.0 g, 270 mmol) was irradiated for 3 hr in a sealed ampoule using filtered light. The ampoule was opened, allowing the excess 1,3-butadiene to boil off. The excess cis olefin was stripped off, leaving a light yellow oil. Analysis of the mixture by nmr showed that both **6** and **7** were present. The trans product (**6**) was the major product (*ca.* 55%), but difficulties in analysis make this number less reliable than the others. It is probably good within 15%.

Registry No.—**1**, 14310-17-9; **2**, 38123-54-5; **3**, 38123-55-6; **4a**, 38123-56-7; **4b**, 38229-30-0; **4c**, 38123-57-8; **4d**, 38123-58-9; **4e**, 38123-59-0; **4f**, 38123-60-3; **4g**, 38123-61-4; **4h**, 38123-62-5; **6**, 38123-63-6; **7**, 38123-64-7.

Amidrazones. II.[1] Tautomerism and Alkylation Studies

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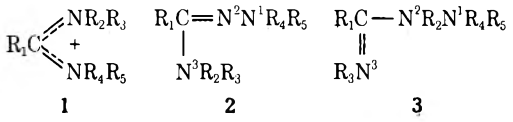
Amidrazone tautomers are exclusively formed from the reaction of *N*-methylbenzimidoyl chloride and 1,1-disubstituted hydrazines. A series of amidrazones and hydrazide imides have been prepared and their sites of alkylation with methyl iodide have been established. With the exception of the N^1,N^1-dimethyl substituted amidrazones **7**, **9**, and **11**, which undergo methylation at N^1, the other compounds displayed amidine-type behavior and afforded charge-delocalized cations resulting from substitution at either N^2 or N^3.

The reaction of amidines with alkyl halides results in alkylation of the imino nitrogen to give amidinium cations with the charge-delocalized structure **1**.[2] However, aside from the diverse results reported on three compounds in paper I[1] of this series, little is known of the site of alkylation in amidrazones (**2**) or hydrazide imides (**3**). The latter compounds possess three potential sites for alkylation and the position of alkylation could be expected to depend on a number of factors, including the nature of the substituents bonded to the nitrogen atoms and whether the compound reacting with the alkylating agent has structure **2** or **3**.



1 **2** **3**

This paper reports a study of structural effects on the site of alkylation of amidrazones and hydrazide imides with methyl iodide and some observations on amidrazone–hydrazide imide tautomerism. The recommended[3] method for numbering the nitrogen atoms in amidrazones and hydrazide imides is employed throughout and is illustrated in structures **2** and **3**.

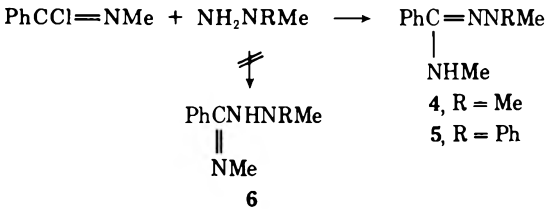
Tautomerism Studies.—Amidrazone–hydrazide imide tautomerism is possible with appropriately substituted compounds **2** and **3** (R_2 = H). In our earlier paper,[1] we established from spectroscopic data that compound **25** exists exclusively in the hydrazide imide form. However, we have found that, when the N^3-phenyl group is replaced by N^3-methyl, the amidrazone is apparently the exclusively formed tautomer. Reaction of *N*-methylbenzimidoyl chloride with 1,1-dimethylhydrazine and 1-methyl-1-phenylhydrazine gave *N*-methylbenzamide dimethylhydrazone (**4**) and *N*-methylbenzamide methylphenylhydrazone (**5**), respectively. The nmr spectrum of both **4** and **5** displayed N^3-methyl signals that are spin coupled to NH. The observed methyl doublets (J = 4 Hz) collapsed to singlets on deuterium exchange. These results are in-

(1) For paper I see R. F. Smith, D. S. Johnson, C. L. Hyde, T. C. Rosenthal, and A. C. Bates, *J. Org. Chem.*, **36**, 1155 (1971).

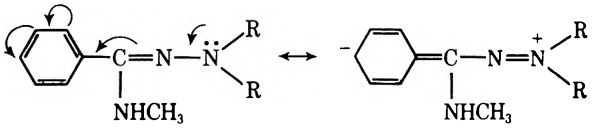
(2) For a discussion of amidinium salts, see P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 1, W. A. Benjamin, New York, N. Y., 1966, p 181.

(3) D. G. Nielsen, R. Roger, J. W. M. Heattie, and L. R. Newlands, *Chem. Rev.*, **70**, 151 (1970).

compatible with the structure of the hydrazide imide tautomer, **6**.

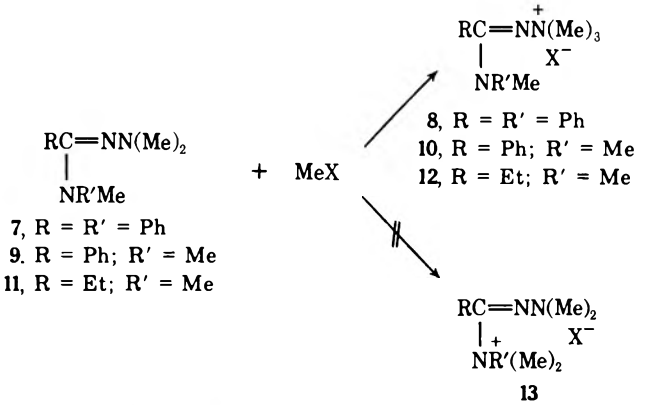


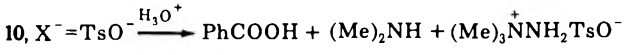
Simple resonance considerations most readily provide an explanation for the selective tautomerism described above. Conjugation of the N^3-phenyl group with the carbon–nitrogen double bond in **25** (and the currently reported **23**) provides enhanced stabilization to these compounds in their hydrazide imide forms. In **4** and **5**, hydrazone resonance[4] can be assumed to provide enhanced stabilization to the amidrazone forms of these compounds. Gol'din and coworkers[5] have



recently shown that N^3-unsubstituted compounds (**2**, $R_2 = R_3 = H$) exist exclusively in the amidrazone form.

Alkylation Studies.—*N*,*N*-Dimethylbenzamide dimethylhydrazone (**9**) and *N*,*N*-dimethylpropionamide dimethylhydrazone (**11**) were found to react with methyl iodide in a manner analogous to that previously reported for *N*-methylbenzanilide dimethylhydrazone (**7**); *i.e.*, alkylation occurred at N^1 providing the N^1-quaternized salts **10** and **12**, respectively. The nmr spectra of **10** and **12** [$-N(CH_3)_2$ and $-{}^+N(CH_3)_3$ singlets] did not permit distinction between their assigned structures and the unlikely structure **13**.





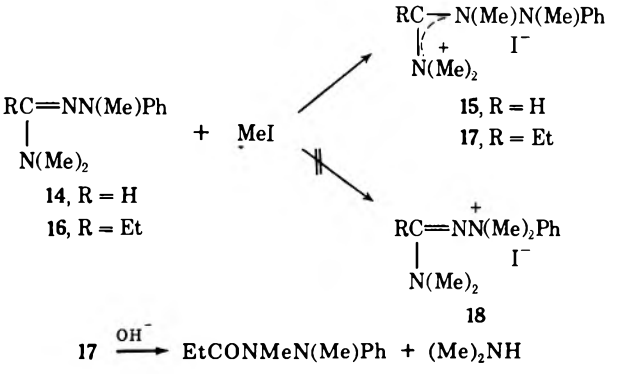
However, hydrolytic degradation provided confirmation of structure **10**. Acid hydrolysis of the latter compound (as its *p*-toluenesulfonate salt) gave benzoic acid, dimethylamine, and 1,1,1-trimethylhydrazinium *p*-toluenesulfonate. The structure of **8** has also been previously confirmed by hydrolytic degradation.[1]

(4) P. A. S. Smith and E. E. Most, Jr., *J. Org. Chem.*, **22**, 358 (1957).

(5) G. S. Gol'din, V. G. Poddubnyi, A. A. Simova, G. S. Shor, and E. A. Rybakov, *Zh. Org. Khim.*, **5** (8), 1440 (1969); *Chem. Abstr.*, **71**, 1123762 (1969).

Reaction of methyl iodide with the *N*,*N*-dimethylformamide methylphenylhydrazone (**14**)[6] and *N*,*N*-dimethylpropionamide methylphenylhydrazone (**16**)[7] resulted in alkylation at N^2, affording the charge-delocalized salts **15** and **17**, respectively. The nmr spectra of these salts show three upfield singlets with integrated intensity ratios of 6:3:3. Structure **18** is also compatible with the nmr spectra if nonequivalence of the two N^3-methyl groups is assumed due to restricted rotation.[8] However, structure **18** was eliminated from consideration by establishing that **17** affords 1,2-dimethyl-1-phenyl-2-propionylhydrazine on basic hydrolysis. Furthermore, no coalescence of the methyl signals in **17** was observed on heating to 140° in DMSO-d_6.

Assuming the planar geometry assigned to amidinium cations,[9a] models indicate some steric crowding in completely substituted salts of the type **15** and **17**. Hence, we conclude that, in the N^1-dimethylamidrazones **7**, **9**, and **11**, the factor which determines N^1 as the site of substitution is predominately steric in nature, since substitution at N^2 would result in the formation of sterically crowded cations. In **14** and **16** the nucleophilicity of N^1 is diminished by the electron-withdrawing resonance effect of the phenyl group and alkylation occurs at N^2 to give the resonance-stabilized (albeit crowded) salts **15** and **17**.



Reaction of amidrazones **4** and **5** with methyl iodide gave N^2-methylated salts to which we have assigned the charge-delocalized structures **19** and **20**, respectively. Neutralization of these salts afforded the hydrazide imides **21** and **22**. A plausible explanation for the alkylation of **4** at N^2 rather than N^1 (as found for the N^1,N^1-dimethylamidrazones **7**, **9**, and **11**) may be found by comparison of the cations obtained from these reactions. If an "inside" position for the strongly deshielded N^3 hydrogen is assumed for **19**, a likely structure for this cation is that shown. This structure is less sterically crowded than the analogous structures which would result from the N^2-methylation of **7**, **9**, or **11**, and it also may be considered to have enhanced stabilization owing to intramolecular hydrogen bonding.

(6) H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Chem. Ber.*, **92**, 837 (1959).

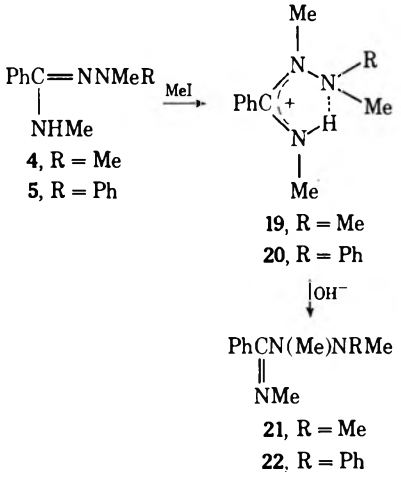
(7) H. Rapoport and R. M. Bonner, *J. Amer. Chem. Soc.*, **72**, 2783 (1950).

(8) For a recent review see C. G. McCarty in "The Chemistry of the Carbon–Nitrogen Double Bond," S. Patai, Ed., Interscience, London, 1969, p 363.

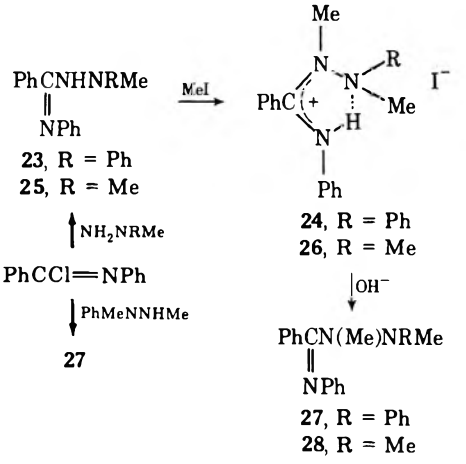
(9) (a) From nmr studies the rotational barrier in amidinium cations has been estimated to be in the same range as that reported for amides (7–18 kcal/mol): G. S. Hammond and R. C. Neuman, Jr., *J. Phys. Chem.*, **67**, 1655 (1963). (b) The C–N rotational barrier in the tetramethylformamidinium cation has been determined as 17.5 ± 1.5 kcal/mol: J. Ranft and S. D. Dähne, *Helv. Chim. Acta*, **47**, 1160 (1964).

An analogous, chelated structure also seems reasonable for **20**. However, the nmr spectra of **20** displays characteristics that are typical of compounds exhibiting hindered bond rotation. When the nmr spectrum of **20** was determined in $CDCl_3$, upfield methyl signals were observed at δ 2.81, 2.87, and 3.30. In addition, two singlets of equal intensity were observed at δ 2.97 and 3.50 which integrated for approximately 0.5 H. The low-intensity peaks were found not to be due to impurities. When the spectrum of **20** was determined in DMSO-d_6, singlets of equal intensity were observed at δ 2.65 (sharp), 2.75 (broad), and 3.18 (broad). Peak sharpening was observed on warming the DMSO-d_6 solution.

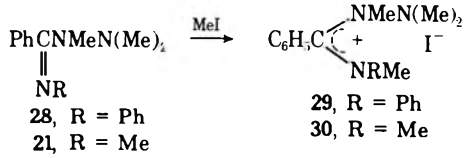
These results, coupled with those described below for **24**, indicate that the N^1- and N^2-methyl groups of **20** assume two unequally populated, magnetically nonequivalent conformations in $CDCl_3$ and the interconversion of these forms is facilitated in DMSO-d_6. Restricted rotation about either the C–N[2] [9] or N–N[10] bonds could account for the spectral characteristics of **20**. Coalescence in DMSO-d_6 could be accounted for by assuming that the rotational barrier (either C–N or N–N) is lowered by affording NH the opportunity to hydrogen bond with the acceptor solvent, thus destabilizing structure **20**.



Results similar to those described above for the conversion of **5** to **20** were obtained for the methylation of **23**. The latter compound also undergoes methylation at N[2] on reaction with methyl iodide to give a salt to which we have assigned the charge-delocalized structure **24** to the cation. In the conversion of **23** to **24**, we have assumed that the alkylation is accompanied by a N[2] to N[3] proton transfer. The latter assumption seems valid, since the N^1,N^1-dimethyl analog (**25**) has been shown by us[1] to give **26** on treatment with methyl iodide. The iodide **24** was amorphous and was characterized by conversion to the picrate and free base **27**. The structure of the latter compound was firmly established by its synthesis from *N*-phenylbenzimidoyl chloride and 1,2-dimethyl-1-phenylhydrazine. The picrate of **24** also displayed a nmr spectrum that indicated hindered rotation about either the C–N[2] or N–N bonds. When determined in DMSO-d_6, **24** picrate displayed methyl singlets of equal intensity at δ 2.95 and 3.45, each of which integrated for approximately 2.5 H, and low-intensity singlets at δ 3.02 and 3.45, each of which integrated for approximately 0.5 H. On warming the DMSO-d_6 solutions from 34 to 50°, coalescence was observed and peak sharpening occurred on further heating. Cooling to 34° restored the original four-singlet pattern. As with **20**, which differs only by having an N^3-methyl substituent in place of the N^3-phenyl substituent in **24**, a choice between C–N[2] and N–N rotation cannot be made with certainty.



In paper I, we reported that the completely substituted hydrazide imide, **28**, gives **29** on reaction with methyl iodide. We have found that substitution of the N^3-phenyl group of **28** by a methyl group does not affect the site of methylation, since the tetramethylated hydrazide imide, **21**, also undergoes substitution at N[3] to give a salt of analogous structure (**30**). It is of interest to note that these two N[1],N[1]-dimethylated hydrazide imides undergo substitution with methyl iodide at N[3] while the N[1],N[1]-dimethylated amidrazones **7**, **9**, and **11** undergo methylation at N[1]. The differences in alkylation site in these compounds can be best explained by simple steric considerations. The nucleophilicity of the hydrazinic moiety of **21** and **28** is decreased by the steric effect of the methyl substituent at N[2] in these hydrazide imides. Thus, the less hindered imino nitrogen (N[3]) becomes the most nucleophilic and the "crowded," charge-delocalized cations **29** and **30** are preferentially formed.



This study indicates that, with the exception of the N^1,N^1-dimethyl-substituted amidrazones, **7**, **9**, and **11**, amidrazones and hydrazide imides exhibit amidine-type behavior when treated with alkyl halides; *i.e.*, alkylation occurs at either N[2] or N[3] to produce charge-delocalized (amidinium type) ions.

Experimental Section

Melting points are uncorrected and were determined with a Mel-Temp apparatus. Nmr spectra were determined with a Perkin-Elmer R-20 spectrometer utilizing hexamethyldisiloxane as the internal standard.

N-**Methylbenzamide Dimethylhydrazone** (**4**).—*N*-Methylbenzimidoyl chloride[11] (15.3 g) was slowly added to a stirred

(10) For discussion of N–N rotational barriers and leading references see M. J. S. Dewar and B. Jennings, *J. Amer. Chem. Soc.*, **91**, 3655 (1969).

(11) I. Ugi, F. Beck, and U. Fetzer, *Chem. Ber.*, **95**, 126 (1962).

solution containing 6.0 g of 1,1-dimethylhydrazine and 10.1 g of triethylamine in 50 ml of dry benzene. After an initial exothermic reaction, the reaction mixture was kept at room temperature overnight. An equal volume of benzene was added to the reaction mixture and the precipitated triethylamine hydrochloride was removed by two extractions with 50 ml of water. The dried benzene extract was evaporated *in vacuo* at 100° and the residue was distilled, giving 10.4 g of product as a light yellow oil: bp 134–136° (20 mm); nmr ($CDCl_3$) δ 2.51 [d, 3, J = 4 Hz, $NHCH_3$ (s with $NDCH_3$)], 2.33 [s, 6, $N(CH_3)_2$], 6.0 (broad, 1, $NHCH_3$), and 7.3 (m, 5).

Anal. Calcd for $C_{10}H_{15}N_3$: C, 67.8; H, 8.5; N, 23.7. Found: C, 67.4; H, 8.5; N, 23.8.

N-**Methylbenzamide Methylphenylhydrazone** (**5**).—Reaction of 10.0 g of *N*-methylbenzimidoyl chloride with a solution containing 7.9 g of 1-methyl-1-phenylhydrazine and 6.6 g of triethylamine in 50 ml of dry benzene afforded (after work-up as described for **4**) a yellow oil which was treated with 50 ml of petroleum ether (bp 60–80°) and refrigerated for 3 days. The partially solidified reaction mixture was filtered and the yellow solid was washed with cold petroleum ether, giving 6.2 g of crude **5**, mp 50–65°. Several recrystallizations from petroleum ether gave yellow crystals: mp 72–73°; nmr ($CDCl_3$) δ 2.62 [d, 3, J = 4 Hz, $NHCH_3$ (s with $NDCH_3$)], 2.92 (s, 3), 5.85 (broad, 1, $NHCH_3$), 7.0 (m, 10).

Anal. Calcd for $C_{15}H_{17}N_3$: C, 75.3; H, 7.2. Found: C, 75.3; H, 7.3.

N,*N*-**Dimethylbenzamide Dimethylhydrazone** (**9**).—This compound was obtained in 54% yield by the condensation of *N*,*N*-dimethylbenzamide with 1,1-dimethylhydrazine.[7] Distillation gave **9** as a yellow oil: bp 124–128° (20 mm); nmr (neat) δ 2.09 (s, 6), 2.57 (s, 6), 7.22 (s, 5).

Anal. Calcd for $C_{11}H_{17}N_3$: C, 69.1; H, 9.0; N, 22.0. Found: C, 69.2; H, 9.0; N, 21.8.

The picrate was recrystallized from ethanol, mp 121–122°.

Anal. Calcd for $C_{17}H_{20}N_6O_7$: C, 48.6; H, 4.8; N, 20.0. Found: C, 48.4; H, 4.7; N, 19.8.

1,1,1-**Trimethyl-2-(α-dimethylaminobenzylidene)hydrazinium Salts** (**10**).—One gram of **9** was treated with 2 ml of methyl iodide. After 24 hr, the solution was diluted with ether to give 1.4 g of **10** iodide, mp 132° (prior sintering). Recrystallization from ethanol gave white crystals: mp 154–155° (sample inserted at 140° and heated 2°/min); nmr (D_2O) δ 2.75 (s, 6), 3.15 (s, 9), 7.5 (m, 5).

Anal. Calcd for $C_{12}H_{20}IN_3$: C, 43.3; H, 6.1; N, 12.6. Found: C, 43.3; H, 5.9; N, 12.6.

The tosylate salt of **10** was obtained by treating 2 g of **13** with 3 ml of methyl *p*-toluenesulfonate. After 24 hr at room temperature, the reaction mixture was warmed on the steam bath, cooled, and diluted with ether. The gummy salt was washed with several portions of dry ether and dried at 100° *in vacuo:* nmr (D_2O) δ 2.92 (s, 9), 2.51 (s, 6), 2.12 (s, 3), 7.2 (m, 9).

Acid Hydrolysis of 10.—A solution containing 10.0 g of **10** iodide in 100 ml of 2 *N* HCl was heated under reflux for 30 hr. On cooling, 4.0 g of crude benzoic acid, mp 113–114° (confirmed by ir), precipitated. A portion of the filtrate was made basic and heated to boiling. Dimethylamine was evolved and trapped as the picrate, mp 160–162°. Treatment of another portion of the basic solution with benzenesulfonyl chloride gave *N*,*N*-dimethylbenzenesulfonamide, mp 41–43°. Identity of the derivatives was established by comparison of their ir spectra with those of authentic samples. Concentration of the acid solution resulted in the formation of iodine and attempts to isolate a 1,1,1-trimethylhydrazinium salt failed.

A solution of the tosylate salt (3.5 g) in 20 ml of 2 *N* HCl was heated under reflux for 24 hr. After filtration of benzoic acid, the solution was evaporated *in vacuo* to a solid. Recrystallization from ethanol afforded 1.2 g of crude 1,1,1-trimethylhydrazinium tosylate, mp 198–202°. Identity was established by comparison of its ir and nmr spectra with that of an authentic sample.[1]

N,*N*-**Dimethylpropionamide Dimethylhydrazone** (**11**).—This compound was obtained in 55% yield by condensation of *N*,*N*-dimethylpropionamide with 1,1-dimethylhydrazine.[7] Distillation gave **11** as a colorless oil: bp 65–66° (25 mm); nmr (neat) δ 0.97 (t, 3, J = 8 Hz), 2.55 (q, 2, J = 8 Hz), 2.20 (s, 6), 2.73 (s, 6).

Anal. Calcd for $C_7H_{17}N_3$: C, 58.7; H, 12.0; N, 29.3. Found: C, 58.9; H, 12.3; N, 29.5.

The picrate was recrystallized from ethanol, mp 136–137°.

Anal. Calcd for $C_{13}H_{20}N_6O_7$: C, 41.9; H, 5.4; N, 22.6. Found: C, 42.1; H, 5.6; N, 22.7.

1,1,1-**Trimethyl-2-(α-dimethylaminopropylidene)hydrazinium Iodide** (**12**).—Two grams of **11** was treated with 4 ml of methyl iodide. After 24 hr at room temperature **12** separated as an oil, which was dissolved in acetone. Addition of dry ether to the acetone solution precipitated the product as a hygroscopic solid, 2.7 g, mp 98–101°. Recrystallization from acetone–ether gave white crystals: mp 99–101°; nmr (D_2O) δ 1.18 (t, 3, J = 8 Hz), 2.70 (q, 2, J = 8 Hz), 2.90 (s, 6), 3.45 (s, 9).

Anal. Calcd for $C_8H_{20}IN_3$: C, 33.9; H, 7.1; N, 14.7. Found: C, 33.6; H, 7.2; N, 14.3.

Dimethyl(1,2-dimethyl-2-phenylhydrazinomethylene)ammonium Iodide (**15**).—Three grams of **14**[6] was treated with 6 ml of methyl iodide. After 2 days at room temperature, the product was precipitated by addition of 20 ml of dry ether, giving 3.2 g of **15**, mp 151–152°. Recrystallization from ethanol gave white crystals: mp 156–157°; nmr ($CDCl_3$) δ 2.81 (s, 3), 3.08 (s, 3), 3.90 (s, 6), 7.5 (m, 5), 8.42 (s, 1).

Anal. Calcd for $C_{11}H_{18}IN_3$: C, 41.4; H, 5.7; N, 13.2. Found: C, 41.8; H, 5.9; N, 13.0.

Dimethyl[α-(1,2-dimethyl-2-phenylhydrazino)propylidene]ammonium Iodide (**17**).—Two grams of **16**[7] was added to 2 ml of methyl iodide. After 24 hr at room temperature the solid product was precipitated with dry ether and recrystallized from acetone–ether to give 2.8 g of **17**, mp 142–143°. Further recrystallization from acetone–ether gave white crystals: mp 149–150°; nmr δ 1.04 (t, 3, J = 8 Hz), 2.75 (q, 2, J = 8 Hz), 3.12 (s, 3), 3.21 (s, 3), 3.30 (s, 6), 7.2 (m, 5).

Anal. Calcd for $C_{13}H_{22}N_3I$: C, 45.0; H, 6.4. Found: C, 44.8; H, 6.6.

Basic Hydrolysis of 17.—A solution of 2 g of **17** in 25 ml of 6 *N* NaOH was heated under reflux for 8 hr. The cooled reaction mixture was saturated with salt and extracted with ether. Evaporation of the dried ether extracts gave 0.43 g of 1,2-dimethyl-1-phenyl-2-propionylhydrazine. The nmr spectrum of this material was found to be identical with that of an authentic sample which was prepared as described below.

1,2-Dimethyl-1-phenyl-2-propionylhydrazine.—Two grams of 1,2-dimethyl-1-phenylhydrazine[12] was treated with 2.0 g of propionic anhydride. The reaction mixture was heated on the steam bath for 30 min, cooled, and dissolved in ether. The ether solution was extracted with dilute sodium carbonate and washed with water. The dried ether solution was evaporated and the residue was distilled to give 1.7 g of product as a colorless oil; bp 165–166° (22 mm); nmr ($CDCl_3$) δ 0.99 (t, 3, J = 8 Hz), 2.30 (q, 2, J = 8 Hz), 2.80 (s, 3), 2.92 (s, 3), 6.8 (m, 5).

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.7; H, 8.4. Found: C, 68.7; H, 8.1.

N-**Methylbenzimidic Acid Trimethylhydrazide** (**21**).—The amidrazone **4** (3.9 g) was slowly added to 12 ml of methyl iodide. The exothermic reaction was moderated with external cooling. Anhydrous ether was added and the crystalline product was filtered off, giving 5.5 g of the hydriodide **19**, mp 203–204°. Recrystallization from ethanol gave white crystals: mp 205–206°; nmr ($CDCl_3$) δ 2.80 [d, 3, J = 2 Hz, $NHCH_3$ (s with $NDCH_3$)], 2.75 (s, 6), 2.97 (s, 3), 9.8 (broad, 1, $NHCH_3$), and 7.60 (s, 5).

Anal. Calcd for $C_{11}H_{18}IN_3$: C, 41.4; H, 5.7; N, 13.2. Found: C, 41.5; H, 5.5; N, 13.1.

The free base **21** was obtained by treating 1.0 g of **19** with 10 ml of 10% NaOH followed by extraction with ether. Evaporation of the dried ether extract gave 0.5 g of **21**, mp 67–71°. Recrystallization from petroleum ether gave white crystals: mp 71–72°; nmr ($CDCl_3$) δ 2.20 (s, 6), 2.70 (s, 3), 2.75 (s, 3), and 7.2 (m, 5).

Anal. Calcd for $C_{11}H_{17}N_3$: C, 69.1; H, 9.0; N, 22.0. Found: C, 68.9 H, 9.1; N, 22.0.

N-**Methylbenzimidic Acid 1,2-Dimethyl-2-phenylhydrazide** (**22**).—Addition of 0.5 g of the amidrazone **5** to 2 ml of methyl iodide resulted in the separation of the hydriodide **20**, which was dissolved in hot ethanol and reprecipitated with ether, giving 0.7 g of white crystals, mp 195–197°. Recrystallization from ethanol–ether gave white crystals: mp 196–197°; nmr ($CDCl_3$) δ 2.81 (s, *ca.* 3), 2.87 (s, *ca.* 2.5), 3.30 (s, *ca.* 2.5), 2.97 (s, *ca.* 0.5), 3.50 (s, *ca.* 0.5), 9.8 (broad, 1), 7.2 (m, 10); nmr (DMSO-d_6) δ 2.65 (s, 3), 2.75 (s, 3), 3.18 (s, 3), 10.1 (broad, 1), 7.4 (m, 10).

(12) C. D. Harries, *Ber.*, **27**, 696 (1894).

Anal. Calcd for $C_{16}H_{20}IN_3$: C, 50.4; H, 5.3. Found: C, 50.6; H, 5.3.

The free base **22** was obtained by the procedure described for **21**. Recrystallization from petroleum ether gave pale yellow crystals: mp 76–78°; nmr ($CDCl_3$) δ 2.64 (s, 3), 2.78 (s, 3), 2.87 (s, 3), and 6.9 (m, 10).

Anal. Calcd for $C_{16}H_{19}N_3$: C, 75.5; H, 7.6. Found: C, 75.6; H, 7.4.

***N*-Phenylbenzimidic Acid 2-Methyl-2-phenylhydrazide (23).**—*N*-Phenylbenzimidoyl chloride[13] (8.6 g) was slowly added to a solution of 5.0 g of 1-methyl-1-phenylhydrazine and 4.0 g of triethylamine in 25 ml of dry benzene. After the exothermic reaction had subsided, the reaction mixture was allowed to stand at room temperature overnight. An equal volume of benzene was added and the reaction mixture was extracted with water. Evaporation of the dried benzene solution gave 11 g of crude product, mp 91–97°. Recrystallization from petroleum ether gave yellow crystals: mp 100–101°; nmr (DMSO-d_6) δ 3.03 (s, 3), 6.5–8.1 (m, 16).

Anal. Calcd for $C_{20}H_{19}N_3$: C, 79.7; H, 6.4; N, 13.9. Found: C, 79.6; H, 6.3; N, 14.1.

***N*-Phenylbenzimidic Acid 1,1-Dimethyl-2-phenylhydrazide (27).**—The hydrazide imide **23** (2.5 g) was added to 10 ml of methyl iodide. After 5 days at room temperature the hydriodide **24** was precipitated with dry ether as an amorphous solid (2.5 g). This material could not be successfully crystallized. Treatment of the hydriodide with 50 ml of 6 *N* NaOH followed by extraction with chloroform afforded, after evaporation of the dried extracts, the free base (1.1 g) as a yellow oil.

The picrate on recrystallization from ethanol formed yellow needles: mp 168–169°; nmr (DMSO-d_6) δ 2.95 (s, *ca.* 2.5), 3.02 (s, *ca.* 0.5), 3.30 (s, *ca.* 2.5), 3.45 (s, *ca.* 0.5), 7.3 (m, 15), 8.5 (s, 2), 12.1 (broad, 1).

Anal. Calcd for $C_{27}H_{24}N_6O_7$: C, 59.6; H, 4.4; N, 15.4. Found: C, 59.6; H, 4.7; N, 15.2.

The picrate was also prepared by the following route. *N*-Phenylbenzimidoyl chloride[13] (4.3 g) was added to a solution containing 2.7 g of 1,2-dimethyl-1-phenylhydrazine[12] and 2.0 g of triethylamine in 25 ml of dry benzene. After 5 days at room temperature the oily product (5.0 g) was isolated as described for **23**. The picrate obtained from this product had a melting point and nmr spectrum identical with that described above.

Dimethyl[α-(Trimethylhydrazino)benzylidene]ammonium Iodide (30).—A solution containing 1 g of **21** in 2 ml of methyl iodide was gently warmed to induce an exothermic reaction. Anhydrous ether was added and the solid product was filtered off, giving 1.4 g of **30**, mp 177–183°. Recrystallization from ethanol gave white crystals: mp 186–188°; nmr ($CDCl_3$) δ 2.72 (s, 6), 2.90 (s, 6), 3.60 (s, 3), 7.6 (m, 5).

Anal. Calcd for $C_{12}H_{20}IN_3$: C, 43.3; H, 6.1. Found: C, 43.3; H, 6.2.

Registry No.—**4**, 38435-15-3; **5**, 38435-16-4; **9**, 38435-17-5; **9** picrate, 38435-18-6; **10** iodide, 38435-19-7; **10** tosylate, 38435-20-0; **11**, 38435-21-1; **11** picrate, 38435-22-2; **12** iodide, 38521-57-2; **13** (R = Ph; R′ = Me; X = TsO), 38435-23-3; **14**, 38435-24-4; **15**, 38435-25-5; **16**, 38435-26-6; **17**, 38435-27-7; **19**, 38435-28-8; **20**, 38435-87-9; **21**, 38435-88-0; **22**, 38435-89-1; **23**, 38554-60-8; **27** picrate, 38435-90-4; **30**, 38435-91-5; *N*-methylbenzimidoyl chloride, 21737-87-1; 1,1-dimethylhydrazine, 57-14-7; 1-methyl-1-phenylhydrazine, 618-40-6; *N*,*N*-dimethylbenzamide, 611-74-5; *N*,*N*-dimethylpropionamide, 758-96-3; 1,2-dimethyl-1-phenyl-2-propionylhydrazine, 38435-93-7; 1,2-dimethyl-1-phenylhydrazine, 29195-01-5; propionic anhydride, 123-62-6; *N*-phenylbenzimidoyl chloride, 4903-36-0.

Acknowledgment.—We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Foundation of State University of New York for support of this project.

(13) J. von Braun and W. Pinkernelle, *Chem. Ber.*, **67B**, 1218 (1934).

Monomethylation of Aromatic Amines *via* Sodium Borohydride Mediated Carbon–Nitrogen Bond Cleavage

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Arylaminomethylsuccinimides (I) displaying a variety of substituents are rapidly and conveniently converted into the corresponding *N*-methyl aromatic amines (II) upon treatment with sodium borohydride in dimethyl sulfoxide. The presence of ester, amide, or nitrile functions does not affect the facility with which this reaction occurs. The reaction mechanism appears to involve base-catalyzed elimination of succinimide from I followed by reduction of the resulting aldimine intermediate.

Of numerous methods available for the monomethylation of primary aromatic amines, none is without serious deficiencies. Direct or Eschweiler–Clarke[1] alkylation is complicated by the formation of tertiary amines as well as other products; hydrolytic cleavage of *N*-methyl-*p*-toluenesulfonanilides or *N*-methylformanilides[2] requires sufficiently drastic conditions as to preclude the use of starting materials exhibiting labile ester, amide, or nitrile groups; lithium aluminum hydride reduction of formanilides or aryl isocyanates is applicable only to those substrates which do not bear substituents which will also be altered under the reaction conditions. We wish to report that sodium borohydride, the use of which in the hydrogenolysis of alkyl and aralkyl halides and tosylates[3a–d] has received increasing attention, can also be employed to effect the cleavage of carbon–nitrogen bonds with the consequential formation of *N*-methyl aromatic amines. Furthermore, the procedure reported herein may be utilized in the presence of ester, amide, or nitrile functions.

The reaction of aromatic amines with aqueous formaldehyde and succinimide in refluxing ethanol was reported by Winstead, *et al.*,[4] to provide good yields of *N*-arylaminomethylsuccinimides (I). Treatment of these aminal-type substances with sodium borohydride

(1) M. L. Moore, *Org. React.*, **5**, 301 (1949).

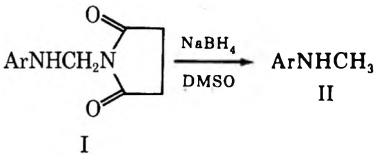
(2) R. M. Roberts and P. J. Vogt, *J. Amer. Chem. Soc.*, **78**, 4778 (1956).

(3) (a) H. M. Bell and H. C. Brown, *ibid.*, **88**, 1473 (1966); (b) H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.*, **34**, 3923 (1969); (c) R. O. Hutchins, D. Hoke, J. Keogh, and D. Koharski, *Tetrahedron Lett.*, 3495 (1969); (d) J. Jacobus, *Chem. Commun.*, 338 (1970).

(4) M. B. Winstead, K. V. Anthony, L. L. Thomas, R. G. Strachan, and H. J. Richwine, *J. Chem. Eng. Data*, **7**, 414 (1962).

in dimethyl sulfoxide (DMSO) resulted in an exothermic reaction which, upon aqueous work-up, furnished the desired *N*-methyl aromatic amines (II) (Scheme I). Yields were generally satisfactory and, as Table

SCHEME I



I II

I illustrates, this procedure is applicable not only to the preparation of aniline derivatives displaying a

TABLE I

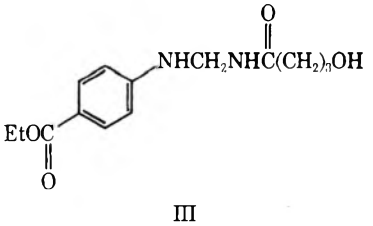
REPRESENTATIVE SODIUM BOROHYDRIDE REDUCTIONS

No.	Aromatic amine	Reactant (I)[a] mp, °C	Product (II)[b] bp, °C (mm)	Yield of II, %
1	Aniline	171.5–173[c]	193	64
2	4-Chloroaniline	152.5–153.5[c]	112–113 (12)	70
3	4-Ethoxyaniline	120.5–121.5[c]	120–122 (8.5)	73
4	2-Bromoaniline	69.5–73[d]	107–109 (12)	72
5	2,4-Xylidine	115–116[c]	107–109 (18)	77
6	Ethyl 4-aminobenzoate	135–136.5[c]	62–63[e]	77
7	4-Aminobenzonitrile	188–190	88–89[e]	59
8	4-Methylthioaniline	127–128	142–146 (10)	84
9	4-Aminobenzamide	207–210[d]	143.5–145.5[e]	40
10	2-Aminopyridine	124.5–125	172–173[e,f]	41
11	3-Aminopyridine	140–141	102 dec[e,g]	34
12	2-Fluorenamine	201–202	76–77[e]	62
13	2-Naphthylamine	189–190	150–155 (7.5)	79

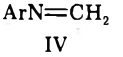
[a] Elemental analyses within ±0.3% of calculated values were obtained for newly reported imides except for those for which recrystallization solvents could not be found. Previously reported imides exhibited melting points in accord with literature values (see ref 4). [b] Elemental analyses within ±0.3% of calculated values were obtained for all *N*-methyl aromatic amines. Boiling points and melting points are in accord with literature values where known. [c] See ref 4. [d] Not purified. [e] Melting point. [f] Isolated and analyzed as hydrochloride salt. [g] Isolated and analyzed as oxalate salt.

variety of substituents, some of which exhibit significant lability under hydrolytic and $LiAlH_4$ conditions, but also to other aromatic carbocyclic and heterocyclic amines.

The reaction of I (Ar = *p*-carbethoxyphenyl) with sodium borohydride in ethanol led to cleavage of the imide ring and isolation of III. Reductive ring



III

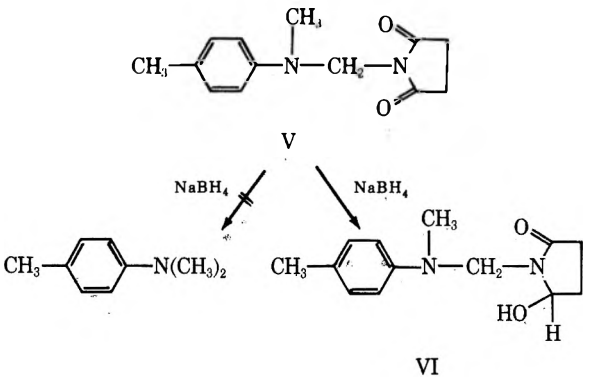


IV

opening of cyclic imides upon treatment with sodium borohydride has been described previously,[5] but this complication was readily avoided when DMSO was employed as the reaction medium. Although the conversion of I into II using Raney nickel has been reported,[6] the high pressure (80 kg/cm²) and temperature conditions (65–130°) required as well as the difficulties posed by the use of Raney nickel with sulfur, nitrile, and certain halogen-containing compounds clearly make the present procedure a more attractive one.

Mechanistically, two pathways for the conversion of I into II appear plausible. The reaction may proceed through (a) base-catalyzed elimination of succinimide followed by reduction of the resulting aldimine intermediate (IV) or (b) direct displacement of the succinimide moiety by borohydride anion. The contribution of pathway b seems minimal since reduction of *N*-methyl-*p*-toluidinomethylsuccinimide[4] (V), which cannot proceed by way of the aldimine mechanism, did not afford *N*,*N*-dimethyl-*p*-toluidine (Scheme II).

SCHEME II



Instead, the product (VI) derived from reduction of the imide ring was isolated. The structure of hydroxypyrrolidinone VI was elucidated by elemental analysis as well as by means of infrared, mass, and nmr spectroscopy. The nmr spectrum was most illuminating and displayed, in addition to the expected aromatic and methyl signals, a pair of doublets centered at δ 4.68 and 5.12 (J_{gem} = 13 Hz) and a doublet at δ 6.05 (J = 6 Hz). The former pair of doublets, produced by the aminal methylene protons, arises as a result of the introduction of an asymmetric center into the N-containing ring while the latter doublet, disappearing on addition of D_2O, is due to the hydroxy proton which is split by the lone methine hydrogen. These results indicate that direct displacement of the imide function by borohydride anion is unlikely and that arylaminomethylsuccinimides derived from primary aromatic amines are apparently reduced *via* the aldimine intermediate. The possibility that steric effects play a dominant role in the reduction of V compared to that of I appears improbable since hydride anion displacement in both substrates would be directed at primary carbon atoms which, in the reduction of alkyl halides and tosylates with sodium borohydride, have been shown to be readily attacked.[3b,c]

The disparate results obtained with DMSO and ethanol also support these conclusions since base-promoted eliminations are known to be facilitated in dipolar aprotic solvents.[7,8] Preferential nucleophilic attack at the imide carbonyl function in ethanol may

(5) Y. Kondo and B. Witkop, *J. Org. Chem.*, **33**, 206 (1968).

(6) M. Sekiya and K. Ito, *Chem. Pharm. Bull.*, **15**, 1339 (1967).

(7) V. J. Traynelis, W. L. Hergenrother, H. T. Hanson, and J. A. Valicenti, *J. Org. Chem.*, **29**, 123 (1964).

(8) A. J. Parker, *Advan. Org. Chem.*, **5**, 1 (1965).

be due either to a comparatively slower rate of elimination in this protic solvent or to a different mode of hydride addition, perhaps analogous to that occurring in the reduction of unsaturated ketones by sodium borohydride in ethanol and pyridine wherein 1,4 addition is favored in the latter solvent.[9,10]

Experimental Section

Melting points are uncorrected. Aromatic amines used as starting materials were commercially available. Infrared spectra were obtained using a Perkin-Elmer Model 21 infrared spectrophotometer. Mass spectra were recorded on an Hitachi Perkin-Elmer RMU-5E mass spectrometer. An Hitachi A-60D spectrometer was used to obtain nmr spectra.

Arylaminomethylsuccinimides (I).—These compounds were prepared by the method of Winstead, *et al.*[4] A solution of 0.1 mol of aromatic amine, 11.9 g of succinimide, and 9.1 ml of 37% aqueous formaldehyde in 100–150 ml of ethanol was refluxed for 2–5 hr (except in those instances where the product precipitated during reflux for which shorter periods of time were used). Cooling usually resulted in precipitation of the desired imide. If this did not occur, evaporation of the ethanol and trituration of the residue with water produced crystalline material.

***N*-Methyl Aromatic Amines (II).**—A warm solution of I in DMSO (2–3 ml of DMSO/g of I) was treated, during 5–10 min, with an equimolar amount of sodium borohydride. An exothermic reaction resulted but was easily controlled, the temperature not rising above *ca.* 100°. After heating on the steam bath for 10–15 min after completion of the borohydride addition, the reaction mixture was poured into cold water. The resulting mixture was extracted three times with ether. The combined ether extracts were dried; the ether was evaporated and the residual oil distilled. (Solid material was recrystallized.) In the case of water-soluble amines, the reaction mixture was poured into 10 *N* KOH instead of water.

***N*-(4-Carbethoxyanilinomethyl)-4-hydroxybutyramide (III).**—A solution of 2.7 g. (0.01 mol) of I (Ar = *p*-carbethoxyphenyl) and 0.42 g (0.011 mol) of sodium borohydride in 40 ml of ethanol was refluxed for 2.5 hr. The ethanol was evaporated under reduced pressure, and the residue was slurried in 50 ml of 3 *N* NH_4OH. The resulting solid was filtered free, dried, and recrystallized from toluene: mp 112–114°; mass spectrum *m/e* 280 (M^+); ir (KBr) 5.9 (ester carbonyl) and 6.05 μ (amide carbonyl).

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 9.99. Found: C, 60.01; H, 7.12; N, 9.92.

***N*-(*N*-Methyl-*p*-toluidinomethyl)-5-hydroxypyrrolidin-2-one (VI).**—A warm solution of 11.6 g (0.05 mol) of V[4] in 20 ml of DMSO was treated, during 10 min, with 1.9 g (0.05 mol) of sodium borohydride. Internal temperature rose to 85°; stirring was continued for 0.5 hr after addition of the borohydride was complete. The reaction mixture was poured into cold water which was then extracted three times with methylene chloride. The combined methylene chloride extracts were dried. The methylene chloride was evaporated and the residue (8.0 g) recrystallized from benzene to yield VI: mp 121–122°; mass spectrum *m/e* 234 (M^+); ir (KBr), 6.0 μ (carbonyl); nmr (DMSO-d_6) δ 2.28 (s, 3, aromatic CH_3), 1.65–2.4 [m, 4, $-C(=O)CH_2CH_2-$], 3.0 (s, 3, NCH_3), 4.68 (d, 1), and 5.12 (d, 1) (J_{gem} = 13 Hz, NCH_2N), 5.15 (m, 1, methine H), 6.05 (d, 1, J = 6 Hz, OH), 6.8–7.2 (m, 4, phenyl). Addition of D_2O caused the disappearance of the doublet at δ 6.05.

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.44; H, 7.74; N, 11.96. Found: C, 66.33; H, 7.58; N, 11.64.

Registry No.—I-1, 13314-99-3; I-2, 38359-09-0; I-3, 38359-10-3; I-4, 38359-11-4; I-5, 38359-12-5; I-6, 17647-08-4; I-7, 38359-14-7; I-8, 38359-15-8; I-9, 38359-16-9; I-10, 18932-40-6; I-11, 38359-18-1; I-12, 38359-19-2; I-13, 38359-20-5; II-1, 100-61-8; II-2, 932-96-7; II-3, 3154-18-5; II-4, 6832-87-7; II-5, 13021-13-1; II-6, 10541-82-9; II-7, 4714-62-9; II-8, 104-96-1; II-9, 38359-26-1; II-10 (mono HCl), 27433-30-3; II-11 (*x*-oxalate), 38359-27-2; II-12, 38359-28-3; II-13, 2018-90-8; III, 38359-29-4; V, 38359-30-7; VI, 38359-31-8.

Acknowledgment.—The author thanks Mr. Charles Lamphere for expert technical assistance and Professor D. S. Kemp for helpful discussions.

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(10) S. B. Kadin, *J. Org. Chem.*, **31**, 620 (1966).

An ESCA Study of the Sulfur–Nitrogen Bond in Sulfimides

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The O(1s), N(1s), and S(2p) binding energies have been measured from the X-ray photoelectron spectra of the sulfoxide, sulfone, *N*-tosylsulfimide, and *N*-tosylsulfoximide derivatives of benzyl methyl sulfide. The sulfur(IV) binding energy in the *N*-tosylsulfimide is found to be 0.4 eV larger than that in the sulfoxide. The sulfur atom in the sulfimide therefore carries a larger positive charge, and the S(IV)–NTs bond has a larger contribution from the semipolar form than in the sulfoxide. The data also indicate that the parent sulfimide bond, S(IV)–NH, is electronically very similar to the S–O bond in the sulfoxide.

The nature of the sulfur–nitrogen bond in sulfimides, like that of the sulfur–oxygen bond in sulfoxides, has perplexed chemists for several decades.[2,3] Two models have been proposed to explain the properties of these functionalities, a covalent form (**1**) and a semipolar

X = O, NH, NTs

form (**2**). The semipolar structure **2** conforms to the octet rule, whereas the covalent formulation does not. The double bond in **1** arises from donation of a 2p electron pair on oxygen or nitrogen to an empty 3d orbital on sulfur. The actual nature of the sulfoxide and sulfimide bonds lies between the canonical extremes, but no general agreement has been reached as to which form should be considered dominant. Recently

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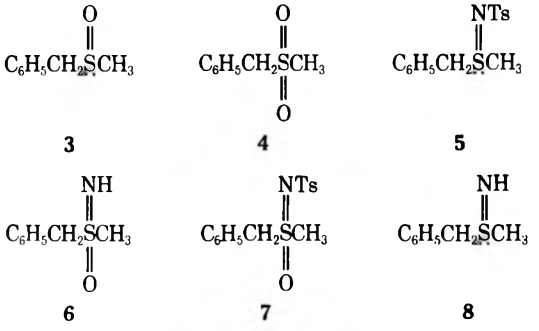
(2) For leading references to the sulfimide question, see (a) Á. Kucsman, F. Ruff, and I. Kapovits, *Tetrahedron*, **22**, 1575 (1966); (b) K. Tsujihara, N. Furukawa, and S. Oae, *Bull. Chem. Soc. Jap.*, **43**, 2153 (1970); (c) N. Furukawa, K. Harada, and S. Oae, *Tetrahedron Lett.*, 1377 (1972).

(3) For a review of the sulfoxide problem, see C. C. Price, *Chem. Eng. News*, 58 (Nov 30, 1964).

Lindberg, *et al.*,[4] approached the sulfoxide problem through the measurement of inner-shell electron binding energies by X-ray photoelectron spectroscopy. Atomic charges calculated for the two extreme structures (**1** and **2**) were compared with the value determined from the measured binding energy, and the ionic character of the bond was found to correspond approximately to a 60% contribution from the covalent form **1**. These authors concluded that the best representation of the bond is a resonance hybrid of the two forms, but, as a single representation, the double-bond form (**1**) is to be preferred.

We have recently been engaged in studies of the conformational properties of cyclic sulfimides[5] and became interested in studying the nature of the sulfur–nitrogen bond in these compounds. Ir, uv, nmr, and crystallographic data have previously been brought to bear on this question.[2] Because of the success of the photoelectron study on the sulfoxide functionality,[4] we have taken a similar approach in the present work. The derivatives of benzyl methyl sulfide were chosen for this investigation by reason of their stable and crystalline nature: the sulfoxide (**3**), the sulfone (**4**), the *N*-tosylsulfimide (**5**), the sulfoximide (**6**), and the *N*-tosylsulfoximide (**7**). The unsubstituted sulfimide (**8**)



was also prepared, but it decomposed on X-irradiation. As a result of these studies, we report that the sulfimide bond with the tosyl group on nitrogen is more polar than the sulfoxide bond and that the best single representation may be the semipolar form (**2**). Furthermore, the parent sulfimide bond (S–NH) is found to be very similar in polarity to the sulfoxide bond.

Results and Discussion

The photoelectron spectra were induced with aluminum K_α X-radiation with a quantum energy of 1486.6 eV. All measurements were made on solid samples prepared by crushing the powders onto an aluminum support. The spectra were recorded at $-100°$ to prevent sublimation and were calibrated by reference to the C(1s) line at 285.0 eV (see Experimental Section). Binding energies with respect to the Fermi level (BE_f) may be calculated for each nucleus from the energy of the exciting radiation ($h\nu$), the measured kinetic energy of the ejected electrons (KE_{sp}), and the work function of the spectrometer (φ_{sp} = 4.6 eV) (eq 1). In practice, the BE for the nucleus of interest was derived from eq 2, which is

$$BE_f = h\nu - KE_{sp} - \varphi_{sp} \quad (1)$$

$$BE_f = KE_{C(1s)} - KE + 285.0 \quad (2)$$

obtained by subtracting the eq 1 that contains the C(1s) values for BE and KE from the analogous equation with parameters for the desired nucleus. The parameters $h\nu$ and φ_{sp} thereby drop out.

The O(1s), N(1s), and S(2p) binding energies for compounds **3**–**7** are listed in Table I. The oxygen and

Table I
Binding Energies for Derivatives of Benzyl Methyl Sulfide[a,b]

Compd		O(1s)	N(1s)	S(2p)
	(**3**)	532.0		166.2
	(**4**)	532.2		168.2
	(**5**)	532.1	398.7	166.6,[c] 168.0[d]
	(**6**)	532.2	398.7	168.1
	(**7**)	532.2	399.1	168.4[d,e]

[a] Units of eV; absolute values are probably ±0.5 eV, depending on the reliability of the reference peak, but relative values are ±0.1 eV. [b] Relative to a C(1s) value of 285.0 eV (reference peak). [c] Binding energy for S(IV). [d] Binding energy for S(VI). [e] There are two nonequivalent S(VI) sulfurs in this molecule, with identical binding energies.

sulfur binding energies are in excellent agreement with published results on other compounds containing the sulfoxide and sulfone functionalities.[4] A difference between line positions of 0.2 eV is easily discernible. The nonequivalent S(VI) sulfurs and the nonequivalent oxygens in the sulfoximide **7** display identical chemical shifts. In the sulfimide **5**, however, the imide sulfur [S(IV)] and the sulfonyl sulfur [S(VI)] have chemical shifts that differ by 1.4 eV.

In our discussion of these results, we shall first approach the problem in a qualitative fashion, and then make a brief quantitative examination of some of the data. The S(2p) binding energies offer the most useful set of data, since sulfur is present as the central atom in all members of the series under consideration (**3**–**8**). In the qualitative approach, the BE is taken simply as a measure of the charge on the atom of interest.[4] Thus the increase of 2 eV on going from the sulfoxide **3** to the sulfone **4** indicates a greater amount of positive charge on the sulfur atom in the latter molecule.

The BE for S(IV) in the *N*-tosylimide **5** is clearly larger (0.4 eV) than that in the sulfoxide. The increase in binding energy corresponds to a more pronounced positive charge on sulfur and to a greater contribution from the semipolar form **2**. This increase in importance of the semipolar form is primarily due to the presence of the *N*-tosyl group, which stabilizes a negative charge on nitrogen by induction, if not by resonance. Although we could not obtain measurements on the unsubstituted sulfimide **8**, the sulfoximides **6** and **7** provide a useful comparison. In this pair of compounds, replacement of N–H with N–Ts results in an increase in the S(2p) BE of ~0.3 eV. Thus an *N*-tosyl group raises the

(4) B. J. Lindberg, K. Hamrin, G. Johansson, U. Gelius, A. Fahlman, C. Nordling, and K. Siegbahn, *Phys. Scripta*, **1**, 286 (1970).

(5) J. B. Lambert, C. E. Mixan, and D. S. Bailey, *J. Amer. Chem. Soc.*, **94**, 208 (1972); J. B. Lambert, D. S. Bailey, and C. E. Mixan, *J. Org. Chem.*, **37**, 377 (1972).

polarity of the S–N bond, placing a larger positive charge on sulfur. Furthermore, the S(2p) BE of the sulfone **4** (168.2) is essentially the same as that for the sulfoximide **6** (168.1). The oxide group and the unsubstituted imide group (NH) therefore place similar charges on sulfur. From these observations, we can conclude that the S–NTs bond is more polar than the S–O bond (larger contribution from **2**), but there is little difference in polarity between the S–NH and S–O bonds.

Some information can also be obtained from the N(1s) binding energies.[6] The amount of negative charge on the nitrogen atom in the *N*-tosylsulfoximide **7** is lower (BE 0.4 eV higher) than that in the parent sulfoximide **6**. Despite the higher polarity of the S–N bond in **7**, the electron-withdrawing nature of the attached tosyl group leaves a smaller negative charge on nitrogen. A comparison of the sulfimide **5** and the sulfoximide **7** shows that introduction of the oxygen atom on sulfur reduces the negative charge on nitrogen.

To analyze the nature of the S(IV)–N bond quantitatively, the atomic charge parameter (q) must be calculated for sulfur in the two extreme structures **1** and **2**, and compared with the value derived from experiment.[4] The charge parameter is the sum of the formal charge (Q) on the atom in question and the contribution (I) from the partial ionic character of all the attached bonds (eq 3). The ionic bond component is expressed

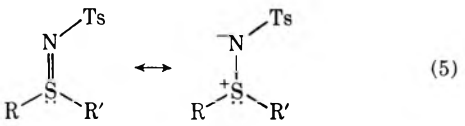
$$q = Q + \Sigma I \tag{3}$$

as a function of the electronegativity difference, adjusted for formal charge, between the atoms of the bond (eq 4).[4] These quantities are available from the

$$I = 1 - e^{-0.25(\chi_A - \chi_B)^2} \tag{4}$$

work of Siegbahn, *et al.*,[4,6] following Pauling. Calculations for the *N*-tosylsulfimides[7] give an atomic charge q at S(IV) of +0.12 for the covalent form **1** and +0.97 for the semipolar form **2**. Reference to Siegbahn's correlation between atomic charge and the S(2p) binding energy[4] indicates that the observed value of 166.6 eV corresponds to a q of +0.6. By comparison of this value with the two extremes, the bond can be described as about 45% covalent. Analogous calculations for sulfoxides[4] gave an estimate of 60% covalency for the S–O bond. The quantitative approach therefore is in agreement with the qualitative approach that the S–NTs bond has a higher polarity than the S–O bond of sulfoxides.

Summary.—Photoelectron studies of *N*-tosylsulfimides have indicated that the S–NTs bond is more polar than the S–O bond in sulfoxides. The dual structures of eq 5, however, provide the best representation. Withdrawal of negative charge from nitrogen into the tosyl group is probably the most important factor contributing to the enhancement of the semipolar nature of the S–NTs bond. Oae and coworkers[2c] have found that *N*-tosylsulfimides racemize considerably more rapidly than sulfoxides. Their explanation of the higher barrier to sulfur inversion, in agreement with our conclusions, is that the sulfoxide bond has greater covalency than the *N*-tosylsulfimide bond. The photoelectron spectra have also demonstrated that the sulfimide bond (S–NH) and the sulfoxide bond (S–O) are very similar in polarity.



(5)

Experimental Section

Melting points were determined in a Hershberg apparatus and are uncorrected. ESCA (electron spectroscopy for chemical analysis) spectra were induced with aluminum K_α X-radiation with a quantum energy of 1486.6 eV and were recorded on an AEI ES-100 electron spectrometer.[8] Binding energies were calculated by means of eq 2. The value of BE_f for the C(1s) reference peak (285.0 eV) has been established previously.[9] The close agreement between our values for the O(1s) and S(2p) binding energies and those measured previously for similar sulfoxides and sulfones[4] indicates that the reference materials used in the two studies must have similar C(1s) binding energies. Because the carbon constitution of molecules **3**–**7** is constant (phenyl, methylene, methyl), the C(1s) binding energy is probably identical for all members of the series. Therefore, reliability of the reported values (Table I) is limited not by differences in referencing but by the standard deviation of the measurement (0.1 eV). We therefore consider that the relative values reported in Table I are reliable to ±0.1 eV, but the absolute values, which depend on the accuracy of the 285.0-eV figure, may be reliable only to ±0.5 eV. The significant conclusions of this study are based on relative values. Elemental analyses were carried out by Miss H. Beck, Analytical Services Laboratories, Department of Chemistry, Northwestern University. The preparation of the derivatives of benzyl methyl sulfide paralleled those previously reported for thiane derivatives.[5] Therefore experimental details are omitted, and only physical properties are reported herein. The nmr data are collected in Table II.

TABLE II

NMR DATA FOR THE DERIVATIVES OF BENZYL METHYL SULFIDE[a]

Compd	Arom[b]	CH_2[b]	CH_3	$ArCH_3$	NH
3	7.35	4.00 (13.0)	2.45		
5	7.20, 7.32 (8.0)	4.10 (12.0)	2.50	2.33	
6	7.37	4.30 (13.0)	2.90		2.65
7	7.40, 7.50 (8.0)	4.70[c]	3.03	2.40	

[a] Chemical shifts are in δ in parts per million from TMS values; coupling constants (in parenthesis) are in hertz; the solvent is CCl_4. [b] The δ values correspond to centers of multiplets. [c] J_{AB} was not observable.

Benzyl methyl sulfide was obtained from Aldrich Chemical Co.

Benzyl methyl sulfoxide (**3**) had mp 57–58°. *Anal.* Calcd for $C_8H_{10}OS$: C, 62.34; H, 6.49. Found: C, 62.40; H, 6.50.

Benzyl methyl sulfone (**4**) was obtained as a gift from Dr. F. G. Bordwell of Northwestern University.

***N*-Tosylbenzylmethylsulfimide** (**5**) had mp 167–168°. *Anal.* Calcd for $C_{15}H_{17}NO_2S_2$: C, 58.63; H, 5.54; N, 4.56. Found: C, 58.29; H, 5.46; N, 4.57.

(6) R. Nordberg, R. G. Albridge, T. Bergmark, U. Ericson, J. Hedman, C. Nordling, K. Siegbahn, and B. J. Lindberg, *Ark. Kemi*, **28**, 257 (1968).

(7) For details of the calculation, see C. E. Mixan, Ph.D. Dissertation, Northwestern University, 1972.

(8) We are grateful to the National Science Foundation for an equipment grant that aided the purchase of this instrument.

(9) W. E. Morgan, W. J. Stec, R. G. Albridge, and J. R. Van Wazer, *Inorg. Chem.*, **10**, 926 (1971); U. Gelius, P. F. Hedén, J. Hedman, B. J. Lindberg, R. Manne, R. Nordberg, C. Nordling, and K. Siegbahn, *Phys. Scripta*, **2**, 70 (1970).

Benzylmethylsulfoximide (6) had mp 81–82°. *Anal.* Calcd for $C_8H_{11}NOS$: C, 56.80; H, 6.51; N, 8.28. Found: C, 56.41; H, 6.35; N, 8.32.

***N*-Tosylbenzylmethylsulfoximide** (7) had mp 128–130°. *Anal.* Calcd for $C_{15}H_{17}NO_3S_2$: C, 55.73; H, 5.26; N, 4.33. Found: C, 56.06; H, 5.29; N, 4.21.

Benzylmethylsulfimide (8) was prepared by the method used previously[6] for thiane 1-imide, but the compound decomposed under X-radiation.

Registry No.—**3**, 824-86-2; **4**, 3112-90-1; **5**, 38401-37-5; **6**, 38401-38-6; **7**, 38401-39-7.

Substituted Ammonium Salts of Benzothiazoline-2-thione. Nuclear Magnetic Resonance Studies of Ion Pairs in Polar and Nonpolar Media[1]

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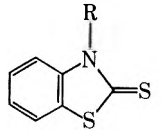
Received May 18, 1972

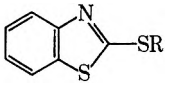
The primary and secondary ammonium salts of benzothiazole-2-thiol exist mainly in the benzothiazoline-2-thione structure. In nonpolar aprotic solvents the substituted ammonium salts of benzothiazoline-2-thione exist in intimate ion pairs. In polar solvents these salts dissociate into solvent-separated ion pairs. The effect of charge separation increases the electron densities around the thiazoline ring, as indicated by the chemical shifts of the aromatic ring hydrogens.

A previous paper[2] described the nmr shifts for the aromatic protons of S- and N-substituted derivatives of benzothiazoline-2-thione and benzothiazole-2-thiol.

This paper reports recent nmr and uv absorption studies on several primary and secondary alkylammonium salts of benzothiazole-2-thiol (Ib), the so-called 2-mercaptobenzothiazole or "MBT" of the rubber industry, which, however, are shown to be salts of benzothiazoline-2-thione, structure Ia.



Ia, R = H
IIa, R = alkylammonium



Ib, R = H
IIb, R = alkylammonium

The uv absorption spectra of the ammonium salts showed a strong absorption band at 320 mμ attributed to the thione structure (Ia) and a band which was present when the spectra were recorded in either polar or nonpolar solvents (Table I). It is concluded, then, that these compounds are salts of benzothiazoline-2-thione, not salts of benzothiazole-2-thiol as traditionally conceived.

The nmr spectra of the primary ammonium salts (IIa, IIb) (example, R = H; R′ = isopropyl) of benzothiazoline-2-thione in a relatively nonpolar medium, such as deuteriochloroform, showed a strong absorption peak at about 265 Hz (4.41 ppm), which was attributed to the ammonium protons of the alkylammonium ion. In addition, a single envelope, AB type splitting pattern at 438 Hz (7.30 ppm) was attributed to the 4, 5, 6, 7 aromatic protons (see Figure 1), indicating the benzothiazoline-2-thione structure by analogy with the earlier results.[3,4] The nmr spectra of the secondary ammonium salts (IIa) (examples, R = ethyl; R′ = ethyl and R = isopropyl; R′ = cyclohexyl) in relatively nonpolar media ($CDCl_3$ or C_6D_6) exhibited a pattern similar to that of the primary ammonium salts, except for the peak position of the ammonium protons of the alkylammonium ion, which appeared at about 516 Hz (8.60 ppm). The values are independent of the concentration. The aromatic protons of the anion again gave the single envelope pattern at the same position, 7.30 ppm.

In a more polar protic solvent, methanol, the nmr spectra of both primary and secondary ammonium salts showed peaks for the ammonium protons at positions 300–320 Hz (5.08–5.20 ppm) (Figure 2). In addition, the pattern for the 4, 5, 6, 7 aromatic protons was noted to separate into the two-envelope A_2B_2 type splitting pattern.[5] Here again the uv absorption at 320 mμ indicates that the thione structure of the benzothiazoline salt is retained.

The chemical shifts caused by the stepwise addition of methanol to solutions of primary and secondary ammonium salts in $CDCl_3$ are in the direction of the results obtained in pure methanol, 5.08 ppm. However, addition of more than 4 equiv of methanol to the solution resulted in little further change in the chemical shift of the ammonium protons.

For example, in the case of the secondary alkyl ammonium salts (R = ethyl; R′ = ethyl; R = methyl or isopropyl; R′ = cyclohexyl), the ammonium proton chemical shift is at 8.60 ppm in pure $CDCl_3$.

Even more striking was the change in the nature of the nmr spectra of the aromatic protons of the anion of Ia. The addition of only 1 mol of methanol per mole of either primary or secondary alkylammonium salt resulted in a change from the single-envelope AB type splitting observed in pure $CDCl_3$ solution to the double-envelope A_2B_2 type splitting observed in pure methanol solution. As shown in Table II, some of this effect is due to dilution, but the major effect is the polarity of the medium. This change was reversed by adding $CDCl_3$. The demonstrated reversibility indicates the existence of equilibrium conditions for both anions and cations in the solutions of these salts, as shown in Scheme I.

In deuteriochloroform, the salts appear to exist

(1) Presented before the Division of Organic Chemistry at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968.

(2) A. F. Halasa and G. E. P. Smith, Jr., *J. Org. Chem.*, **36**, 636 (1971).

(3) H. P. Koch, *J. Chem. Soc.*, 401 (1949).

(4) C. G. Moore and E. S. Wright, *ibid.*, 4237 (1952).

(5) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 147.

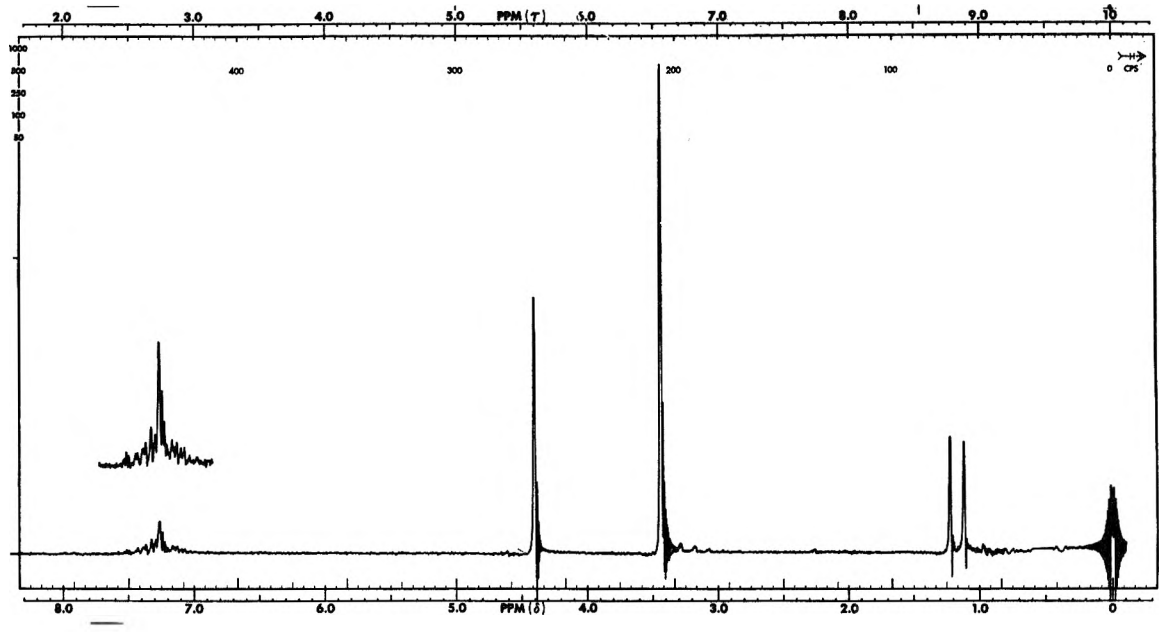
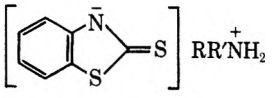


Figure 1.—Nmr spectrum of secondary ammonium salt of benzothiazoline-2-thione in pure $CDCl_3$. One mole of MeOH added.

TABLE I

UV AND NMR SPECTRA OF AMINE SALTS I OF BENZOTHIAZOLINE-2-THIONE



I

Registry no.	I R	I R′	Uv max, mμ[a] $CHCl_3$	Uv max, mμ[a] MeOH	Nmr of $RR'NH_2^+$, ppm $CDCl_3$	$CDCl_3$ + 1 mol MeOH	$CDCl_3$ + 2 mol MeOH	$CDCl_3$ + 3 mol MeOH	$CDCl_3$ + 4 mol MeOH	$CDCl_3$ + 5 mol MeOH	100% MeOH
38456-42-7	H	$CH(CH_3)_2$	245 (m)	238 (m)							
			293 (m)	253 (w)							
			320 (vs)	320 (vs)	4.41	4.58	4.66	4.80	4.70	4.93	5.08
38456-43-8	Cyclohexyl	$CH(CH_3)_2$	240 (m)	240 (m)							
			290 (w)	250 (w)							
			320 (vs)	320 (vs)	8.60	7.50	6.59	5.83	4.86	4.86	4.86
38456-44-9	Cyclohexyl	CH_3	240 (m)	238 (m)							
			245 (w)	249 (w)							
			320 (vs)	320 (vs)	8.33	7.30	6.72	5.95	5.01	5.01	5.01
38456-45-0	CH_2CH_3	CH_2CH_3	245 (m)	240 (m)							
			296 (w)	255 (w)							
			320 (vs)	320 (vs)	8.60	7.23	6.46	5.88	5.36	5.20	5.20

[a] m = medium; w = weak; vs = very strong.

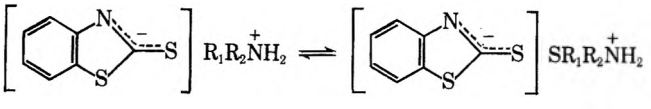
TABLE II

EFFECT OF CONCENTRATION CHANGES ON THE NMR OF $RR'N^+H_2$[a]

I R	I R′	1 ml	2 ml	3 ml	4 ml	5 ml
H	CH_2CH_3	5.35	4.91	4.63	4.43	4.23
CH_2CH_3	CH_2CH_3		5.08	4.70	4.25	

[a] 0.001 mol of amine salt and 0.05 mol of MeOH in $CDCl_3$.

SCHEME I



(Scheme I) as intimate ion pairs[6] in which the cation causes localization of the negative charge resulting in little influence of the negative charge on the aromatic protons. This effect results in the typical AB splitting pattern (Figure 1).

In more polar solvents (*e.g.*, CD_3OD, DMSO-d_6, MeOH–$CDCl_3$), the intimate ion pairs are dissociated, resulting in delocalization of the negative charge into the aromatic ring (Scheme II). This effect produces the typical A_2B_2 splitting pattern (Figure 2).

The changes in chemical shifts of the ammonium ion protons noted when methanol is added to $CDCl_3$ solutions of the salts may be explained by an equilibrium solvation–ion[7] separation effect (Scheme III). This phenomenon reaches a limiting value of $\Delta\delta = 1.7 \pm 0.2$ ppm at 3–4 equiv of the polar solvent.

Some preliminary dilution studies (see Table II) indicate that the ion-pair aggregates of the more soluble salts of this study dissociate and solvate in polar, as dis-

(6) S. Winstein, P. E. Klinedienst, and G. C. Robinson, *J. Amer. Chem. Soc.*, **83**, 885 (1961).

(7) T. E. Hagen Esch and J. Smid, *J. Amer. Chem. Soc.*, **88**, 307, 318 (1966).

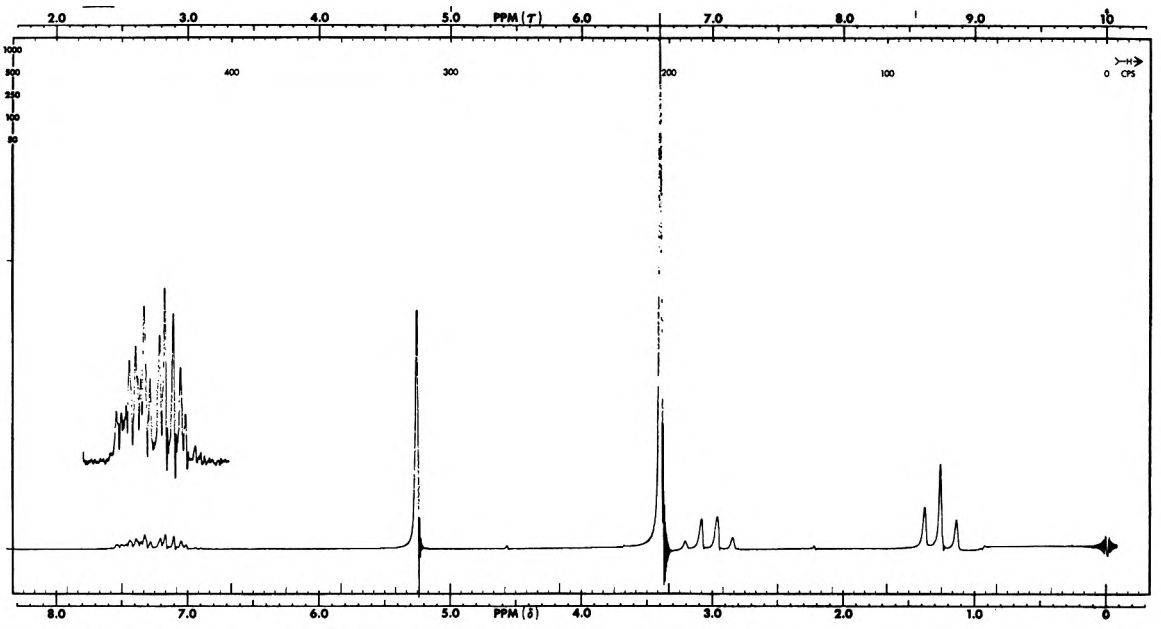
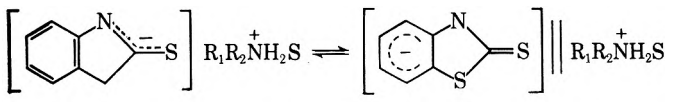
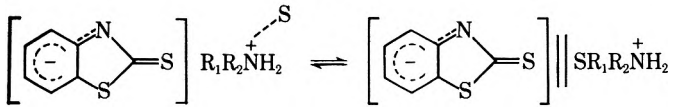


Figure 2.—Nmr spectrum of primary ammonium salt of benzothiazoline-2-thione in $CDCl_3$. Five moles of MeOH added.

SCHEME II



SCHEME III



tinct from nonpolar, solvents, with ion separation as the environment changes from concentrated to very dilute solutions. In the primary ammonium salts, Ia (R = H; R′ = alkyl), a chemical shift from 5.35 ppm at 11% concentration to 4.23 ppm at 0.5% concentration is produced. A similar chemical shift was noted in the nmr spectra of secondary ammonium salts Ia (R = ethyl; R′ = ethyl) in changing the concentration. Thus the dilution effect, in the case of the secondary ammonium cations, is smaller, distinct, and separable from the effect produced by changing from a nonpolar, aprotic to a polar, protic environment.[8,9]

Experimental Section

Reagents.—Benzothiazoline-2-thione was recrystallized several times from benzene solution. The amines used were purified by distillation.

Ammonium salts of benzothiazoline-2-thione were prepared in anhydrous ether by the addition of the appropriate amine to an ether slurry of 2-benzothiazole-2-thiol. The white salts formed immediately. The salts were filtered and washed several times with ether and dried in a vacuum oven. The nmr spectra were run on the salts in nmr grade $CDCl_3$, C_6D_6, CD_3OD, and DMSO-d_6 and methanol distilled from Mg metal.

Registry No.—Ia, 4464-58-8; Ib, 149-30-4.

(8) G. Fraenkel, *J. Chem. Phys.*, **39**, 1614 (1963).
(9) G. Fraenkel and J. P. Kim, *J. Amer. Chem. Soc.*, **88**, 4203 (1966).

Pyrolysis and Mass Spectra of the 2-Thiones of Benzothiazole, Benzimidazole, and Benzoxazole

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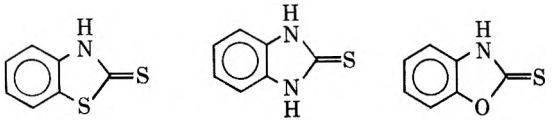
Received October 25, 1972

The electron-impact and chemical-ionization mass spectra of benzothiazole-2-thione (**1**), benzimidazole-2-thione (**2**), and benzoxazole-2-thione (**3**) have been compared with those of their pyrolysis products and parallels have been found. In each case, the loss of S from the molecular ions and from the (M + H) ions is the lowest energy fragmentation. At 800°, **1** gives a 23% yield of benzothiazole (**4**) and a 13% yield of cyanobenzene (**5**). Loss of S accounts for the formation of **4**. Compound **5** arises from **1** by loss of S_2 and from **4** by loss of S. The one-step loss of S_2 is observed also in the mass spectrum of **1**. At 950°, **2** gives 62.5% of benzimidazole (**6**) and 7.5% of 2-cyanoaniline (**8**), which are formed from the loss of S from **2** and rearrangement of **6** to **8**. At 1000°, **3** gives 1.3% of benzoxazole (**10**) and 38% of 2-cyanophenol (**11**) from the loss of S. Compound **10** is readily converted to **11** at 1000°. Compound **3** also gives 12 and 15% of 1- and 2-cyanonaphthalene (**13** and **14**), respectively, and 7% of naphthalene, presumably by an initial loss of COS from **3**, a low-energy loss also observed in the mass spectrum.

As part of a series of studies[2,3] in which we compare the formation of pyrolysis products with mass spectral fragmentations of organic molecules, we wish to report results obtained from benzothiazole-2-thione (**1**), benzimidazole-2-thione (**2**), and benzoxazole-2-thione (**3**).



1 **2** **3**

These thiones have been pyrolyzed at a variety of temperatures with the aim of observing the effect of temperature on the distribution of products. When it was deemed necessary, methanol was introduced into the system as an agent for trapping radicals and high-energy intermediates. Also, whenever possible, we pyrolyzed compounds which were identified in the pyrolysis mixtures from **1**–**3**, in order to see if other products arise from them by secondary pyrolysis.

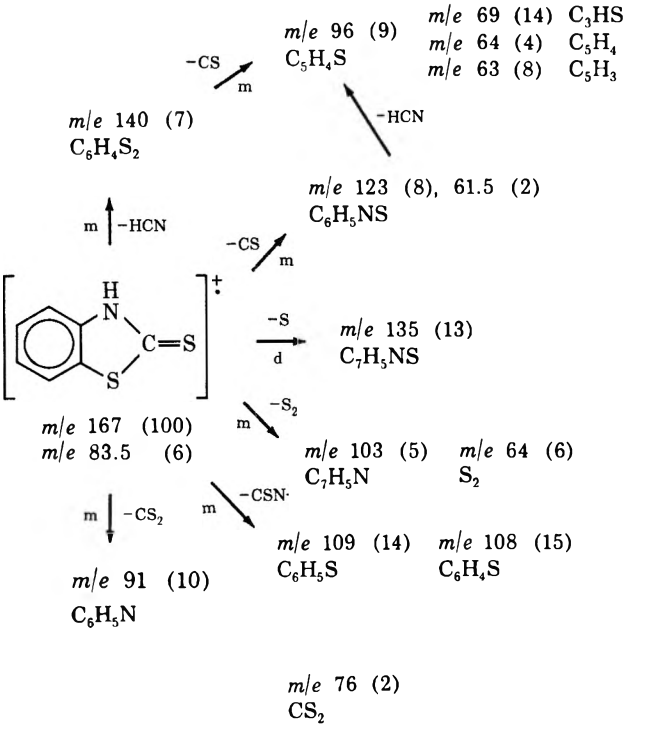
Extensive studies using, for example, ir[4] and ^{14}N nmr[5] techniques have shown that **1** exists in the thione form rather than in the tautomeric thiol form, both in the solid and in solution. Similar results have been obtained from studies on **2**[6] and **3**.[7] We do not know which form is present under our conditions of pyrolysis and in the mass spectrometer. However, our results can better be discussed in terms of the thione form; thus it will be used in the figures and schemes.

The mass spectra of **1**[8] and **2**[9] have been published previously. The mass spectrum of **3** is given in Figure 1. High-resolution data and metastable transitions are given in the schemes for the three compounds. Certain features of the mass spectra taken at low ionizing voltages are presented in the text. Chemical ionization mass spectra are discussed in the case of compounds **1** and **3**.

Results and Discussion

Benzothiazole-2-thione (1).—The 70-eV mass spectrum of benzothiazole-2-thione (**1**) is summarized in Scheme I. The elimination of S (*m/e* 167 → 135) from

Scheme I[a]



[a] m denotes a metastable peak in the mass spectrum; d denotes the detection of a metastable transition when the instrument is operated in the defocused mode; the elemental compositions result from exact-mass measurements; the values in parentheses are relative intensities.

the molecular ions is the only fragmentation when the electron voltage is lowered below 15 eV. Metastable transitions were detected for this loss of S and for the loss of S_2 (*m/e* 167 → 103); however, no metastable peak is detectable for the loss of S from *m/e* 135, which would give *m/e* 103 from the molecular ions by a two-

(1) Correspondence regarding this work should be addressed to Case postale 6128, Montréal 101, Québec.

(2) D. C. DeJongh and G. N. Evenson, *J. Org. Chem.*, **37**, 2152 (1972), and references cited therein.

(3) D. C. DeJongh and R. Y. Van Fossen, *Tetrahedron*, **28**, 3603 (1972).

(4) H. Larivé, A. J. Chambonnet, and J. Metzger, *Bull. Soc. Chim. Fr.*, 1675 (1963).

(5) A. Mathias, *Mol. Phys.*, **12**, 381 (1967).

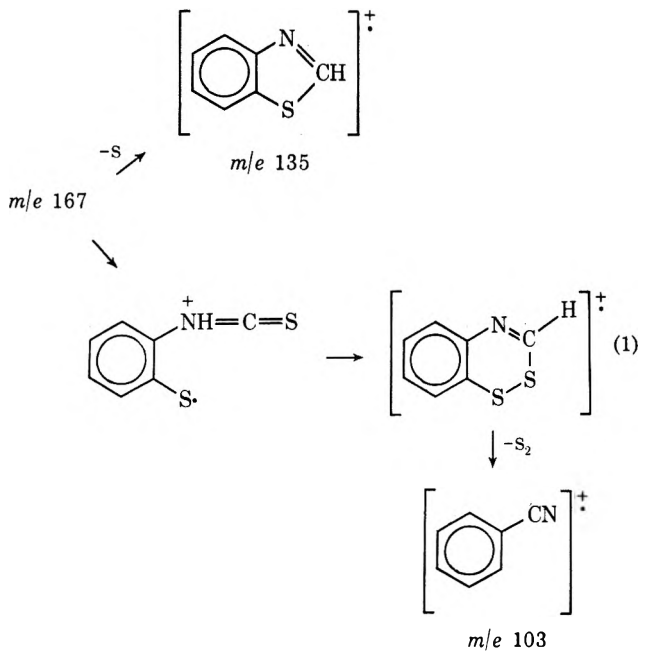
(6) P. Nuhn, G. Wagner, and S. Leistner. *Z. Chem.*, **9**, 152 (1969).

(7) N. L. Aryutkina, A. F. Vasil'ev, N. A. Poznanskaya, N. I. Shvetsov-Shilovskii, S. N. Ivanova, and N. N. Mel'nikov, *Zh. Obshch. Khim.*, **40**, 1872 (1970).

(8) B. J. Millard and A. F. Temple, *Org. Mass Spectrom.*, **1**, 285 (1968).

(9) H. Lund and L. G. Feoktistov, *Acta Chem. Scand.*, **23**, 3482 (1969).

step process. Possible rationals for the loss of S and S_2 from *m/e* 167 are given in eq 1; the ions corresponding

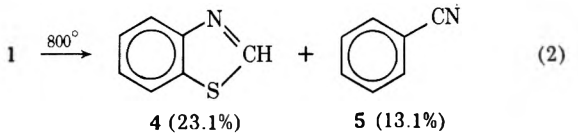


to the molecular ions of benzothiazole (**4**) and cyanobenzene (**5**) are shown as possibilities for *m/e* 135 and 103. Other fragmentations of the molecular ions of **1** involve losses of molecules and radicals from the heterocyclic ring, such as CS, CS_2, HCN, and CNS·. The mass spectrum of the closely related *o*-phenylene trithiocarbonate has been published and discussed.[10]

In the chemical ionization mass spectrum the (M + H) ion (*m/e* 168, 100%) and the (M + H − S) ion (*m/e* 136, 6%) are the only prominent peaks associated with **1**. In this case also, the loss of S is a low-energy path.

We were interested in trying to duplicate some of these losses from the molecular ions of **1** by means of thermal excitation. Therefore, we pyrolyzed **1** by subliming it in a stream of N_2 through a zone heated by an electric furnace. The apparatus and procedure are described in the Experimental Section. A range of temperatures (700–950°) was used; the details are given in the Experimental Section.

The pyrolysis products from **1** are benzothiazole (**4**) and cyanobenzene (**5**), eq 2. The percentages of **4** and



5 varied with the temperature used; the formation of **5** is favored at higher temperatures. In order to determine whether or not **5** forms from secondary pyrolysis of **4**, we pyrolyzed **4** under the same conditions that we had pyrolyzed **1**. At 750°, 64% of **4** was recovered and 0.6% of **5** was isolated; however, at 950°, only 7% of **4** was recovered and 44% of **5** was obtained. Thus, it is likely that **5** forms directly from pyrolysis of **1**, as well as from a secondary pyrolysis of **4**.

(10) E. K. Fields and S. Meyerson, *Int. J. Sulfur Chem., Part C*, **6**, 51 (1971).

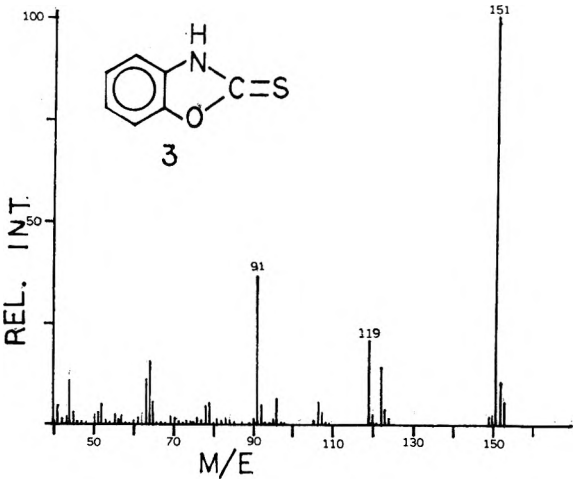


Figure 1.—Mass spectrum (70 eV) of benzoxazole-2-thione (**3**).

We used eq 3 in order to relate the pyrolyses of **1** and of **4**. Although the equation ignores conventional

$$\frac{A}{A+B} = \frac{D-X}{C+D-X} \qquad (3)$$

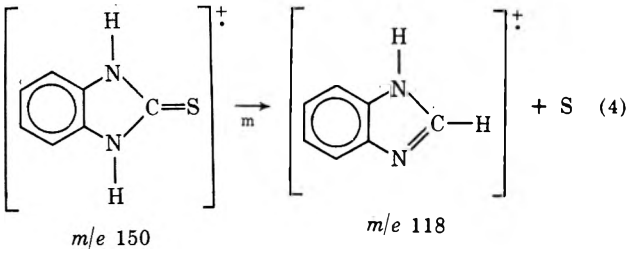
kinetics, it gives a crude idea of the relative amount of **5** which forms directly from **1** and the amount which forms indirectly from **1** *via* secondary pyrolysis of **4**. The term *A* equals the per cent of **5** formed from **4** in the pyrolysis of **4** and *B* represents the per cent of **4** recovered from the pyrolysis of **4**. The per cent of **4** isolated from the pyrolysis of **1** is *C*; *D* is the per cent of **5** isolated from the pyrolysis of **1**. The unknown quantity *X* is the per cent of **5** formed directly from **1** *via* a one-step process and $D - X$ is the per cent of **5** from **1** *via* the two-step path.

Using the results in the Experimental Section from the pyrolyses of **1** and **4**, at 750°, we calculated *X* and $D - X$. At 750°, a yield of 4.6% of **5** is formed from **1**; of this 4.4% is from the one-step path and 0.2% from the two-step path. At 900°, a yield of 34.1% of **5** is formed from **1**; of this 17.6% comes from the one-step path and 16.5% from the two-step path.

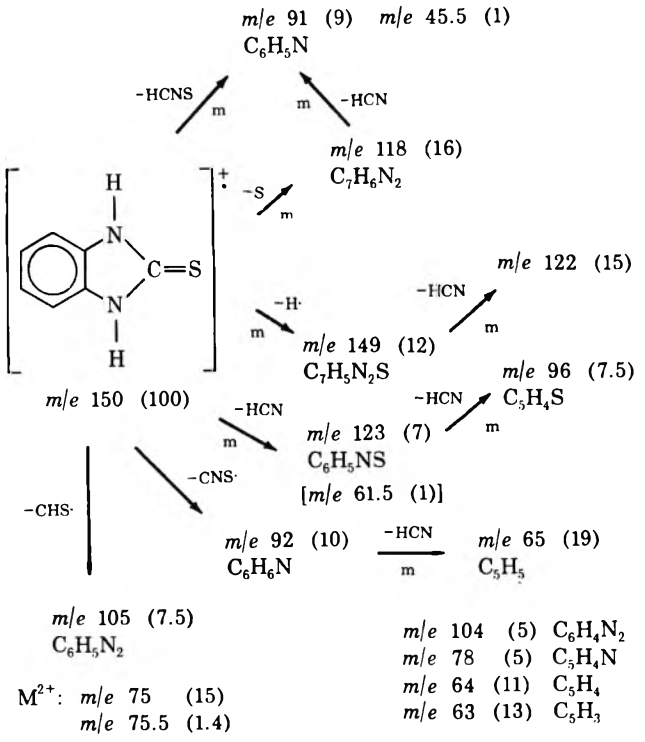
Thus, the formation of the pyrolysis products can be explained by the same competing paths observed in the mass spectrum (eq 1): the molecules lose S or S_2. In addition, at high temperatures, a further pyrolysis of **4** begins, giving **5** *via* two steps from **1**.

Benzimidazole-2-thione (**2**).—The 70-eV mass spectrum of benzimidazole-2-thione (**2**) is summarized in Scheme II.

The lowest energy path, *i.e.*, the only path to survive below 14 eV, is the loss of S, giving *m/e* 118. This fragmentation is accompanied by a metastable peak. The ions at *m/e* 118 probably correspond to the molecular ions of benzimidazole (**6**) (eq 4).

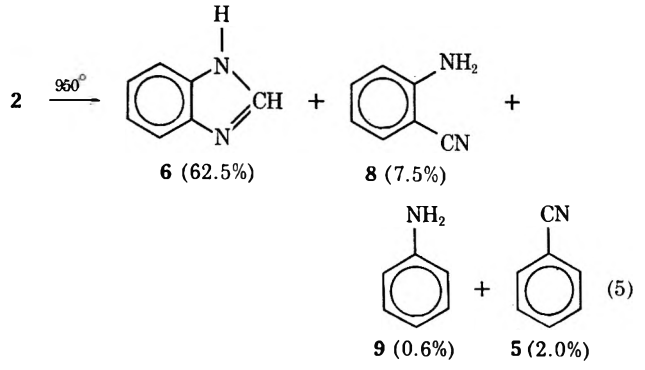


Scheme II



Other prominent ions are *m/e* 92 and 91, which correspond to ions in the mass spectrum of aniline, and *m/e* 123, formed by the loss of HCN from the molecular ions. At 15 eV, the intensities are *m/e* 150 (100), 123 (3), 118 (9.5) and 92 (2.0); and at 12 eV they are *m/e* 150 (100) and 118 (8.0). The C_6H_5N ion at *m/e* 91 could have the structure of the molecular ions of cyanocyclopentadiene (**7**).

Benzimidazole-2-thione (**2**) was pyrolyzed at various temperatures between 850 and 1000°. The products and percentages obtained at 950° are given in eq 5.



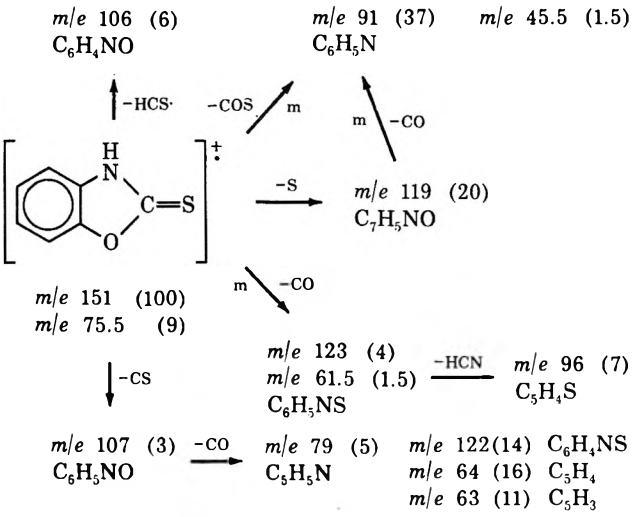
No starting material was recovered at 850° or above. Benzimidazole (**6**) and 2-cyanoaniline (**8**), the major products, are isomers and account for 70% of the starting material. The yield of **6** is at a maximum at 950° and decreases to 27% at 1000°, whereas the yield of **8** increases to 13% at 1000°.

Benzimidazole (**6**) was pyrolyzed at 900 and 1000° under the same conditions as used in the pyrolyses of **2**. At 900°, 91% of **6** was recovered and 2.6% of **8** was isolated. At 1000°, the yields were 83.6 and 13.8%, respectively. At 1000°, the pyrolysis of **8** gave 1.5% of aniline (**9**) and 71.6% of recovered **8**. Therefore, **8** is formed from **6** as the result of a secondary pyrolysis, and **9** is formed from **8**. The small amount of **5** probably comes from a higher energy path.

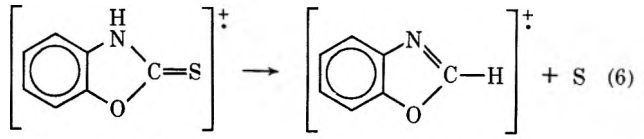
Thus, the major products in the pyrolysis and the major fragmentation in the mass spectrum result from initial elimination of S.

Benzoxazole-2-thione (3).—The 70-eV mass spectrum of benzoxazole-2-thione (**3**) is given in Figure 1 and is summarized in Scheme III. At 8 eV, the paths

Scheme III

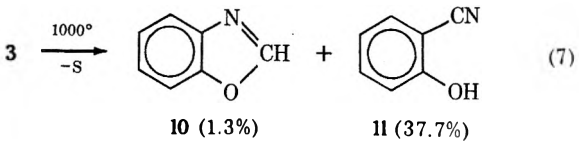


involving the initial loss of S and COS are the only ones remaining: *m/e* 151 (100), 119 (25), and 91 (11). Other fragmentations at 70 eV of the molecular ions commence with initial losses of neutral molecules and radicals such as CO and CS. The ions formed from *m/e* 151 by loss of S can be visualized as the molecular ions of benzoxazole (**10**) (eq 6).



In the chemical ionization mass spectrum of **3**, there is no evidence of the loss of COS from the (M + H) ions. The peak at *m/e* 120 (M + H − S) is 6% of the intensity of *m/e* 152 (M + H). There are no other prominent fragments of the (M + H) ion.

Pyrolysis of **3** is first observed, under our conditions, at 850° and no starting material is recovered above 950°. At 1000°, benzoxazole (**10**, 1.3%) and its isomer 2-cyanophenol (**11**, 37.7%) account for 39% of the starting material (eq 7), resulting from the initial loss

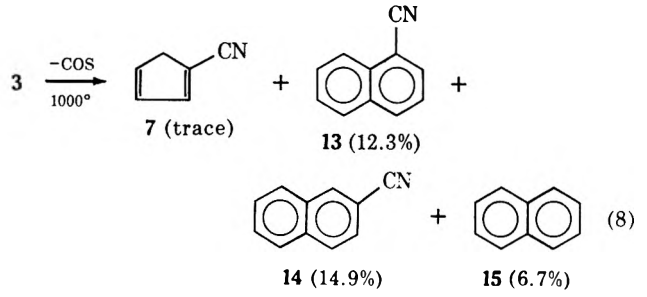


of S. The pyrolyses of **10** and **11** were also performed in this study, at 900 and 1000°. Benzoxazole (**10**) is converted to **11** in 82% yield at 900°. It is interesting to note that **11** irreversibly cyclizes to **10** upon photolysis.[11]

(11) J. P. Ferris and F. R. Antonucci, *Chem. Commun.*, 126 (1972).

Aniline (**9**, 3.2%), cyanobenzene (**5**, 2.0%), and phenol (**12**, 3.2%) are also isolated at 1000° from **3**. At 1000°, a small amount of phenol is formed from **10**; also phenol and cyanobenzene are formed from **11** when it is pyrolyzed at 900–1000°, in small yields.

Another series of products is observed from **3**. They are probably related to one another because they are not formed when CH_3OH is added to the stream, although **10**, **11**, **9**, **5**, and **12** still are. These compounds are cyanocyclopentadiene (**7**, trace), 1-cyanonaphthalene (**13**, 12.3%), 2-cyanonaphthalene (**14**, 14.9%), and naphthalene (**15**, 6.7%), eq 8. The origin of these



(8)

products is being studied in detail and will be the subject of another report. The products are best explained by a loss of COS from **3** (eq 8) competing with the loss of S (eq 7).

The products shown in eq 7 and 8 account for 81.3% of the starting material, assuming that two molecules of **3** are necessary to form one molecule of **13**–**15**. Thus two main processes are taking place when benzoxazole-2-thione (**3**) is pyrolyzed: the initial loss of S and the initial loss of COS. If the yields of the products associated with the initial loss of S are added together and those associated with the initial loss of COS are added, the ratio of path S to path COS is 4 at 850° and 1.1 at 1000°. As the temperature increases, the loss of COS competes more successfully with the loss of S.

At 10 eV the ratio of the relative intensities of *m/e* 119 (M − S) and *m/e* 91 (M − COS) is 1.1; at 7 eV, it is 4.7. Eventually, *m/e* 91 disappears and only *m/e* 119 remains, along with the molecular ion. Thus both at the lower voltages and the lower pyrolysis temperatures, the initial loss of S predominates.

Conclusions

The pyrolytic and electron-impact fragmentations of the thiones **1**–**3** are similar, showing that the lowest energy paths in the mass spectra can be compared with the lowest energy pyrolytic paths. In these molecules, there are no alkyl groups or other substituents which would give stable ions having no equivalent in pyrolysis. Thus, the mass-spectral fragmentations seem to be governed by the elimination of small, neutral species rather than by the stability of the charged species. Also, the pyrolytic fragmentations are driven by the elimination of the same molecules.

In summary, in their low-energy paths, **1** and its molecular ions eliminate S and S_2; **2** and its molecular ions eliminate S; and **3** and its molecular ions eliminate S and COS. Always, the loss of S is the lower energy process; it is the only path observed from the (M + H) ions upon chemical ionization. Yields are relatively high from the pyrolyses, ranging from 40 to 80% under conditions which do not give any recovered starting material. Since all the products which were isolated are known compounds, these pyrolyses are not obviously useful from a synthetic standpoint. The interesting aspects of this work are the parallels observed between the mass-spectral and pyrolytic fragmentations.

Experimental Section

Melting points were determined by the open capillary method with a Thomas-Hoover or a Mel-Temp melting point apparatus and were corrected. Infrared spectra were recorded with a Perkin-Elmer Infracord or Beckman IR-8 spectrometer. Ultraviolet spectra (1 cm path) were determined on a Bausch and Lamb Spectronic 505. Nmr spectra were taken on a Varian T-60 or a JEOLCO A-60 spectrometer using 1% TMS as an internal standard. Low-resolution mass spectra were obtained from AEI-MS 902, Hitachi RMU-6D, and LKB 9000 mass spectrometers. Electron voltage readings were taken directly from the dial, since more precise values were not needed. Exact-mass measurements were obtained from an AEI-MS 902 mass spectrometer equipped with a PDP-8 computer. For 72.2% of the peaks studied, the deviations between the calculated and experimental masses were $\leq \pm 0.001$ mass units (mu). For 25.0% of the peaks studied, the deviations were 0.003–0.001 mu; and for 2.8% of the peaks, the deviations were 0.005–0.003 mu. Metastable peaks were observed in the low-resolution spectra, and, in addition, some metastable transitions were studied with the MS 902 while scanning in the defocused metastable mode.

The chemical ionization mass spectra were obtained from an AEI-MS 902 mass spectrometer, using isobutane. A source temperature of 250° and a probe temperature of 70–80° were used.

The glpc work was carried out using a Hewlett-Packard 5752B research chromatograph with a thermal conductivity detector. Columns were prepared with 0.25 in. copper tubing and 60/80 mesh Chromosorb W as a solid support, unless otherwise stated. A total of 17 columns was used; during the initial stages of analysis of the pyrolysis mixtures, most of the columns were tried. However, only the column that gives the best separations is reported in the Experimental Section. Comparison of the areas under the peaks of the pyrolysis products with the areas under peaks of solutions of known concentrations of the same compound was used to determine yields.

Chemicals.—Benzothiazole-2-thione (**1**) and benzimidazole-2-thione (**2**) were obtained from Aldrich Chemical Co., and benzoxazole-2-thione (**3**) was obtained from Eastman Organic Chemicals. Compounds **1**–**3** were recrystallized prior to use, and their purities were further checked by glpc, tlc, and mass spectrometry: **1**, mp 180–181° (lit.[12] mp 178–180°); **2**, mp 299–301° (lit.[13] mp 303–304°); and **3**, mp 194–195° (lit.[13] mp 193–195°).

Benzothiazole (**4**), 2-cyanoaniline (**8**), benzoxazole (**10**), and 2-cyanophenol (**11**) were purchased from the Aldrich Chemical Co. Benzimidazole (**6**) and 1- and 2-cyanonaphthalene (**13** and **14**) were purchased from Eastman Organic Chemicals.

Pyrolysis Apparatus.—Dry N_2 was passed through a tube fitted with a fritted disc on which were placed solid samples. The N_2 flow rate was monitored and controlled with a rotometer which was placed before the sample holder. Heating tape wrapped around the outside of the sample holder was used to sublime the sample into the pyrolysis tube. An auxiliary inlet was connected to a round-bottomed flask from which liquid samples were distilled into the pyrolysis tube; this inlet was also used to introduce a trapping agent (*e.g.*, CH_3OH) into the pyrolysis zone. Thus, the sample, N_2, and the trapping agent can pass through the pyrolysis zone simultaneously (trapping method A).

The sample holder was connected to a 24 × 1 in. (i.d.) hollow quartz pyrolysis tube. A 12-in. Hoskin electric furnace surrounded the quartz tube. The temperature of the furnace was controlled and read on a Thermolyne Corp. Temcometer. The temperature reported is approximately that of the internal portion of the quartz tube in the center of the oven.

A variety of traps was placed between the quartz tube and a vacuum pump. These traps were cooled by air and/or liquid N_2. Sometimes, the pyrolysis products were condensed on a cold

(12) D. J. Banks and P. Wiseman, *Tetrahedron*, **24**, 6791 (1968).

(13) J. A. VanAllen and B. D. Deacon, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 569.

finger (Dry Ice–2-propanol) on which a trapping agent (*e.g.*, CH_3OH) was refluxing (trapping method B). A manometer and a McLeod gauge placed before the pump were used to read the pressure of the system.

Pyrolysis Procedure.—In a typical experiment approximately 2 g of sample was placed on the fritted disc (for solid samples) or in the round-bottomed flask (for liquid samples). Then the pyrolysis system was evacuated and flushed with dry N_2. After a few minutes the N_2 flow was adjusted to the desired rate. The electric furnace was then brought to temperature while the coolants were added to the dewar flasks surrounding the traps. The sample was sublimed or distilled through the pyrolysis tube. Upon completion of the pyrolysis, the oven was turned off and the quartz tube was allowed to cool to about 200°. Then dry N_2 was used to bring the system to atmospheric pressure and a solution was made of the material in the traps. This solution was worked up using glpc and tlc.

Pyrolysis of Benzothiazole-2-thione (1).—The conditions used in the pyrolyses of benzothiazole-2-thione (1) and the results are summarized in Table I. In each case, three traps were employed;

Table I

Conditions[a] Used in the Pyrolysis of Benzothiazole-2-thione (1) and Results

Quantity, g	Temp, °C	1, % recovd	4, %	5, %	Total, %
1.141	700	31.6	8.4	0.8	40.6
1.500	750	16.7	17.1	4.6	38.4
1.210	800	0.0	23.1	13.1	36.2
1.410	850	0.0	16.3	24.3	40.6
1.288	900	0.0	6.6	34.1	40.7
1.199	950	0.0	0.0	44.4	44.4

[a] A N_2 flow rate of 0.20–0.28 l./min and a system pressure of 2.10–2.75 Torr were used.

the first was air cooled and the next two were cooled with liquid N_2. The products were identified as benzonitrile (5) and benzothiazole (4) by comparison of their retention times and their ir and mass spectra with those of commercial compounds. A 6-ft 20% SE-30 column, programmed between 50 and 260° at 10°/min, was used to analyze the pyrolysis mixtures.

Pyrolysis of Benzothiazole (4).—The conditions used and yields from the pyrolyses of benzothiazole (4) are summarized in Table II.

Table II

Conditions[a] Used in the Pyrolysis of Benzothiazole (4) and Results

Quantity, g	Temp, °C	4, % recovd	5, %	Total, %
1.36	750	64.4	0.6	65.0
1.600	800	49.0	3.0	52.0
1.438	850	26.8	11.2	38.0
1.778	900	12.8	32.0	44.8
1.376	950	6.9	44.2	51.1

[a] A N_2 flow rate of 0.20–0.22 l./min and a system pressure of 2.0–3.5 Torr were used.

The sample was distilled into the pyrolysis zone from a 25-ml round-bottomed flask. One air-cooled and two liquid N_2 cooled traps were used. Glpc, with a 20% SE-30 column, was used to analyze chloroform solutions of the pyrolysis products. The temperature rise was programmed between 50 and 260° at 15°/min. Benzonitrile (5) was the only major product, other than recovered starting material.

Pyrolysis of Benzimidazole-2-thione (2).—The conditions used for the pyrolyses of benzimidazole-2-thione (2) and the results are summarized in Table III.

The pyrolysis products were eluted with methanol and chloroform from the air-cooled and the two liquid N_2 cooled traps. Then the solutions were analyzed with a 6-ft 10% Carbowax 20M column programmed at 50–250° at 15°/min, by thin layer chromatography, and/or by the LKB-9000 gc/mass spectrum combination using a 6-ft 3% OV-1 CHROM HP 80/100 mesh column, isothermal at 110°.

Table III

Conditions[a] Used in the Pyrolyses of Benzimidazole-2-thione (3) and Results

Quantity, g	Temp, °C	5, %	9, %	8, %	6, %	Total, %
1.483	850	2.0	0.2	4.7	55.8	62.7
1.302	900	2.6	0.6	7.5	61.1	71.8
1.671	950	2.0	0.6	7.5	62.5	72.6
1.451	1000	1.1	2.1	13.0	26.6	42.8

[a] A N_2 flow rate of 0.20–0.22 l./min and a system pressure of 2–5 Torr were used.

Aniline (9), benzonitrile (5), 2-cyanoaniline (8), and benzimidazole (6) were identified by comparison of the products with commercial samples.

Pyrolysis of Benzimidazole (6).—The conditions used for the pyrolyses of benzimidazole and the results are given in Table IV.

Table IV

Conditions[a] Used in the Pyrolyses of Benzimidazole (6) and Results

Quantity, g	Temp, °C	6, % recovd	8, %	Total, %
1.424	900	91.3	2.6	93.9
1.613	1000	83.6	13.8	97.4

[a] A N_2 flow rate of 0.22 l./min and a system pressure of 2–5 Torr were used.

The pyrolysis mixtures were analyzed with a 10% QF-1 column, programmed at 150–230° at 15°/min; the temperature was then held at 230° for 5 min. The presence of 2-cyanoaniline (8) and starting material was detected.

Pyrolysis of 2-Cyanoaniline (8).—At 1000°, 1.552 g of 2-cyanoaniline (8) (N_2 flow rate 0.22 l./min at 3 Torr) was pyrolyzed. The traps were eluted with methanol and chloroform. The resulting dark brown solution was analyzed using the same chromatographic column (10% QF-1) and conditions as in the previous pyrolysis. Using retention times and areas under the peaks (by weighing), it was determined that 1.5% of aniline (9) and 71.6% of starting material (8) were in the traps.

Pyrolysis of Benzoxazole-2-thione (3).—The pyrolyses of benzoxazole-2-thione (3) were performed under the conditions described in Table V along with the results. The pyrolysis products were washed from the traps with methanol, acetone, and chloroform to give a total volume of approximately 300 ml. Then, most of the solvent was removed under vacuum to give 20–30 ml of solution, which was analyzed chromatographically. Two glpc columns were used. The first column (6-ft 10% Carbowax 20M) was programmed at 150-230° at 15°/min and was then held at 230° for 10 min. Under these conditions, six major components were separated.

The second column (6-ft 3% OV-1 CHROM HP 80/100 mesh) was programmed at 90–200° at 6°/min and revealed a seventh component. Its mass spectrum has peaks at m/e 128 ($M\cdot^+$), 127, 102, 64, 51, and 39. There also is a metastable peak at m/e 82.5 which corresponds to the loss of C_2H_2 from the molecular ion. It has the same retention time as naphthalene and was enhanced upon addition of naphthalene to the pyrolysis mixture.

At 1000°, no more starting material was present in the mixture of products but a new compound was detected when both columns were used. This product was determined to be benzonitrile (5) by its glpc characteristics and its smell.

A very minor component was detected when gc/mass spectrum was employed. Its molecular ion was found at m/e 91 and loses 27 mass units to give an ion at m/e 64. The structure of this component is tentatively assigned as 1-cyanocyclopentadiene (7).

The rest of the products were identified by comparison of their retention times, ir, uv, and mass spectra, and, in the case of 11, melting point, with those of commercial samples.

Pyrolysis of Benzoxazole (10).—Conditions for the pyrolyses of benzoxazole (10) and results are given in Table VI. The traps

TABLE V

CONDITIONS[a] USED IN THE PYROLYSES OF BENZOXAZOLE-2-THIONE (3) AND RESULTS

Quantity, g	Temp, °C	3, % recovd	10, %	9, %	12, %	13, %	14, %	11, %	15, %	5, %	Total, %
1.854	850	59.9	1.3	0.2	2.0	0.9	1.0	8.6	0.9	0	74.8
1.620	900	33.9	1.3	1.3	4.1	3.6	4.1	24.1	4.4	0	76.8
1.603	950	14.2	1.5	2.0	5.1	6.2	7.4	27.3	11.1	0	74.8
1.603	1000	0	1.3	3.2	3.2	12.3	14.9	37.7	6.7	2.0	81.3
1.914[b]	1000	0	1.2	1.7	1.8	8.2	12.8	24.3	0	0	50.0
1.769[c]	1050	0	3.6	4.7	5.2	0	0	55.7	0	0	69.2

[a] A N_2 flow rate of 0.20–0.22 l./min was used and a system pressure of 1–4 Torr was maintained. [b] CH_3OH was used as a trapping agent following method B. [c] CH_3OH was used as a trapping agent following method A.

TABLE VI

CONDITIONS[a] USED FOR THE PYROLYSES OF 10 AND RESULTS

Quantity, g	Temp, °C	10, % recovd	11, %	12, %	Total, %
1.960	900	4.0	81.6	0	85.6
1.728	1000	2.8	55.0	1.6	59.4

[a] A N_2 flow rate of 0.25 l./min and a system pressure of 1–2 Torr were used.

TABLE VII

CONDITIONS[a] USED IN THE PYROLYSES OF 11 AND RESULTS

Quantity, g	Temp, °C	11, % recovd	5, %	12, %	Total, %
1.464	900	74.1	1.5	0	75.6
1.498	1000	58.5	3.6	6.1	68.2
1.807[b]	1000	88.8	2.1	0	90.9

[a] A N_2 flow rate of 0.22 l./min and a system pressure of 1–3 Torr were used. [b] CH_3OH was used as a trapping agent *via* method B.

were eluted with a mixture of solvents, *ca.* 300 ml, and then the volume was reduced to 20–30 ml under vacuum. Gas chromatographic analyses using the same columns and the same programming used in the pyrolyses of **3** were used.

Pyrolysis of 2-Cyanophenol (11).—The conditions used in the pyrolyses of 2-cyanophenol (**11**) and the results are given in Table VII. The glpc work-up was the same as that used in the study of the pyrolyses of **3**. In addition to **5** and **12**, gc/mass spectrum revealed a minor amount of a component with a molecular ion at *m/e* 91 which loses 27 mu, probably cyanocyclopentadiene (**7**). A minor amount of toluene was also detected by the LKB 9000.

Registry No.—**1**, 4464-58-8; **2**, 2080-59-3; **3**, 14955-23-8; **4**, 95-16-9; **6**, 51-17-2; **8**, 1885-29-6; **10**, 273-53-0; **11**, 611-20-1.

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Reaction of 1,1-Dichloro-2-phenylsulfonylcyclopropanes with Sodium Alkoxides[1]

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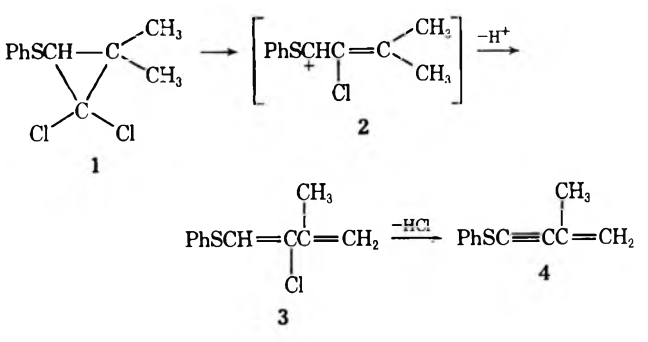
Reaction of 1,1-dichloro-2,2-dimethyl-3-phenylsulfonylcyclopropane (**5**) with sodium methoxide in methanol or sodium ethoxide in ethanol at room temperature gives excellent yields of the corresponding cyclopropyl ketals (**6a, 6b**); the corresponding thioketal (**7**) is formed with thiophenoxide. The cyclopropyl ketals are unstable in hot alcohols and are converted quantitatively into ortho esters (**8a, 8b**) or mixed ortho esters (**8c**). Reactions with two other analogous dihalocyclopropanes (**13**) are described; conversion to ortho esters proceeds generally and in high yield.

We have previously shown that 2,2-dichlorocyclopropyl phenyl sulfides of type **1** are unstable in hot alcohols, and in the presence of the strong base potassium *tert*-butoxide[3] give enynes (**4**) as illustrated for **1** in Scheme I. The accelerating effect of the sulfur atom is considered to be a driving force for this exocyclic ring opening reaction, since sulfur can stabilize the positive charge developed in the transition state (or intermediate **2**).

Replacement of the phenylmercapto group in **1** by the phenylsulfonyl group (as in **5**) would destabilize an intermediate ion corresponding to **2**, and, as expected, dihalo-2-phenylsulfonylcyclopropanes have been found to be comparatively thermally stable. These sulfones do, however, react readily with alkoxides

SCHEME I



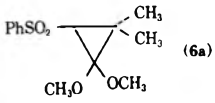
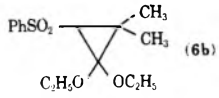
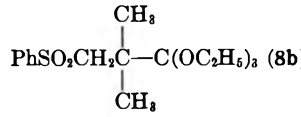
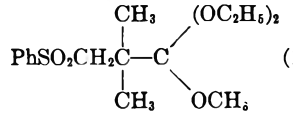
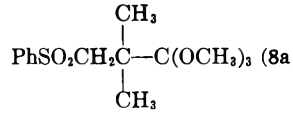
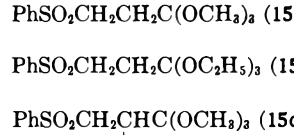
(1) Supported in part by National Science Foundation Grant GP-11918.

(2) Paul M. Gross Chemical Laboratory, Duke University, Durham, N. C.

(3) W. E. Parham, S. Kajigaeshi, and S. H. Groen, *Bull. Chem. Soc. Jap.*, **45**, 509 (1972).

TABLE I

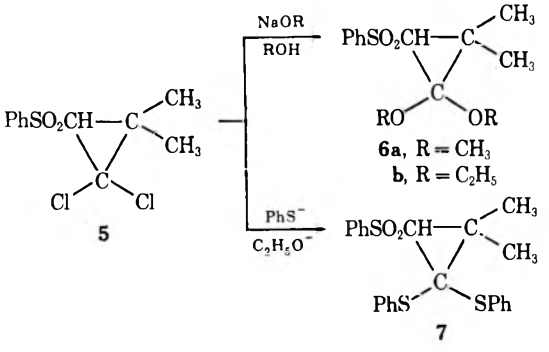
FORMATION OF 1,1-DIALKOXY-3-PHENYLSULFONYLCYCLOPROPANES AND ALKYL β-PHENYLSULFONYL ORTHOPROPIONATES[a]

No.	Sulfone	Sodium alkoxide (ROH)	Δ, °C (hr)	Product	Mp [bp (mm)], °C	Yield, % (isolated, pure)	Anal. Found (calcd) C, %	H, %	S, %	Formula
1	5	$NaOCH_3$ (CH_3OH)	32 (15) 65 (4)	 (6a)	70.5–72 [95–97 (0.04)]	93	57.57 (57.76)	6.73 (6.71)		$C_{13}H_{18}O_4S$
2	5	$NaOC_2H_5$ (C_2H_5OH)	32 (24)	 (6b)	86–87	92	60.63 (60.37)	7.62 (7.43)	10.45 (10.75)	$C_{15}H_{22}O_4S$
3	5	$NaOC_2H_5$ (C_2H_5OH)	78 (23)	6b 8b	86–87 50.5–52	~45 ~45				
4	6b	C_2H_5OH	78 (72)	 (8b)	50.5–52	71	59.42 (59.27)	8.05 (8.19)	9.07 (9.31)	$C_{17}H_{28}O_5S$
5	6b	CH_3OH	65 (72)	 (12)	49–50.5	71	58.22 (58.16)	8.01 (7.93)		$C_{16}H_{26}O_5S$
6	6a	CH_3OH	65 (72)	 (8a)	52–55	65	55.42 (55.61)	7.20 (7.33)	10.71 (10.60)	$C_{14}H_{22}O_5S$
7	13a	$NaOCH_3$ (CH_3OH)	65 (2)	$PhSO_2CH_2CH_2C(OCH_3)_3$ (15a)	Oil	90				$C_{12}H_{18}O_5S$
8	13a	$NaOC_2H_5$ (C_2H_5OH)	78 (4) 32 (6)	$PhSO_2CH_2CH_2C(OC_2H_5)_3$ (15b)	49.5–51.0	85 65	56.93 (56.94)	7.75 (7.65)		$C_{15}H_{24}O_5S$
9	13b	$NaOCH_3$ (CH_3OH)	65 (4)	 (15c)	48–49.5	86	53.36 (54.16)	6.77 (6.99)		$C_{13}H_{20}O_5S$

[a] The 1,1-dialkoxy-2-phenylsulfonylcyclopropanes and alkyl β-phenylsulfonylorthopropionates are converted to alkyl π-phenylsulfonylpropionates (9, 16) by moisture in air.

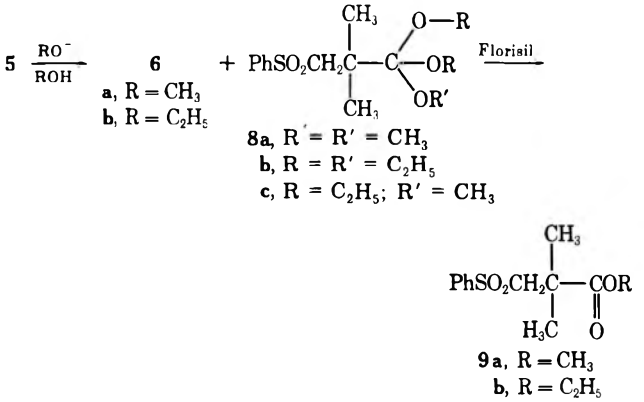
to give cyclopropyl ketals and/or ortho esters, a study which constitutes the subject of this report.

When **5** was treated with sodium methoxide in methanol either at room temperature (15 hr) or at the reflux temperature (4 hr), or with sodium ethoxide in ethanol at room temperature, the corresponding cyclopropyl ketals (**6a** and **6b**, respectively) were formed in



high yield (86–93%). These reactions are believed to occur by two successive processes, each of which involves elimination of hydrogen chloride to give the corresponding cyclopropene which subsequently adds alcohol to give product, a sequence of reactions for which there is ample precedent.[4] Treatment of **5** with thiophenol in ethanol containing more than 2 equiv of ethoxide gave the corresponding thioketal **7**, which was isolated in 100% yield. The thioketal **7** was quite stable and was recovered unchanged after prolonged treatment with hot aqueous sodium hydroxide, hot dilute hydrochloric acid, hot ethanol (17 days), and sodium ethoxide in boiling ethanol (67 hr).

When the reaction of **5** with ethoxide was carried out in boiling ethanol (23 hr), the product was a mixture of ketal **6b** and the ortho ester **8b** (~45% yield



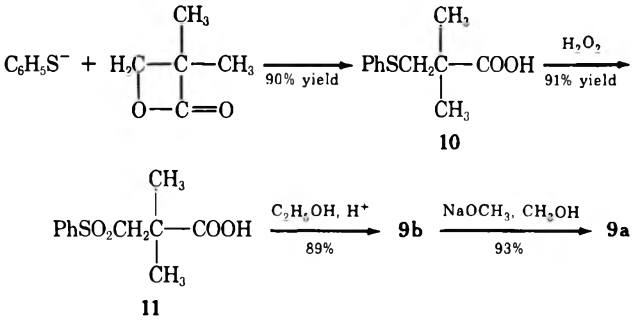
of each) which was resolved by recrystallization. This result suggested that the ketals **6** were unstable in hot alcohol, and this was shown to be the case. Prolonged treatment of **6b** with hot ethanol gave **8b**, and reaction of **6b** with hot methanol gave the mixed ortho ester **8c**. Similarly, reaction of **6a** with hot methanol gave **8a**. These conversions required reaction times of 48–72 hr and gave essentially quantitative yields of ortho esters (see Table I). While the exact mechanism

(4) (a) T. C. Shields and P. D. Gardner, *J. Amer. Chem. Soc.*, **89**, 5425 (1967); (b) K. B. Baucom and G. B. Butler, *J. Org. Chem.*, **37**, 1730 (1972).

for the conversion of **6** to **8** is not known, the products are those expected by cleavage of a carbon–carbon bond in the cyclopropane ring in a manner consistent with the ability of the phenylsulfonyl group to stabilize a developing negative charge and the oxygen atoms of the ketal carbon atom to stabilize a developing positive charge (as represented in Scheme III). Conversion of **6** to **8** does not require acid catalysis, since **8** was formed from **6** in hot alcohol containing excess alkoxide.

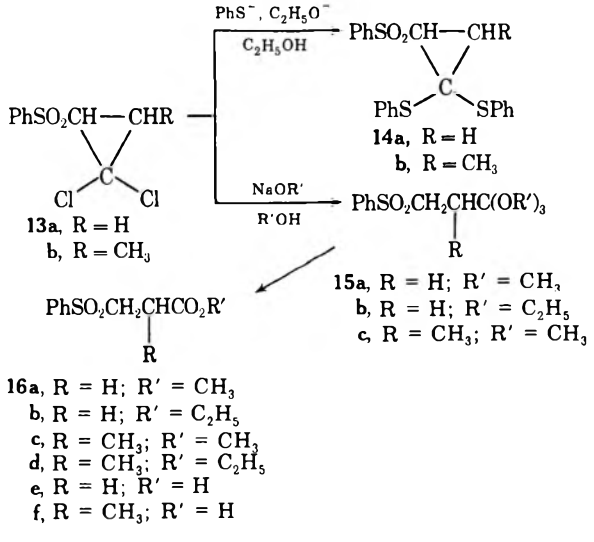
Both **6** and **8** were quite sensitive to acid or moisture in the air, and reaction of either with Florisil in benzene gave the esters **9** in essentially quantitative yield. Similar treatment of **8c** gave a mixture of **9a** and **9b** in the approximate ratio of 1:2. The esters **9** were readily hydrolyzed by alkali (or acid) to the corresponding acid **11**, and the structures of **9** and **11** were established by their independent synthesis as shown in Scheme II.

SCHEME II



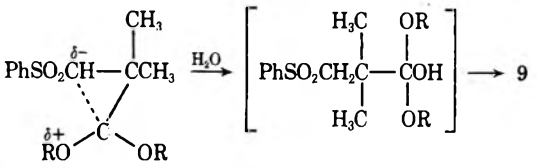
The ketals **6** react with water to give esters **9** and with hot aqueous sodium hydroxide to give the salt of **11** (100% yield). While these reactions could involve the intermediate cyclopropanone, followed by a Favorskii rearrangement, we believe that they involve ring opening by water to give **12** (Scheme III) in a manner analogous to that described above for methanol and ethanol.

Formation of ortho esters from 1,1-dichlorocyclopropanes appears to be general from cyclopropanes of type **13**. Reaction of **13a** and **13b** with thiophenol



and excess sodium ethoxide in ethanol gave the thioketals **14a** and **14b**, which were isolated in 88 and 74% yield, respectively. Reaction of **13a** and **13b** with

SCHEME III



sodium methoxide in boiling methanol (4 hr) gave only the ortho esters **15a** and **15c** (see Table I). Similarly, **13a** gave only the ortho ester **15b** when treated with sodium ethoxide in ethanol at room temperature. It is apparent that geminal alkyl substitution on carbon (as in **6**) increases the stability of the cyclopropyl ketal, and it is assumed that the basis of this stabilization of the cyclopropane by dialkyl substitution is steric in origin.[5]

The ortho esters **15a–c** were converted in high yields to esters **16a–c**[6] by action of acid, which were in turn hydrolyzed to the corresponding acids **16e**[7] and **16f**[8] by alkaline hydrolysis or by acid-catalyzed hydrolysis and ester interchange.

Experimental Section

1,1-Dichloro-2,2-dimethyl-3-phenylsulfonylcyclopropane (**5**) was obtained by oxidation of 2,2-dichloro-3,3-dimethylcyclopropyl phenyl sulfide[9] in acetic acid with hydrogen peroxide (80°, 3.5 hr): mp 102–103° (from ethanol); nmr (CCl_4) δ 1.46, 1.68 (two s, 6, CH_3), 2.58 (s, 1, CH), 7.40–8.00 (m, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{12}Cl_2O_2S$: C, 47.32; H, 4.33; S, 11.48. Found: C, 47.33; H, 4.41; S, 11.36.

1,1-Dichloro-2-phenylsulfonylcyclopropane (**13a**) **and 1,1-dichloro-2-methyl-3-phenylsulfonylcyclopropane** (**13b**) were prepared as previously described.[9]

Reactions of 5 and 13 with Alkoxide in Alcohol.—A typical experimental procedure is as follows. Sodium metal (0.7 g, 0.03 g-atom) was dissolved in anhydrous ethyl alcohol (55 ml) in a dry nitrogen atmosphere. A solution of **13a** (2.5 g, 0.01 mol) in anhydrous ethanol (30 ml) was added slowly, and the resulting mixture was heated at the reflux temperature for 4 hr. The mixture was poured into water (200 ml) and then extracted with ether (200 ml) and dried ($MgSO_4$). Evaporation of the ether solution afforded white crystals of **15b**, mp 49.5–51.0° (from *n*-hexane).

Results of similar reactions including those of **6a** and **6b** with anhydrous alcohols are summarized in Table I.

The mass spectra of **15a** (75 eV) showed *m/e* (rel intensity) 243 (13), 141 (9), 105 (100), 101 (75), 87 (20), 77 (48), 59 (35), 55 (40); **15c** (30 eV) showed *m/e* (rel intensity) 288 (0.3, M^+), 257 (34), 141 (2), 115 (30), 105 (100), 101 (10), 77 (5), 59 (13). In general, intensities of molecular peaks of the ortho esters were very weak; the molecular peak of **15a** was not confirmed.

A.—Compound **6a** (from pentane) had nmr ($CDCl_3$) δ 1.20 and 1.58 (two s, 6, CH_3), 2.13 (s, 1, SO_2CH–), 3.12, 3.46 (two s, 6, OCH_3), 7.40–8.00 (m, 5, C_6H_5).

B.—Compound **6b** (from pentane) had nmr (CCl_4) δ 0.93–1.53 [m, 12, $-C(CH_3)_2$ and OCH_2CH_3], 2.13 (s, 1, $-SO_2CH$), 3.0–4.0 (m, 4, OCH_2), 7 54 and 7.92 (two m, 5, C_6H_5).

C.—**6b** and **8b** (17.32 g) were separated by fractional crystallization from pentane (300 ml); **6b** was less soluble.

D.—**8b** (from pentane) had nmr ($CDCl_3$) δ 1.13 (t, J = 7 Hz, OCH_2CH_3), 1.26 [s, $C(CH_3)_3$, area between 1.0 and 1.3, total

(5) *Cf.* E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, pp 196–198.

(6) For **16a** and **16c** see C. D. Hurd and L. L. Gershbein, *J. Amer. Chem. Soc.*, **69**, 2328 (1947). For **16b** see (a) O. Achmatowicz[2] and J. Michalski, *Rocz. Chem.*, **30**, 243 (1956); (b) P. Buckus, R. Stonite, and A. Buckiene, *Zh. Vses. Khim. Obshchest.*, **11** (4), 468 (1966).

(7) (a) B. Holmberg and E. Schjanberg, *Ark. Kemi. Mineral. Geol.*, A15, No. 20, 14 (1942) [*Chem. Zentralbl.*, **I**, 388 (1943)]. (b) T. L. Gresham, *et al.*, *J. Amer. Chem. Soc.*, **74**, 1323 (1952).

(8) E. Larsson, *Trans. Chalmers Univ. Technol., Gothenburg*, **No. 35**, 3 (1944).

(9) W. E. Parham, L. Christensen, S. H. Groen, and R. M. Dodson, *J. Org. Chem.*, **29**, 2211 (1964).

weight 15], 3.37 (s, 2, SO_2CH_2), 3.60 (q, J = 7 Hz, 6, OCH_2CH_3), 7.59 and 7.59 (two m, 5, C_6H_5); nmr (CCl_4) shows shift of SO_2CH_2 to δ 3.14.

E.—**12** (from pentane) had nmr (CCl_4) δ 1.15 (t, J = 7 Hz, OCH_2CH_3), 1.25 [s, $C(CH_3)_3$, area 1.0–1.3, weight 12], 3.15 (s, 2, SO_2CH_2), 3.32 (s, 3, OCH_3), 3.63 (q, J = 7 Hz, 4, OCH_2CH_3), 7.55 and 7.90 (two m, 5, C_6H_5).

F.—**8a** (from pentane) had nmr (CCl_4) δ 1.23 [s, 6, $-C(CH_3)_2$], 3.07 (s, 2, SO_2CH_2), 3.32 (s, 9, OCH_3), 7.48–7.83 (two m, 5, C_6H_5).

G.—**15a** was an oil ($n^{22}D$ 1.504) which decomposed on distillation. While satisfactory C and H analyses were not obtained, the spectra (ir, nmr, and mass) were consistent with assigned structure; nmr (CCl_4) δ 1.96–2.12 (m, 2, CH_2C), 2.92–3.06 (m, 2, SO_2CH_2), 3.10 (s, 9, OCH_3), 7.36–7.90 (m, 5, C_6H_5).

H.—**15b** (from nonane) had nmr ($CDCl_3$) δ 1.16 (t, J = 7 Hz, 9, OCH_2CH_3), 2.08–2.26 (m, 2, $-CH_2C$), 3.10–3.28 (m, 2, SO_2CH_2), 3.46 (q, J = 7 Hz, 6, OCH_2CH_3), 7.50–8.00 (m, 5, C_6H_5).

I.—**15c** (from nonane) had nmr (CCl_4) δ 1.10 (d, J = 6 Hz, 3, CH_3), 2.40–2.90 (m, 2, CH_2), 3.10–3.40 (m, 1, -CH), 3.18 (s, 9, OCH_3), 7.40–7.90 (m, 5, C_6H_5).

β-Phenylmercaptopivalic Acid (10).—Thiophenol (44.0 g, 0.4 mol) was added to a solution of potassium hydroxide (16.0 g, 0.29 mol) in ethanol (100 ml). The resulting solution was cooled (0°) and a solution of pivalolactone[10] (20.0 g, 0.2 mol) in dioxane (50 ml) was added dropwise (vigorous stirring under nitrogen). The mixture was maintained at 40° during the addition and the resulting solution was heated at 50° for 30 min. The resulting mixture was concentrated (until solid formed) and the mixture was dissolved in aqueous sodium bicarbonate (5%, 300 ml) and extracted with ether (300 ml total). Acidification of the alkaline solution gave **10** (37.8 g, 90% yield): mp 116–117°; nmr ($CDCl_3$) δ 1.30 [s, 6, $C(CH_3)_2$], 3.18 (s, 2, CH_2), 7.07–7.57 (m, 5, C_6H_5), 11.7 (br s, 1, COOH).

Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.82; H, 6.71. Found: C, 62.68; H, 6.67.

β-Phenylsulfonylpivalic acid (11) was prepared (90% yield) by oxidation of **10** with hydrogen peroxide in acetic acid (80°, 4 hr): mp 147–148°; nmr ($CDCl_3$) δ 1.48 [s, 6, $C(CH_3)_2$], 3.52 (s, 2, CH_2), 7.63–7.97 (m, 5, C_6H_5), 10.1 (br s, 1, COOH).

Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82; S, 13.23. Found: C, 54.26; H, 6.01; S, 13.42.

Ethyl β-phenylsulfonylpivatate (9b)w as prepared by esterification of **11** by a procedure adapted from that of Harrison and coworkers:[11] mp 56–57° (from ethanol–water); 85% yield; nmr (CCl_4) δ 1.25 (t, J = 7 Hz, OCH_2CH_3), 1.35 [s, $C(CH_3)_2$, area between 1.1 and 1.4, weight 9), 3.40 (s, 2, SO_2CH_2), 4.08 (q, J = 7 Hz, 2, OCH_2CH_3), 7.53–7.90 (m, 5, C_6H_5).

Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71; S, 11.86. Found: C, 57.77; H, 6.51; S, 11.98.

Methyl β-Phenylsulfonylpivatate (9a).—Reaction of **9b** (1.9 mmol) with sodium methoxide (50 mmol) in methanol (25 ml) at 0° for 2 hr resulted in ester interchange to give **9a** (mp 94–96°, 93% yield): nmr ($CDCl_3$) δ 1.43 [s, 6, $C(CH_3)_2$], 3.50 (s, 2, SO_2CH_2), 3.70 (s, 3, OCH_3), 7.65–7.98 (m, 5, C_6H_5).

Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.23; H, 6.29; S, 12.51. Found: C, 56.03; H, 6.03; S, 12.72.

1,1-Diphenylmercapto-2,2-dimethyl-3-phenylsulfonylcyclopropane (7).—Thiophenol (1.1 g, 10 mmol) was added to a solution of sodium ethoxide prepared from sodium (0.3 g, 13 mg-atoms) and absolute ethanol (25 ml). Dihalocyclopropane **5** (1.20 g, 4.3 mmol) was added and the mixture was stirred at 30° for 24 hr. The mixture was poured into water (25 ml) and the resulting mixture was extracted with chloroform (100 ml total) and washed with sodium hydroxide (10%, 15 ml) and then with water (25 ml). The extract was dried ($MgSO_4$) and concentrated to give nearly pure **7** (1.80 g, 98% yield): mp 138.5–140°; mp 139.5–141° from chloroform–hexane; nmr ($CDCl_3$) δ 1.70 and 1.88 [two s, 6, $-C(CH_3)_2-$], 2.95 (s, 1, SO_2CH-), 7.14 and 7.32 (two m, C_6H_5S-), 7.57 and 7.84 (two m, $C_6H_5SO_2-$, area between 7.1 and 8.0, weight 15).

Anal. Calcd for $C_{23}H_{22}O_2S_3$: C, 64.75; H, 5.20; S, 22.54. Found: C, 64.72; H, 5.10; S, 22.41.

1,1-Diphenylmercapto-2-phenylsulfonylcyclopropane (14a) was prepared from **13a** essentially as described above for **7**: mp 144–145.5° from chloroform–heptane; yield 100%; nmr ($CDCl_3$) δ 1.83–2.33 (AB portion of ABX, 2, $-CH_2-$), 3.17–3.42 (X portion of ABX, 1, SO_2CH), 7.24–8.00 (m, 15, C_6H_5-).

Anal. Calcd for $C_{21}H_{18}O_2S_3$: C, 63.28; H, 4.55; S, 24.13. Found: C, 63.09; H, 4.45; S, 24.00.

1,1-Diphenylmercapto-2-methyl-3-phenylsulfonylcyclopropane (14b) was prepared (74% yield, mp 94–96°) as described for **7**: mp 96.5–97.5° from chloroform–hexane; nmr ($CDCl_3$) δ 1.42–1.83 (d of d, 3, cis and trans CH_3), 2.04–2.68 (m, 1, $-CHCH_3$), 2.92–3.20 (d of d, 1, $-SO_2CH$, cis and trans), 7.17–8.00 (m, 15, aromatic H).

Anal. Calcd for $C_{22}H_{20}O_2S_3$: C, 64.04; H, 4.89; S, 23.31. Found: C, 64.03; H, 4.94; S, 23.54.

Conversion of 1,1-Dialkoxycyclopropanes and β-Phenylsulfonylorthopropionates to Alkyl β-Phenylsulfonylpropionates.—The cyclopropane ketals **6** and the ortho esters **8** and **15** were readily converted to β-phenylsulfonylpropionates (**9**, **16**) by action of hydronium ion or by treatment with Florisil. Typical experiments follow.

A.—A mixture of **8a** (0.27 g, 1 mmol), Florisil (2.5 g), and benzene (10 ml) was stirred at room temperature for 18 hr. The mixture was filtered (sintered-glass funnel), and the Florisil was washed with three 25-ml portions of chloroform. The combined organic solutions was dried ($MgSO_4$) and concentrated (rotary evaporator) to give essentially pure methyl β-phenylsulfonylpivalate (100% yield, mp 93–94°, mmp with material mp 94–96° was 93–94°).

B.—A mixture of **15a** (3.6 g, 0.013 mol), hydrochloric acid (3 ml, 12 N), and methyl alcohol (35 ml) was stirred for 19 hr at 25°. The solution was concentrated (rotary evaporator) and poured into water (200 ml) and then extracted with ether (200 ml). Evaporation of the dried ($MgSO_4$) ether extract gave **16a** (2.8 g, 94% yield, mp 74.5–75.5°): ir (Nujol $\nu_{C=O}$ 1730 cm^{-1}; nmr ($CDCl_3$) δ 2.82 (t, J = 8 Hz, 2, CH_2CO), 3.48 (t, J = 8 Hz, 2, SO_2CH_2), 3.66 (s, 3, OCH_3), 7.52–8.00 (m, 5, C_6H_5).

Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30. Found: C, 52.42; H, 5.52.

A.—Reaction of **15b** (24 hr at 25°) gave **16b**: bp 143–144° (0.09 mm); 88% yield; ir (Nujol) $\nu_{C=O}$ 1725 cm^{-1}; nmr (CCl_4) δ 1.18 (t, J = 7 Hz, 3, CH_2CH_3), 2.62 (t, J = 8 Hz, 2, CH_2CO), 3.32 (t, J = 8 Hz, 2, SO_2CH_2), 4.00 (q, J = 7 Hz, 2, $-OCH_2CH_3$), 7.40–7.92 (m, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82. Found: C, 55.07; H, 5.73.

B.—Reaction of **15c** (1 hr at 25°) gave **16c**: mp 50–52°; 100% yield; ir (Nujol) $\nu_{C=O}$ 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.35 (d, J = 6 Hz, 3, CH_3CH-), 2.80–3.30 (m, 2, CH_2), 3.60 (s, 3, OCH_3), 3.60–4.00 (m, 1, CH), 7.40–8.00 (m, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82. Found: C, 54.77; H, 6.14.

C.—Ester **16d** was obtained directly by reaction of **13b** with sodium ethoxide in ethanol (4 hr): mp 46–48° (94% yield); ir (Nujol) $\nu_{C=O}$ 1720 cm^{-1}; nmr (CCl_4) δ 1.00–1.40 (m, 6, CH_3CH_2 and CH_3CH), 2.60–3.10 (m, 2, SO_2CH_2), 3.36–3.68 (m, 1, CH), 3.97 (q, J = 7 Hz, 2, CH_2CH_3), 7.20–7.90 (m, 5, C_6H_5).

Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.23; H, 6.29. Found: C, 55.70; H, 6.32.

Preparation of Acids 11, 16e, and 16f.—Cyclopropyl ketals (**6**), ortho esters (**8** and **15**), and alkyl β-phenylsulfonylpropionates (**9** and **16**) were readily converted to the corresponding acid by conventional acid- or base-catalyzed hydrolysis. Some typical examples follow.

A.—Acid **11** was isolated (a) by reaction of ketal **6b** in aqueous sodium hydroxide (100°, 4 hr) with subsequent acidification of the alkaline solution, 100% yield; (b) by reaction of ketal **6b** with hot 6 N hydrochloric acid (100°, 4 hr), yield 96%; (c) by alkaline hydrolysis of ortho ester **8b** (100°, 2 hr), 91% yield; (d) by alkaline hydrolysis of **9b** (100°, 2 hr), 86% yield; and (e) by reaction of **9b** with 6 N hydrochloric acid (100°, 2.5 hr, 96% yield.

B.—Reaction of alkyl β-phenylsulfonylpropionates with hydronium ion in alcohols at reflux gave a mixture of β-phenylsulfonylpropionic acids (**11**, **16e**, **16f**) and alkyl β-phenylpropionates formed by ester interchange.

A typical procedure is as follows. A mixture of the methyl ester **16a**, hydrochloric acid (3 ml, 12 N), and ethyl alcohol was heated at the reflux temperature for 4 hr, and was concentrated. There was obtained from the concentrate the ethyl ester **16b** (59% yield) and β-phenylsulfonylpropionic acid (40% yield), mp 123.5–124.5° (reported[7] mp 119–120°).

(10) Kindly supplied by Pioneering Division of the Textile Fibers Department, E. I. du Pont de Nemours and Co., Wilmington, Del.

(11) H. R. Harrison, W. M. Haynes, P. Arthur, and E. J. Eisenbraun, see L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 705.

Similar treatment of 16c gave 16b (60%) and α-methyl-β-phenylsulfonylpropionic acid (30% yield), mp 107–109° (reported[8] mp 113°).

Registry No.—**1**, 35347-56-9; **5**, 38434-93-4; **6a**, 38434-94-5; **6b**, 38434-95-6; **7**, 38434-96-7; **8a**, 38434-97-8; **8b**, 38434-98-9; **9a**, 38434-99-0; **9b**, 38435-00-6; **10**, 27943-35-7; **11**, 38435-02-8; **12**, 38435-03-9; **13a**, 38435-04-0; **13b**, 38435-05-1; **14a**, 38435-06-2; **14b**, 38435-07-3; **15a**, 38435-08-4; **15b**, 38435-09-5; **15c**, 38435-10-8; **16a**, 10154-72-0; **16b**, 10154-73-1; **16c**, 38435-13-1; **16d**, 38435-14-2; pivalolactone, 1955-45-9.

The Reactions of Bromothianaphthenes with Piperidine. A Reinvestigation[1]

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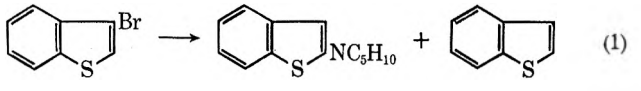
The reaction of 3-bromothianaphthene (1) with piperidine was reinvestigated and found to give primarily the normal (3) but also some of the cine-substitution product 2 which is also the only product from the reaction of 2-bromothianaphthene (5). The previously reported results can be rationalized by the effects of air, metals, and impure starting material on the reaction. 2,3-Dibromothianaphthene (6) also gives 2 under these conditions, probably *via* the bromamine 7 which was isolated under milder conditions, could be converted to 2 in high yield, and was synthesized from 2 *via* the iminium salt 9. The diamine 8 was isolated in trace amounts from the reactions of 6 and 7 with piperidine. Possible mechanisms for some of these reactions are discussed.

Although five-membered hetarynes have been proposed as reaction intermediates for over 70 years,[2-4] closer examination[5,6] has invariably revealed these claims to be false.[7] One of those cases which has not been reexamined is the reaction of 3-bromothianaphthene (1) with piperidine, which, because it was reported[8] to give exclusively the cine (2) rather than the normal (3) substitution product (eq 1), might[4] involve



1 2 4 (1)

an elimination–addition mechanism *via* 2,3-dehydrothianaphthene. As part of the study of the reactions of halothiophenes[9-11] and halothianaphthenes[12-13] with bases a reexamination of the reactions of bromothianaphthenes with piperidine therefore was undertaken (Table I).

In agreement with the report of Brower and Amstutz[8] 2-bromothianaphthene (5) reacted cleanly with piperidine to give the normal substitution product 2 (expt 1). In contrast to this report (eq 1), however, the major product from 3-bromothianaphthene (1) was also that of normal substitution, 3-piperidinothianaphthene (3). A small amount of the 2 isomer (2) was found but thianaphthene (4) was not (expt 2). A possible explanation for this discrepancy may lie in differences in the reaction conditions and in the purity of the 3-bromothianaphthene (1). For example, when this reaction was repeated without precautions for removing air (expt 3), thianaphthene (4) was, as reported,[8] a minor product. Furthermore, when the starting material 1 was prepared, as reported,[8] by the direct bromination of thianaphthene,[14] substantial quantities of the 2 isomer (2) and thianaphthene (4) were present even after

TABLE I

REACTIONS OF BROMOTHIANAPHTHENES WITH PIPERIDINE

Expt	Reactant	Temp, °C (time, hr)	Products (yield, %)
1	5	220 (26)[a]	2 (70)
2	1	250 (80)	1 (73), 2 (2), 3 (15)
3	1	250 (80)[b]	1 (60), 2 (5)
			3 (25), 4 (4)
4	1	250 (40)[a,c]	1 (13), 2 (4)
			3 (67), 4 (9)
5	1	250 (40)[a,d]	1 (70), 2 (1)
			3 (4), 4 (4)
6	1	250 (40)[a,e]	1 (67), 2 (2)
			3 (15), 4 (4)
7	6	200 (15)	2 (73), 8 (trace)
8	6	106 (60)[f]	6 (71), 7 (5)
			2 (trace), 8 (trace)
9	7	180 (40)	2 (83), 8 (trace)
10	1 + 7 (1:1)	180 (40)	2 (83),[g] 1 (70), 8 (trace)

[a] A Fischer and Porter aerosol compatibility tube with stainless steel valve was the reaction vessel. [b] No precautions for prior removal of air. [c] Valve top etched (see discussion). [d] 0.05 g of powdered Fe per 0.02 mol of 1. [e] 0.05 g of $FeCl_3$ per 0.02 mol of 1. [f] Reflux. [g] Based on added 7.

(1) Taken in part from the Masters Thesis of W. B. M., Texas Christian University, 1969; reported in preliminary form at the 24th Southwest Regional Meeting of the American Chemical Society, Austin, Texas, Dec 1968.

(2) R. Stoermer and B. Kahlert, *Ber.*, **35**, 1633 (1902).

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

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

(5) G. Wittig and M. Rings, *Justus Liebigs Ann. Chem.*, **719**, 127 (1968).

(6) D. A. de Bie, H. C. van der Plas, and G. Geurtsen, *Recl. Trav. Chim. Pays-Bas*, **90**, 594 (1971).

(7) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967, p 293; H. J. den Hertog and H. C. van der Plas in "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, p 1149.

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

(9) M. G. Reinecke and H. W. Adickes, *J. Amer. Chem. Soc.*, **90**, 511 (1968).

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

(11) M. G. Reinecke, H. W. Adickes, and C. Pyun, *J. Org. Chem.*, **36**, 2690, 3820 (1971).

(12) M. G. Reinecke and T. A. Hollingworth, *ibid.*, **37**, 4257 (1972).

(13) D. A. de Bie, H. C. van der Plas, G. Geurtsen, and K. Nijdam, *Recl. Trav. Chim. Pays-Bas*, submitted.

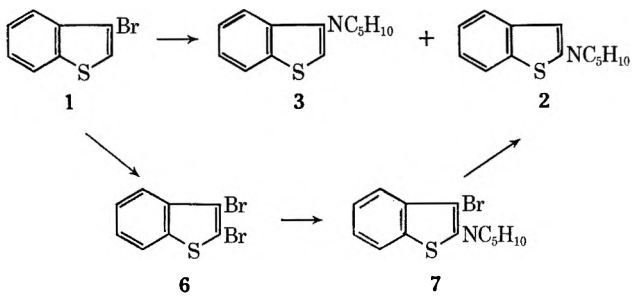
(14) G. Komppa, *J. Prakt. Chem.*, **122**, 319 (1929).

fractional distillation. Treatment of such a mixture with piperidine would have resulted in the preferential reaction of the more reactive[8] 2-bromo isomer which would have led, particularly at the shorter reaction times used by Brower and Amstutz,[8] to **2** as a major product. In our reactions (Table I) a modified bromination procedure[15] was used to prepare **1** and the last traces of 2-bromo isomer and thianaphthene were removed by reaction with piperidine and by preparative vpc, respectively.

A further example of the sensitivity of the reaction of **1** → **3** to reaction conditions was noted when (expt 4) the usual reaction vessel, a sealed glass ampoule, was replaced by a pressure tube containing a stainless steel valve which had been etched by exposure to 48% HBr at elevated temperatures for prolonged periods. The yield of **3** was more than quadrupled even though the reaction time was halved. An unetched valve had no effect on the product yield (expt 1). The possible role of either iron (expt 5) or iron salts (expt 6) in bringing about this catalysis was examined, but they had little effect on the course of the reaction.

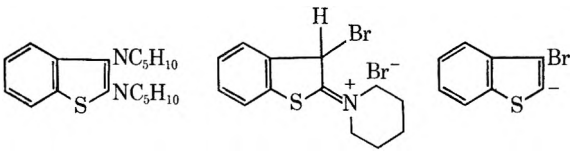
While cine substitution therefore is not a major process in the reaction of 3-bromothianaphthene (**1**) with piperidine, it does occur to some extent. Possible mechanisms for this process include elimination–addition,[4] abnormal addition–elimination,[8] or even a mechanism involving rearrangement of **1** → **5** prior to substitution.[16] Analogy to the reactions of halothiophenes[9,10] and halothianaphthenes[12,13] with metal amides in liquid ammonia requires that a transbromination mechanism similar to that in Scheme I also be considered. As a test of the feasibility of this mechanism the reactions of the proposed intermediates 2,3-dibromothianaphthene (**6**) and 3-bromo-2-piperidinothianaphthene (**7**) with piperidine were investigated.

SCHEME I



The feasibility of the step **6** → **2** was shown by the formation of the latter compound in 73% yield from **6** and piperidine at 200° (expt 7). A trace product detected and isolated by tlc proved to be the diamine **8** and not the proposed bromamine intermediate **7**. When the reaction temperature was reduced to 106°, however, **7** was obtained (expt 8), thereby providing evidence for its role in the step **6** → **2**. Final verification for the sequence **6** → **7** → **2** comes from the conversion of **7** to **2** in 83% yield (expt 9).

The structure of **7** was proven by independent synthesis. Bromination of **2** with dioxane dibromide gave the iminum salt **9**, which on treatment with pyridine was converted to the free base **7** in 74% yield.



8 **9** **10**

The mechanism of the step **6** → **7** may be considered as a typical nucleophilic aromatic substitution in which the more reactive 2-bromine atom[8] is preferentially removed. The debromination of **7** → **2** could be related to the radical-induced deiodination of certain aryl iodides,[17,18] but, since similar debrominations of bromothianaphthenes[12,13] and bromothiophenes[9,10] with metal amides in liquid ammonia apparently involve nucleophilic displacements on bromine, such a process is more probable. The fact that added 3-bromothianaphthene (**1**) does not increase the conversion of **7** → **2** (expt 10) indicates that *o*-halocarbanions such as **10** are not required. Mechanisms involving piperidine as the nucleophile can be written, however, and have the advantage of producing *N*-bromopiperidine as a by-product which might be capable of converting **1** to **6** under the more severe conditions of expt 2, thereby accounting for the whole process **1** → **2**.

In conclusion, cine substitution is only a minor process in the reaction of 3-bromothianaphthene with piperidine. Among the possible mechanisms for this process must be included the transbromination outlined in Scheme I.

Experimental Section

Melting points and boiling points are uncorrected. Ir spectra were recorded on a Perkin-Elmer 237 instrument as films (liquids) or KBr discs (solids) and calibrated with a polystyrene film. Nmr spectra were measured on a Varian A-60A spectrometer as 30% solutions in CCl_4 with TMS as an internal standard unless otherwise noted. Gas chromatographic analysis was performed on an Aerograph Autoprep A-700 using a 20 ft × 0.375 in. column of 30% SE-30 on Chromosorb W. Analytical tlc was carried out with Brinkman silica gel PF-254 on 1 × 3 in. plates and preparative tlc on 20 × 20 cm plates with a 1.5 mm thick layer. The plates were developed with 6:1 (v/v) low-boiling petroleum ether–benzene. Analyses were performed at M-H-W Laboratories, Garden City, Mich.

Starting Materials.—3-Bromothianaphthene (**1**),[15] 2-bromothianaphthene (**5**),[19] and 2,3-dibromothianaphthene (**6**)[20] were prepared by the cited procedures and in the latter two instances purified by recrystallization. The sample of **1** obtained by distillation (68–72°, 0.05 mm) and containing 7% **4** and 3% **5** (vpc) was heated in a sealed tube at 240° for 40 hr with half again its weight of piperidine. The neutral fraction of the resulting mixture was purified of thianaphthene (**4**) by preparative vpc to give vpc-pure 3-bromothianaphthene, bp 96.5–97° (1.4 mm) [lit.[15] bp 90–105° (1.5 mm)], $n^{20}D$ 1.6677.

Reaction of Bromothianaphthenes with Piperidine (Table I).—A mixture of the appropriate bromothianaphthene and a 4–8-fold excess of piperidine was placed in a 20 × 120 mm borosilicate glass tube, saturated with N_2 for 15 min, repeatedly frozen and

(15) J. Szmuszkovicz and E. Modest, *J. Amer. Chem. Soc.*, **72**, 571 (1950).

(16) The possibility that **2** is formed by rearrangement of **3** was eliminated by recovering the latter in 88% yield to the exclusion of **2** (vpc) under typical reaction conditions.

(17) J. F. Bunnett and C. C. Wamser, *J. Amer. Chem. Soc.*, **89**, 6712 (1967).

(18) F. Pietra, M. Bartolozzi, and F. Del Cima, *Chem. Commun.*, 1232 (1971).

(19) D. A. Shirley and M. D. Cameron, *J. Amer. Chem. Soc.*, **74**, 664 (1952).

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

thawed under vacuum, and finally sealed under vacuum. After the tube had been heated for the indicated time and temperature (Table I) it was cooled and opened and 30 ml of H_2O was added. The solution was acidified to litmus with 3 *N* HCl and extracted with three 30-ml portions of ether, and the combined ether extracts were dried (K_2CO_3), concentrated on a rotary evaporator, and analyzed by tlc and vpc. The products were separated by preparative chromatography and identified by comparison of their ir spectra with those of authentic samples or as indicated below. Yields were calculated from the vpc trace taking into account the response factors of the individual products. Variations from these reaction conditions are noted in Table I.

Product Identification.—2-Piperidinothianaphthene (**2**), mp 100–100.5° (lit.[8] mp 98–100°), and 3-piperidinothianaphthene (**3**), mp 65–66° (lit.[21] mp 64–65°), were prepared for comparison purposes by the cited methods. 2-Piperidino-3-bromothianaphthene (**7**) was compared with the independently synthesized sample described below and 2,3-dipiperidinothianaphthene (**8**), mp 101–102.5°, was identified from its nmr spectrum [δ 7.0–7.7 (m, 4, ArH), 3.2 (m, 4, CH_2N), 2.9 (m, 4, CH_2N), 1.6 (m, 12, CH_2)] and analysis.

Anal. Calcd for $C_{18}H_{24}N_2S$ (**8**): C, 71.94; H, 8.06; N, 9.33. Found: C, 72.02; H, 7.93; N, 9.17.

2-Piperidino-3-bromothianaphthene (7).—To a solution of 5.4 g of **2** in 25 ml of dry, distilled dioxane was added with stirring 4.0 g of Br_2 in 25 ml of dioxane over a period of 20 min. The yellow precipitate which formed was filtered and washed with dioxane and $CHCl_3$ to give 9.4 g (100%) of the highly insoluble iminium salt **9**: nmr (DMSO) δ 7.1–7.6 (m, 4, ArH), 3.8 (s, 1, CHBr), 1.5–1.8 (m, 6, CH_2); the CH_2N peaks (*ca.* 3.1) are partially blocked out by the DMSO absorption; ir 1622 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}Br_2NS$ (**9**): C, 41.38; H, 4.01; N, 3.72. Found: C, 41.15; H, 4.27; N, 3.63.

To a mixture of 5.7 g of **9** and 50 ml of anhydrous ether was added 1.5 g of pyridine. After about 5 min the yellow salt **9** was replaced by white pyridinium bromide. Filtration, evaporation of the filtrate to dryness, and recrystallization of the residue from low-boiling petroleum ether gave 3.3 g (74%) of **7**: mp 76–77°; nmr δ 7.0–7.7 (m, 4, ArH), 3.0 (m, 4, CH_2N), 1.5 (m, 6, CH_2); sodium fusion indicated the presence of N, S, and Br.

Anal. Calcd for $C_{13}H_{14}BrNS$ (**7**): C, 52.68; H, 4.77; N, 4.73. Found: C, 52.90; H, 4.82; N, 4.63.

7 is unstable at room temperature and sensitive to air and moisture. It was stored under N_2 at 0°.

Registry No.—**1**, 7342-82-7; **2**, 33880-37-4; **5**, 5394-13-8; **6**, 6287-82-7; **7**, 38359-65-8; **8**, 38359-66-9; **9**, 38359-67-0.

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

(21) G. van Zyl, D. C. DeJongh, V. L. Heasley, and J. W. van Dyke, *J. Org. Chem.*, **26**, 4946 (1961).

tert-Butylacetylene Revisited. An Improved Synthesis. Methyl Migration during Bromination

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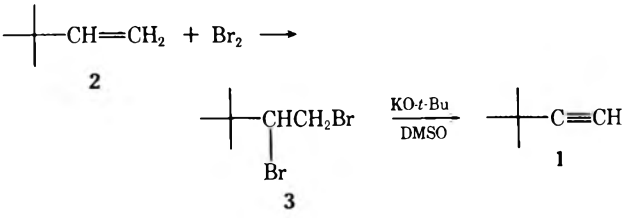
A synthesis of *tert*-butylacetylene, superior in all respects to the conventional procedure, is described involving bromination of *tert*-butylethylene (**2**), and double dehydrobromination of the *vic*-dibromide (**3**) with potassium *tert*-butoxide–dimethyl sulfoxide in overall yields of 81%. The bromination of **2** was found to give 70–90% yields of **3**, accompanied by 1-bromo-3,3-dimethylbutane and a crystalline product formulated as tetra(bromomethyl)ethylene (**4**), a new compound. The mechanism of formation of **4** and its ineffectiveness as a dienophile are described.

tert-Butylacetylene (**1**) is a highly useful synthetic reagent, serving for example as the source of the *tert*-butylethynyl group in a great many propargyl alcohols and related compounds. The usual preparation[1] of **1** involves the reaction of pinacolone with phosphorus pentachloride to form a relatively sensitive *gem*-dichloride, which is then treated with a sodium hydroxide melt to promote a double dehydrochlorination. Both steps in the sequence are only moderately efficient, owing to the lability of the intermediate dichloride and the harsh conditions required for the elimination.

We attempted to improve the overall yield by substituting potassium *tert*-butoxide in dimethyl sulfoxide (DMSO) for the sodium hydroxide, and found that this substantially increases the yield in the second step to >90%. Still, the difficulties encountered in the first step precluded significant improvement.

Recently we devised an obvious alternative preparation of **1** which is superior in all respects (simplicity, time requirements, yields, and economy) to the original method. This procedure involves the bromination of *tert*-butylethylene (**2**) and subsequent double dehydrobromination of the *vic*-dibromide with KO-*t*-Bu–DMSO. The reaction of **2** with either bromine[2] or *N*-bromosuccinimide[3] has been reported to give the desired dibromide **3**. In our hands, the addition of bromine to **2** at



−78° afforded **3** in 90% yield, and this was treated with 2 equiv of KO-*t*-Bu in DMSO, from which **1** could be isolated in 91% yield. The overall yield from olefin to acetylene was 81%.

The bromination of **2** is interesting in another regard. When the addition of bromine to **2** was carried out at room temperature, gaseous HBr was liberated in significant amounts. Moreover, two side products could then be readily isolated. The first of these, formed in 10% (isolated) yield, was found to be 1-bromo-3,3-dimethylbutane,[4] which is known to arise from the anti-Mar-

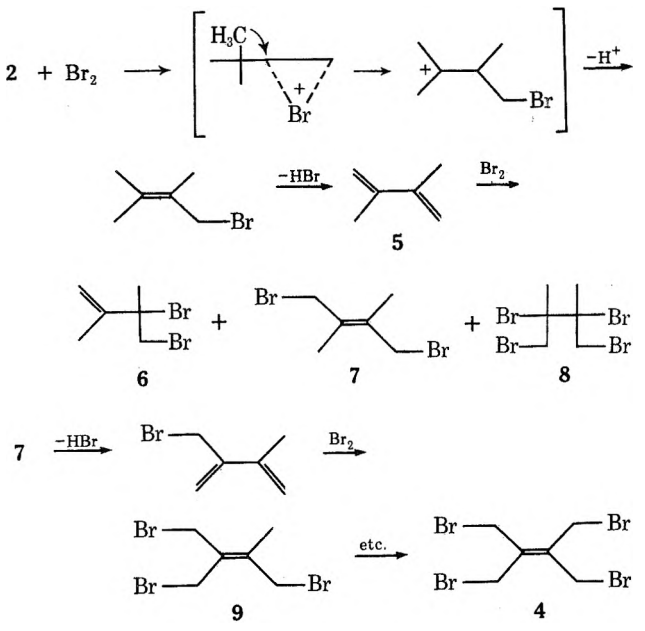
(1) (a) P. Ivitzky, *Bull. Soc. Chim. Fr.*, **35**, 357 (1924); (b) P. D. Bartlett and L. J. Rosen, *J. Amer. Chem. Soc.*, **64**, 543 (1942).

(2) M. F. Claessens, *Bull. Soc. Chim. Fr.*, **5**, 113 (1909).

(3) A. Guillemonat, G. Peiffer, J.-C. Traynard, and A. Leger, *ibid.*, 1192 (1964).

(4) Interestingly, the earlier report[2] included a vague description of a lower boiling monobromide then believed to be $C_6H_{11}Br$ on the basis of bromine content (calcd 49.08; found 46.48). We feel that compound was the same monobromide we have identified (calcd for $C_6H_{13}Br$: Br, 48.41). An allusion was also made to a liquid tribromide of unknown structure (**9**?) and an undescribed crystalline solid.

kovnikov addition of HBr to 2.[5] The second side product, a straw-colored, crystalline solid (sparingly soluble in most organic solvents), exhibited a mass spectrum with parent ions at *m/e* 404, 402, 400, 398, and 396 in the ratio 1:4:6:4:1—four bromine atoms! The molecular formula $C_6H_8Br_4$ was confirmed by elemental analysis. Surprisingly the compound showed no outstanding functionality in its infrared spectrum, and its pmr spectrum consisted of a lone singlet at δ 4.19. We believe this to be the previously unknown symmetrical tetrabromide **4** [tetra(bromomethyl)-ethylene].[6] Some evidence can be advanced regarding the mechanism by which **4** arises under these conditions, realizing that a methyl migration must be involved at some stage.[7] A possible pathway to **4** is shown below.



It has in fact been reported[8] that the bromination of 2,3-dimethyl-1,3-butadiene (**5**) at −15° gives two bromides, solid **7** (80%, stereochemistry unspecified, but probably trans considering steric effects) and a minor amount of a liquid dibromide (presumably **6**), which could be interconverted at 100°. We found that bromination of **5** at −10° yields two compounds with similar glc characteristics. They were initially present in comparable amounts, but upon standing the later eluting one (**6**) isomerized to the other, which was identical with **7**. (The more highly substituted double bond in **7** should render it more stable than **6**.) However, bromination of **5** with excess bromine, or bromination of **7**, led to several new products, including tetrabromide **4** (5%), a second tetrabromide (**8**, 20%) and a compound believed to be tribromide **9** (60%). Interestingly, **8** was easily isolated from the bromination product mixture of **5**, while **4** was not. Yet, although reexamination of the bromination products from **2** by glc revealed the presence of **8** (**8**/**4** = 4), it was **4** that could be isolated, not **8**! This must reflect the fact that **8** is less soluble than **4** in **9**, while **4** is less soluble than **8** in dibromide **3**. The yields of **4** from **2** and **5** were functions of the reaction conditions; excess bromine, higher temperatures, and extended reaction times favored its formation. Thus, bromination of **2** at −78° gave only **3** and negligible amounts of side products, while reaction at room temperature afforded **4** in yields as high as 2%. It is thus highly likely that **5** is formed during the bromination of **2** at room temperature, and that **4** arises from reactions of the type shown above. Further work on the details of these transformations is in progress.

There remained the possibility that **4** could exhibit some degree of dienophilicity if the electron-withdrawing inductive effect of the four bromine atoms compensated for their unfavorable steric bulk. Attempts were made to thermally cycloadd **4** to anthracene, but, after 18 hr at reflux in toluene, no reaction could be detected by glc.[9] Thus, **4** exhibits no tendency to undergo Diels–Alder addition to a moderately reactive diene.

Experimental Section[10]

General.—Instruments used were as follows: pmr, Varian A-60 and T-60 (referred to internal TMS); ir, Perkin-Elmer Model 700 and 337, and Beckman IR-12 (carbon tetrachloride solution unless otherwise noted); mass spectra, Hitachi RMU-7; analytical glc, Hewlett-Packard Model 700 (TC detection) fitted with dual 8 ft × 0.125 in. aluminum columns packed with 12% silicon oil 550 on 80–100 Chromosorb W-AW, DMSC (helium flow rate 30 cc/min, injection port 215°, initial column temperature 85° for 2 min, then programmed to 215° at 30°/min). These conditions gave the following relevant retention times (min): 1-bromo-3,3-dimethylbutane (2.1), **3** (5.9), **7** (7.0), **6** (7.2), **9** (9.8), **8** (12.0), and **4** (12.4). Melting points were measured with an oil bath and are uncorrected. Microanalyses were performed by Chemalytics, Tempe, Ariz.

Bromination of 2.—*tert*-Butylethylene (**2**) (42 g, 0.50 mol) was magnetically stirred at room temperature in a three-neck flask fitted with an addition funnel and a reflux condenser, while bromine (80 g, 0.50 mol) was added dropwise over 2 hr. During the addition and subsequent stirring, HBr (identified by trapping in water) was evolved in significant amount. After stirring for an additional 21 hr, water (50 ml) was added. The organic phase was separated and the aqueous phase was extracted with 3 × 35 ml of ether. The combined organic phases were dried (anhydrous magnesium sulfate) and then rotary evaporated under vacuum, leaving 109.6 g of a clear yellow liquid. Glc showed 8.6% 1-bromo-3,3-dimethylbutane[11] and 84% **3**. Distillation through a 9-in. Vigreux column at 12 mm afforded 8.5 g of the monobromide, bp 40–41° (pot 80–100°), and 87.2 g (72%) of **3**, bp 81–83° [lit.[3] bp 84–85° (12 mm)] (pot 100–145°). Compound **3** exhibited the following spectral data: mass spectrum (70 eV) *m/e* 242, 244, 246 (1:2:1); ir 2955 (vs), 1470 (s), 1375 (s), 1257 (s), and 1223 cm^{-1} (s); pmr[12] δ 1.14 (s, 9 H), 3.35–4.20 (overlapping multiplets, 3 H). The monobromide showed the following spectral characteristics: mass spectrum (70 eV) *m/e* 164, 166 (1:1); ir 2930 (s), 2840 (m), 1450 (m), 1350 (m), 1237 (m), and 640 cm^{-1} (m); pmr[12] δ 0.97 (s, 9 H), 1.84 (t, *J* = 8.5 Hz, 2 H), 3.37 (t, *J* = 8.5 Hz, 2 H).[13] The boiling point of this compound

(5) Patent application abstracted in *Chem. Abstr.*, **63**, P2897*b* (1965).

(6) The double bond in **4** (invisible in its ir spectrum owing to the dipole moment selection rule) is resistant to further bromination, but the compound does give a positive test with potassium permanganate.

(7) Previous attempts to detect rearrangement during the bromination of **2** in methanol were unsuccessful: W. H. Puterbaugh and M. S. Newman, *J. Amer. Chem. Soc.*, **79**, 3469 (1957).

(8) E. H. Farmer, C. D. Lawrence, and W. D. Scott, *J. Chem. Soc.*, 510 (1930).

(9) For comparison, maleic anhydride reacts with anthracene to yield >50% of the adduct after 2–3 hr at 80°: G. R. Robinson and T. L. Jacobs, "Laboratory Practice of Organic Chemistry," Macmillan, New York, N. Y., 1962.

(10) Caution: a number of the polybrominated compounds prepared here are potent lachrymators. Due caution should be exercised in all stages of the work.

(11) Glc percentages are not corrected for differences in response factors, which may be significant for compounds with differing numbers of heavy atoms.

(12) Carbon tetrachloride solution.

(13) The two triplets were somewhat complex, but bore an exact mirror image relationship to each other.

at 1 atm was 137–139° (lit.[14] bp 137–138°), and its reaction with KO-*t*-Bu–DMSO gave **2**.

If the addition of bromine was carried out at −78° over 3 hr (with 2 hr additional stirring) using chloroform as solvent, glc showed less than 2% of product other than **3**, which could be isolated as above in 90% yield.

Isolation of 4.—If the undistilled product mixture from the room-temperature bromination of **2** was allowed to sit at −20° for 4 days, 4.1 g of straw-colored crystals could be isolated by filtration. The melting point was found to be 159–161° after recrystallization (chloroform) and sublimation (80–100°, 1 mm). The partial mass spectrum (70 eV) was as follows: *m/e* 404, 402, 400, 398, 396 (1:4:6:4:1), 323, 321, 319, 317 (1:3:3:1, M − Br), 242, 240, 238 (1:2:1, M − 2Br), 161, 159 (1:1, M − 3Br). Additional spectral data follow: ir (KBr) 3045 (w), 2993 (w), 1465 (s), 1441 (s), 1237 (s), 1205 (s), 1121 (w), 1098 (m), 877 (s), 866 (s), 740 (s), 665 (vs), 568 (m), and 499 cm^{-1} (m); pmr^{15} δ 4.19 (s); uv (pentane) λ_{max} 218 nm (log ε 4.09) and 251 (4.03).

Anal. Calcd for $C_6H_8Br_4$: C, 18.03; H, 2.02; Br, 79.96. Found: C, 18.12; H, 1.93; Br, 80.14.

***tert*-Butylacetylene (1).**—To 115 g (0.710 mol) of KO-*t*-Bu[16] was added 150 ml of fresh (dry) DMSO, and the suspension was stirred for 30 min. Dibromide **3** (87.2 g, 0.357 mol) was added dropwise over 1 hr, and then the mixture was warmed slowly and distilled through a 9-in. Vigreux column to give 26.7 g (0.326 mol, 91.3%) of the acetylene, bp 36–38° (lit.[1] bp 36.4–37.8°). The product was >99% pure by glc. Spectral data for **1** follow: ir 3310 (vs), 2985 (vs), 2145 (m), 1480 (s), 1460 (s), 1370 (s), 1260 (vs), 1215 cm^{-1} (s); pmr^{12} δ 1.21 (s, 9 H), 1.91 (s, 1 H).

Bromination of 5.—Reaction of **5** with 1 equiv of bromine at −10° as previously described[8] led to a mixture of two products as described in the text. Dibromide **7** could be isolated therefrom, showing (after recrystallization from chloroform) mp 43–44° (lit.[8] mp 47°); ir (chloroform) 3000 (m), 2940 (m), 1450 (m), 1385 (m), 1200 (s), 1070 (m), 930 (m), 870 cm^{-1} (m); pmr^{15} δ 1.88 (s, 6 H), 4.00 (s, 4 H).

Bromination of 5 with Excess Bromine.—To 1.82 g (22.2 mmol) of the diene in a flask fitted with a reflux condenser atop an addition funnel was added 7.10 g (44.4 mmol) of bromine over 30 min. The addition is highly exothermic, with the reaction mixture staying at 60°. During the last half of the addition HBr was liberated copiously, and crystalline material began to form. Chloroform (5 ml) was added, and the solution was filtered to give 550 mg of **8**: mp (after recrystallization from chloroform) 138–140°; pmr^{15} δ 2.12 (s, 6 H), 4.09 (d, J = 11.5 Hz, 2 H), 4.36 (d, J = 11.5 Hz, 2 H);[17] ir (chloroform) 2850 (m), 1440 (w), 1380, (w), 1257 (w), 1010 (w), 855 cm^{-1} (w); mass spectrum, no parent ion from 20 to 70 eV, very intense isotope clusters in the region *m/e* 322 (q, M − Br) and 242 (t, M − 2Br).

Anal. Calcd for $C_6H_{10}Br_4$: C, 17.94; H, 2.51; Br, 79.56. Found: C, 17.74; H, 2,06; Br, 79.56.

The filtrate from above was further diluted with 40 ml of chloroform, washed with dilute sodium thiosulfate, and dried over magnesium sulfate. Removal of solvent and two short-path distillations afforded **9**, bp 76–78° (0.15 mm). The yield of **9** was 1–2 g, depending on the pot temperature, as decomposition took place. Spectral data follow: pmr^{15} δ 1.97 (s, 3 H), 4.05 (s, 2 H), 4.15 (s, 2 H), 4.20 (s, 2 H); ir (neat) 2960 (m), 1640 (m), 1450 (s), 1380 (s), 1300 (m), 1200 (vs), 948 (m), 880 (s), 860 (s), 700 cm^{-1} (s); mass spectrum (45 eV) *m/e* 318, 320, 322, 324 (1:3:3:1).

Anal. Calcd for $C_6H_9Br_3$: C, 22.46; H, 2.83; Br, 74.71. Found: C, 22.57; H, 2.28; Br, 75.14.

Registry No.—**1**, 917-92-0; **2**, 558-37-2; **3**, 640-21-1; **4**, 30432-16-7; **5**, 513-81-5; **7**, 34619-20-0; **8**, 24173-07-7; **9**, 38400-50-9; 1-bromo-3,3-dimethylbutane, 1647-23-0.

Acknowledgment.—The authors gratefully acknowledge the financial assistance provided by Research Corporation in the form of a Frederick Gardner Cottrell Grant.

(14) L. Schmerling and J. P. West, *J. Amer. Chem. Soc.*, **74**, 3592 (1952).

(15) Deuteriochloroform solution.

(16) This was prepared in the conventional way (L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967) from metallic potassium and *tert*-butyl alcohol. After evacuation for 2 hr at 145° (1 mm), the product was 73% (w/w) butoxide and 27% alcohol.

(17) The absorptions at δ 4.09 and 4.36 actually constitute an (AB) pattern, the nonequivalence caused by the neighboring asymmetric center

Reactions of Lone Pair Electron Donors with Unsaturated Electrophiles. I. The Addition of Tetrahydrofuran and Oxetane to Dimethyl Acetylenedicarboxylate[1]

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Tetrahydrofuran and oxetane give cis–trans isomeric 1:1 adducts with dimethyl acetylenedicarboxylate. The reaction can be initiated thermally, photochemically, or by free-radical sources. All three processes are shown to be free-radical chain reactions, presumably involving a vinyl radical intermediate, formed by addition of an ether radical to the dimethyl acetylenedicarboxylate. Possible mechanisms for the chain initiations in the thermal and photochemical reactions are discussed. Secondary isomerizations take place in the photochemical reactions, yielding vinyl ethers through a shift of the double bond.

The addition of cyclic ethers to unsaturated substrates has attracted some attention in recent years. Tetrahydrofuran (THF) adds to maleic anhydride,[3] diethyl maleate,[3] and azodicarboxylate[4] to give α-substituted tetrahydrofuranes by formal addition of the α-C–H ether bond across the unsaturated linkage. These reactions take place by initiation with dibenzoyl peroxide or azoisobutyronitrile and by direct irradiation; they are believed to be radical chain reactions involving THF radicals. Similarly, THF has been added to 7,7,8,8-tetracyanoquinodimethane and tetracyanoethylene by direct irradiation.[5] Tetrahydropyran and *p*-dioxane will not produce 1:1 adducts with unsaturates under these conditions.[3] They can, however, be added to diethyl maleate and various simple olefins under ketone-sensitized uv irradiation[6]; in this case, a radical chain reaction was believed to be initiated by hydrogen abstraction by the excited ketone.[6]

Recently, Singh reported on the photochemical addition of THF, tetrahydropyran, and *p*-dioxane to dimethyl acetylenedicarboxylate (DMAD).[7] He found that THF adds to DMAD by direct irradiation to give

(1) Presented in part at the XXIII International Congress of Pure and Applied Chemistry, Boston, Mass., 1971.

(2) Department of Chemistry, University of California, Berkeley, Calif. 94720, where this work was completed.

(3) R. L. Jacobs and G. C. Ecke, *J. Org. Chem.*, **28**, 3036 (1963).

(4) R. Askani, *Chem. Ber.*, **98**, 2551 (1965).

(5) J. Diekmann and C. J. Pedersen, *J. Org. Chem.*, **28**, 2879 (1963).

(6) I. Rosenthal and D. Elad, *Tetrahedron*, **23**, 3193 (1967).

(7) P. Singh, *J. Org. Chem.*, **37**, 836 (1972).

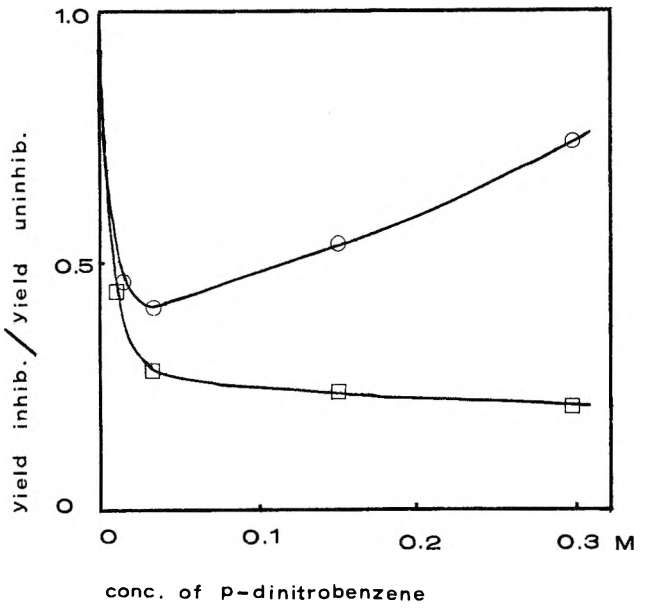
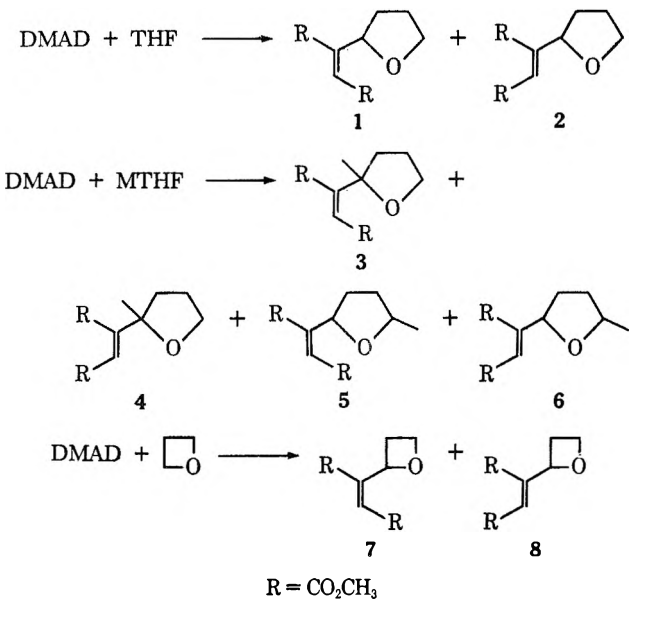


Figure 1.—Yields of trans product (1) (□) and cis product (2) (○) in the presence of scavenger relative to the yields in the unscavenged reaction *vs.* scavenger concentration.

a mixture of dimethyl tetrahydro-2-furylfumarate (1) and dimethyl tetrahydro-2-furylmaleate (2) (Scheme I);

SCHEME I



tetrahydropyran and *p*-dioxane give the corresponding products by sensitization with acetone. A free-radical chain mechanism was proposed; in the unsensitized THF addition, the radical chain was postulated to be initiated by unidentified and undetected impurities. In our study of the free radical, thermally, and photochemically initiated additions of cyclic ethers to DMAD, we have reached a different conclusion regarding the mechanism of radical formation in these systems. Furthermore, our primary results from the photochemical addition of THF to DMAD differ somewhat from those reported by Singh.

Results

Free Radical Initiated Additions.—A solution of DMAD and a small amount of dibenzoyl peroxide in excess THF give the adducts **1** and **2** in a ratio of *ca.* 70:30[8] at 65°. The total yield is 62%. Similarly, 2-methyltetrahydrofuran (MTHF) gives a mixture of products **3**–**6** in a total yield of *ca.* 90% with relative ratios of *ca.* 6:2:1:1.[8] Dibenzoyl peroxide will also initiate addition of oxetane to DMAD, resulting in a mixture of the products **7** and **8** in a ratio of *ca.* 2:1. Tetrahydropyran and oxepane do not add to DMAD under these conditions.

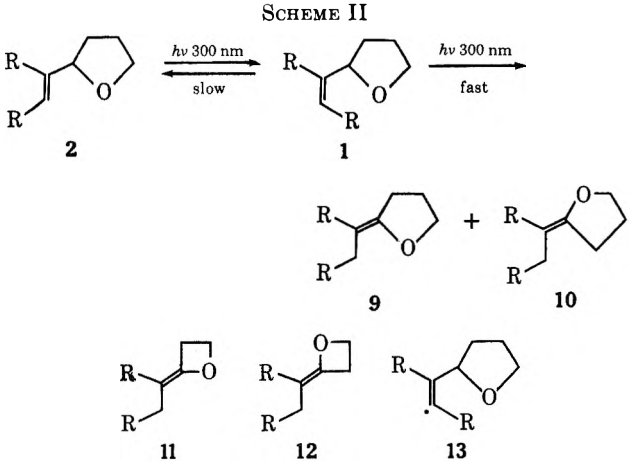
Thermal Additions.—In the absence of radical initiators, the addition of THF to DMAD still takes place, but at a much slower rate. The ratio of the adducts **1** and **2** is similar to that obtained in the free-radical initiated addition. A slight variation in the ratio with respect to change in temperature was observed, ranging from 76:24 at 5° to 70:30 at 135.° The yield at 135° is 20% based on the total amount of DMAD used; this cannot be increased further by prolonged reaction time and/or higher temperatures (150°). Most of the remaining DMAD is left unreacted.

The reaction is partially quenched when *p*-dinitrobenzene is present in the reaction mixture. At high concentrations of *p*-dinitrobenzene, the formation of the cis isomer **2** is promoted while the amount of trans isomer **1** formed remains approximately at the same residual level (Figure 1). The adducts **1** and **2** do not undergo cis–trans isomerization when heated in THF in the presence of *p*-dinitrobenzene.

With MTHF, a mixture of products **3**–**6** is formed in the same relative ratios as in the radical addition. The total yield is *ca.* 30%. Similarly, oxetane adds to DMAD, giving the adducts **7** and **8** in a ratio of *ca.* 2:1. Tetrahydropyran and oxepane do not give any adducts with DMAD under these conditions.

Photochemical Additions.—Irradiation of a THF solution of DMAD at 3000 Å initially gives the adducts **1** and **2** in a ratio similar to that obtained in the free-radical initiated and thermal additions (*ca.* 70:30). With continued irradiation, however, the ratio of **1** to **2** decreases while the build-up of two new products, vinyl ethers **9** and **10** (Scheme II), is observed. After

SCHEME II



(8) Initial ratios; the product mixture isomerized slightly under the experimental conditions. (See Experimental Section.)

48 hr of irradiation the total yield of 1:1 adducts is 80%, with a product ratio of *ca.* 1:5:2:2 (1:2:9:10). Separate irradiation of the primary trans adduct **1** in a methanol solution results in rapid and virtually quantitative formation of a 3:2 mixture of the vinyl ethers **9** and **10**. Similar treatment of the cis isomer **2** also yields a 3:2 mixture of **9** and **10** but at a considerably slower rate.

Furthermore, the photochemical addition of MTHF to DMAD will also initially give the products **3**–**6** in ratios similar to those obtained in the free-radical initiated and thermal additions.

In agreement with the report by Singh,[7] we found that tetrahydropyran does not add photochemically to DMAD by direct irradiation. This is also the case with oxepane. Oxetane, however, adds smoothly to DMAD, giving products analogous to those obtained with THF. The final products are a mixture of the isomers **11** and **12**.

Product Isomerization.—In order to determine the thermodynamic ratio of the cis–trans isomers **1** and **2**, each of these was treated with a small amount of thiophenol in benzene solution.[9] After exposure to sunlight for 1 week, both samples showed a 50:50 composition of **1** and **2**. When **1** and **2** were heated separately to 150° in THF solution for 24 hr no isomerization occurred.

Characterization of Products and Analysis of Product Mixtures.—The composition of the product mixtures was determined by vpc and the different isomers were separated by preparative vpc and characterized by their spectral properties (*i.e.*, ir, mass spectra, and nmr).

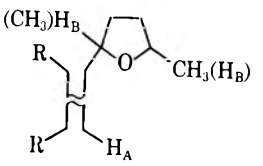
The products **1**–**4** as characterized by Singh[7] are in perfect agreement with our structural assignments to these adducts based on spectral and chemical behavior. Nmr data which are crucial for the structure determination of compounds **5**–**8** and **9**–**12** are given in Tables I and II, respectively. For comparison the previously characterized products **1**–**4** are also described (Table I). The cis isomers **2**, **4**, and **6** were separated from their trans counterparts by hydrolysis of the product mixtures with subsequent distillation; this produced the cyclic anhydrides, which were then reesterified. In the product mixture from the addition of MTHF, the isomers **4** and **5** could not be separated by vpc. The cis isomer **4** was separated by preparative vpc from the mixture of cis isomers **4** and **6** obtained from the hydrolysis–distillation–reesterification sequence. Thus, the only isomer which could not be isolated was **5**. The ratio of the isomers **4** and **5** in the product mixtures was obtained by integration of the vinylic region in the nmr spectra of the crude product mixtures; the absolute yields were obtained from the vpc peak corresponding to the sum of **4** and **5**.

The products from the addition to the 2 and 5 position of MTHF were identified by inspection of their nmr spectra. The olefinic protons and the 2-methyl group of the isomers **3** and **4** appear as singlets, in contrast to the isomers **5** and **6**, in which the corresponding absorptions appear as doublets owing to allylic coupling of the vinyl protons and vicinal coupling of the methyl groups.

The secondary photoproducts **9** and **10** show the strong –C=C– ir absorbtions characteristic of vinyl ethers. However, the stereochemical assignment of the individual cis and trans isomers is only tentative and is based on the difference in shielding in the nmr spectra of the isomeric pairs, as inferred from inspection of molecular models.

(9) C. Walling and W. Helmreich, *J. Amer. Chem. Soc.*, **81**, 1144 (1959); J. C. Kampmeier and G. Chen, *ibid.*, **87**, 2608 (1965).

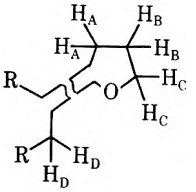
TABLE I[a]



Compd	H_A	H_B	CH_3
1	6.55 d J = 1.0 Hz	5.2 t b J = 7 Hz	
2	6.15 d J = 1.3 Hz	4.7 t b J = 6 Hz	
3	6.70 s		1.5 s
4	6.10 s		1.5 s
5	6.55 d J = 1.0 Hz	5.2 t b J = 7 Hz	Two doublets centered at 1.2[b]
6	6.20 d J = 1.5 Hz	4.7 t b J = 7 Hz	1.30 d J = 5 Hz[b] 1.35 d J = 6 Hz
7	6.7 d J = 0.5 Hz	6.0 t b J = 8 Hz	
8	6.4 d J = 1 0 Hz	5.5 t b J = 8 Hz	

[a] Nmr data for the products from the addition of THF, MTHF, and oxetane to DMAD. Chemical shifts are given in δ units in $CDCl_3$ solution relative to TMS as internal standard. [b] Two absorptions due to syn and anti isomerism. Abbreviations: s, singlet; d, doublet; t, triplet; b, broadened.

TABLE II[a]



Compd	H_A	H_B	H_C	H_D
9	3.2 t J = 8 Hz	2.2 m	4.2 t J = 7 Hz	3.4 s
10	2.8 t J = 7 Hz	2.2 m	4.4 t J = 7 Hz	3.2 s
11	3.5 t J = 6 Hz		4.9 t J = 6 Hz	3.1 s
12	3.4 t J = 6 Hz		4.9 t J = 6 Hz	3.0 s

[a] Nmr data for the secondary products in the photoaddition of THF and oxetane to DMAD. Chemical shift values are given in δ units in $CDCl_3$ solution relative to TMS as internal standard. Abbreviations: s, singlet; t, triplet; m, multiplet. In addition, these compounds all show an absorption at 3.7, two partially overlapping singlets (CH_3O–).

Discussion

The rather effective and clean free-radical initiated additions of THF, MTHF, and oxetane to DMAD should be of some preparative value. As has been pointed out by others in regard to analogous reactions,[3] the reaction is apparently a radical chain reaction involving ether radicals formed by hydrogen abstraction

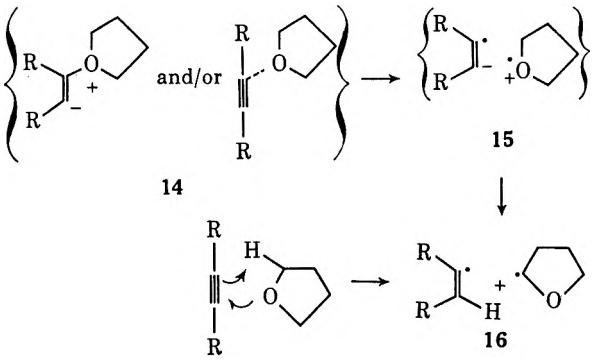
of the radicals from the decomposing initiator. In our case, the vinyl radical **13**, formed by addition of a THF radical to DMAD, is likely to be the chain-carrying species, as proposed by Singh for the photochemical addition.[7]

As we have shown, the product ratio is not the thermodynamic ratio. The stereochemical features of vinyl radicals have recently been reviewed by Singer.[10] Vinyl radicals can assume either linear (sp-hybridized) or bent (sp^2-hybridized) configurations. In the latter case, inversion can be either fast or slow in relation to hydrogen abstraction from a solvent molecule. In the case of a linear or bent and rapidly inverting vinyl radical, the product ratio depends only on the difference in the free energy levels of the two transition states leading to cis and trans product, respectively, and is in no way related to the free energy levels of the products, or to the populations of the two bent forms (Curtin–Hammet principle).[11] When the rate of inversion of a bent radical decreases in relation to the rate of scavenging (product formation), the relative populations of the two bent forms become important. In the limiting case, the product ratio reflects the stereochemistry of the initial addition step. This does not seem to be a likely alternative in our case, since radicals are generally considered to add stereospecifically trans to acetylenes.[10] Assuming a linear or bent and rapidly inverting radical, the product ratio 70:30 corresponds to a *ca.* 0.6 kcal/mol difference in free energy between the transition states giving **1** and **2** from the vinyl radical **13**.

The thermal and primary photochemical additions of THF, MTHF, and oxetane to DMAD are, in our opinion, of considerable mechanistic interest. These additions give product ratios similar to those obtained in the free-radical initiated additions (Scheme I). This shows that vinyl radicals are intermediates also in the former cases. Thus, the photochemical and thermal additions are also radical chain reactions, involving ether radicals. This is further supported by the fact that the thermal addition is partially quenched by a radical scavenger such as *p*-dinitrobenzene.[12] The thermal addition seems to be self-inhibiting, since complete conversion of DMAD cannot be achieved.

THF is known to be extremely prone to peroxide formation in the presence of oxygen. To avoid the possibility of a free-radical reaction initiated by the decomposition of peroxides and other impurities, great care was taken to purify the reactants. Excluding the possibility of initiation by peroxide impurities, we will discuss some reasonable mechanisms for the thermal and photochemical formation of THF radicals i in these systems. Even though no evidence for a charge-transfer complex (**14**) could be found by inspection of the uv spectrum of DMAD in THF,[13] the photochemical addition may proceed *via* an anion–cation radical pair **15** formed by the excitation of such a complex (**14**), since this seems to be a frequent process in related systems. A related mechanism is believed to operate in the photochemical oxidation of THF, where a charge-transfer complex between THF and oxygen has been shown to be an intermediate.[14] Photoaddition of THF to quaternary salts of pyridylethylenes is also believed to proceed *via* electron transfer–proton transfer–radical coupling.[15] Tetracyanoethylene has been shown to form a charge-transfer complex with THF, which on irradiation gives the tetracyanoethylene anion radical.[16] In addition, THF adds photochemically to tetracyanoethylene (see above). In our case, proton transfer within the anion–cation radical pair **15** should give the radical pair **16**, which by diffusion gives free radicals to start a radical chain reaction. A similar mechanism may also be important in the thermal reaction. Alternatively, the electron transfer–proton transfer process may be concerted, giving the radical pair **16** directly (Scheme III). This should be

SCHEME III



an attractive alternative, particularly for the thermal addition, since formation of high-energy intermediates would be avoided.

The behavior of the thermal reaction in the presence of high scavenger concentrations deserves attention (Figure 1). The yield of the trans product **1** decreases sharply to a constant value on increasing concentrations of scavenger, while the yield of the cis isomer **2**, after an initial sharp decrease, shows a steady increase. This indicates that an alternative mechanism for the formation of the cis isomer **2** becomes important. *p*-Dinitrobenzene is an acceptor and may catalyze a polar addition when present in high concentrations.[17] Furthermore, the residual formation of the trans isomer **2** at a constant level at high concentrations of scavenger indicates that the reaction has partial cage character, with a cage factor of 0.2.

Only the four- and five-membered cyclic ethers add to DMAD in the free-radical initiated, thermally, and direct photochemically initiated reactions, while the six- and seven-membered cyclic ethers are unreactive under these conditions. This behavior parallels the reports of the free-radical and photochemical additions of cyclic ethers to substrates such as diethyl maleate

(10) L. A. Singer, "Selective Organic Transformations," Vol. II, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1972.

(11) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, pp 237–239.

(12) E. G. Janzen and B. L. Blackburn, *J. Amer. Chem. Soc.*, **91**, 4481 (1969); E. G. Janzen and J. L. Gerlock, *ibid.*, **91**, 3108 (1969).

(13) When DMAD was added to carefully purified MTHF at room temperature a faint but distinct pink color developed in the solution, which remained for several days. Product formation occurred simultaneously.

(14) V. I. Stenberg, C. T. Wang, and N. Kulevsky, *J. Org. Chem.*, **35**, 1774 (1970); V. I. Stenberg, R. D. Olson, C. T. Wang, and N. Kulevsky, *ibid.*, **32**, 3227 (1967).

(15) J. W. Happ, M. T. McCall, and D. G. Whitten, *J. Amer. Chem. Soc.*, **93**, 5496 (1971).

(16) D. F. Ilten and M. Calvin, *J. Chem. Phys.*, **42**, 3760 (1965).

(17) Reflux of a THF solution of DMAD in the presence of boron trifluoride etherate gave pure cis adduct **2**. However, this result has been shown not to be readily reproducible, the reason for which is under investigation.

and simple olefins and has been mentioned above. Generally, six-membered cyclic ethers add to unsaturates only by ketone-sensitized irradiation.[6] This divergent behavior in the series of cyclic ethers may be related to the stereochemical features of their α hydrogens. In the relatively planar four- and five-membered cyclic ethers, the α hydrogens are eclipsed with the oxygen lone pairs, while the α hydrogens of the less rigid six- and seven-membered cyclic ethers are less sterically restricted.[18] This special feature of the former ethers might render their α hydrogens more susceptible to both hydrogen abstraction by a chain-transfer agent and to radical initiation *via* a mechanism as outlined above. In our opinion, this stereochemical feature of the cyclic ethers should be more important than the effect of decreasing donor strength with increasing ring size,[19,20] which might be associated with their interaction with electrophiles. The differences in donor strength in the series of cyclic ethers are not great enough to account for the striking change in behavior within the series.

From this discussion it can be concluded that the ketone-sensitized photochemical additions of cyclic ethers to unsaturates are different in nature from the corresponding reaction in the presence of free radical initiators and by direct irradiation. Ketone–ether exciplexes may be intermediates in the sensitized photochemical abstractions.

The secondary photochemical isomerizations of **1** and **2** and **7** and **8** to vinyl ethers **9**–**12** should be of some preparative interest. Our results indicate that **9** and **10** are formed solely from the trans isomer **1** (Scheme II). The cis isomer **2** probably gives **9** and **10** *via* slow cis–trans isomerization. As soon as it is formed, the trans isomer undergoes isomerization to **9** and **10**. This process is another example of photodeconjugation of acyclic α,β-unsaturated esters. Our results are in complete agreement with what has been found to be general behavior in similar systems.[21,22] These reactions have been shown to proceed from an excited singlet state *via* a cyclic transition state to give an enol, which is subsequently ketonized. The hydrogen transfer step has been looked upon as a sigmatropic 1,5 shift or an intramolecular hydrogen abstraction.[22]

Experimental Section

Spectra.—Ir data are given in reciprocal centimeters. The nmr spectra were run on a Varian T-60 spectrometer in $CDCl_3$ solution. Chemical shifts are given in δ units relative to TMS as internal standard. The mass spectra were run on a LKB 9000 gas chromatograph–mass spectrometer at an electron potential of 70 eV. (For vpc columns, see below.)

Gas Chromatography.—In the analytical work, products **1**–**6** were separated on a 6 ft × 0.125 in., 5% PDEAS (phenyldiethanolamine succinate), Chromosorb W column at 180–200°. Products **9**–**12** were separated on a UC-298 (silicone rubber) Hewlett-Packard column at 160–200°. The chromatograms were integrated with a Varian 480 electronic digital integrator and/or by the cutting and weighing technique. For the preparative work, a 12 ft × 0.25 in., 30% PDEAS, Chromosorb W column and a 6 ft × 0.25 in., 10% SE-30 Chromosorb W column were used.

Materials.—THF (Mallinckrodt analytical grade) and MTHF (Fluka) were purified by refluxing over potassium benzophenone ketyl in an atmosphere of purified nitrogen followed by distillation. Oxetane (Aldrich) was refluxed over $LiAlH_4$. Tetrahydropyran (Merck) and oxepane (Aldrich) were used as received. DMAD (Aldrich) was vacuum distilled and stored at 5° before use. Before use, THF, MTHF, and oxetane were subjected to the ferric thiocyanate peroxide test.[23] No peroxides could be detected. By applying this test to ethyl ether solutions of dibenzoyl peroxide, it was found that peroxide was easily detected down to concentrations of 1×10^{-5} *M*.

Dibenzoyl Peroxide Initiated Additions. A. Addition of THF to DMAD.—Three 200-mg (0.83 mmol) portions of Bz_2O_2 were added to a refluxing solution of 5.0 g (35.2 mmol), in 25 ml (0.3 mol) of THF, with 12-hr intervals. After 36 hr, excess THF was evaporated and the residue was taken up in ether and washed with saturated aqueous $NaHCO_3$ solution and water. After drying and evaporation, 7.2 g of a crude material was isolated. For further purification, the material was distilled to give 4.7 g of a 64:36 mixture of **1** and **2** at 90–100° (0.1 mm), yield 62.5%. The isomers were isolated by preparative vpc. Spectral data of **1** and **2** were in general accord with those given by Singh.[7] Before the second addition of Bz_2O_2 the ratio of **1** and **2** was 70:30. When more Bz_2O_2 was added in order to complete the reaction, partial isomerization of the initial product mixture took place to a mixture that was enriched in the cis isomer **2**. This was due to secondary isomerization, as shown by treating a refluxing THF solution of a 70:30 mixture of **1** and **2** with Bz_2O_2. This resulted in isomerization of the 70:30 mixture to the thermodynamic 50:50 mixture.

B. Addition of MTHF to DMAD.—A 50-mg (0.2 mmol) portion of dibenzoyl peroxide was added to a refluxing solution of 0.84 g (5.9 mmol) of DMAD in 5 ml (50 mmol) of MTHF. After 12 hr all the DMAD had reacted (vpc) and the total yield of 1:1 adducts was estimated to be 90% (vpc, naphthalene as internal standard). Excess MTHF was evaporated and the isomers **3** and **6** were isolated by preparative vpc. On all columns tried the isomers **4** and **5** did not separate but eluted as a mixture. However, the isomer **4** could be isolated by preparative vpc of the mixture of cis isomers **4** and **6** (see below). Having isolated **4**, the nmr spectrum of **5** was obtained by subtracting the spectrum of **4** from that of the mixture of **4** and **5**. Our spectral data for **3** and **4** are in general agreement with what has been reported by Singh.[7] Nmr data for **5** and **6** are given in Table I and, for comparison, nmr data for **3** and **4**. By the method mentioned previously, the relative ratios of the products **3**, **4**, **5**, and **6** were found to be 6:2:1:1.

C. Addition of Oxetane to DMAD.—A 50-mg (0.2 mmol) portion of Bz_2O_2 was added to a refluxing solution of 0.2 g (1.4 mmol) of DMAD in 2 ml (30 mmol) of oxetane. After refluxing for 8 hr, two partially resolved peaks in the vpc showed the formation of two 1:1 adducts in a ratio of *ca.* 2:1. The yield was estimated to be 50%. After evaporation of excess oxetane, nmr of the crude mixture showed the major adduct to be **7** and the minor **8** by comparison with the nmr spectra of the corresponding THF adducts. For nmr see Table I.

Solutions of DMAD in tetrahydropyran and oxepane were subjected to the same treatment. No 1:1 adducts or other products could be detected or isolated.

Thermal Additions.—For analytical work, a stock solution of 5.0 g (35.2 mmol) of DMAD, 0.1 g (0.78 mmol) of naphthalene (internal vpc standard), and 25 ml (0.31 mol) of THF (MTHF respectively) was prepared and kept under nitrogen before immediate use.

A. Addition of THF to DMAD.—Samples (1 ml) were syringed from the stock solution and placed in glass ampoules which were sealed after purging with nitrogen. Samples were kept at 5°, room temperature, and 135°. In each case, **1** and **2** were formed in ratios ranging from 76:24 at 5° to 70:30 at 135° (vpc). A maximum yield of 20% was achieved after 24 hr at 135° (based on the total amount of DMAD and measured by vpc in comparison with standard solutions of **1** and **2**). No other products could be detected by vpc, and the remaining 80% DMAD seemed to be left largely unreacted.

To a series of samples, 2 mg (0.012 mmol), 5 mg (0.030 mmol), 25 mg (0.149 mmol), and 50 mg (0.298 mmol) of *p*-dinitrobenzene were added, respectively. These were kept at 135° for 4

(18) E. M. Arnett and C. Y. Wu, *J. Amer. Chem. Soc.*, **84**, 1684 (1962).
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hr, and subsequently analyzed by vpc. Yields of 1 and 2 relative to an untreated sample heated similarly are given in Figure 1.

B. **Addition of MTHF to DMAD.**—A 1-ml sample from the stock solution was kept at 135° for 24 hr in a sealed tube, and subsequently analyzed by vpc. The yield of 1:1 adducts was 30% based on the total amount of DMAD (vpc). The main part of the DMAD was left unreacted and the ratio of the isomers 3, 4, 5, and 6 was 6:2:1:1. After 0.2 hr at room temperature, a faint pink color developed in the stock solution. Vpc showed simultaneously an initially fast product formation; after 4 days at room temperature, the pink tinge faded away. A substantial amount of products 3–6 had formed at that time.

C. **Addition of Oxetane to DMAD.**—A 0.1-g (0.7 mmol) portion of DMAD in 1 ml (15 mmol) of oxetane was kept at 135° in a sealed tube for 4 hr. Vpc showed the formation of 7 and 8 in a ratio of *ca.* 2:1. The yield was estimated to be 30%.

Solutions of DMAD in tetrahydropyran and oxepane were subjected to similar treatment. No 1:1 adducts or other products could be detected or isolated.

Photochemical Additions. A. **Photoaddition of THF to DMAD.**—A solution of 3.0 g (21.1 mmol) of DMAD in 50 ml (0.62 mol) of THF was degassed by purging with nitrogen and then irradiated in a Pyrex vessel in a Rayonet photoreactor equipped with 3000-Å lamps. After very low conversion (*ca.* 5 min), the ratio of the products 1 and 2 formed was 70:30 (vpc). After 48 hr of irradiation, excess THF was evaporated. Vpc analysis showed the presence of four products. By distillation of the crude mixture (4.3 g), 2.2 g of a 1:5 mixture of 1 and 2 was collected at 90–100° (0.1 mm). In addition, at 130–140° (0.1 mm), 1.4 g of a 1:1 mixture of 9 and 10 was collected. The total yield of 1:1 adducts was 80%. The mixture of 9 and 10 was separated by preparative vpc (SE-30). Elementary analyses follow. *Anal.* Calcd for 9: C, 56.07; H, 6.59. Found: C, 55.85; H, 6.45. For 10: Found: C, 55.78; H, 6.47. 9 and 10 showed the following spectral characteristics. 9: nmr, see Table II; ir C=O 1740, 1710, -C=C- 1640 (strong); mass spectrum parent ion *m/e* 214, base peak *m/e* 123. 10: nmr, see Table II; ir C=O 1735, 1680, -C=C- 1640 cm^{-1} (strong); mass spectrum parent ion *m/e* 214, base peak *m/e* 155. The photoproducts 9 and 10 were also obtained by irradiation (3000 Å) of 1 and 2 in a methanol solution. After 12 hr irradiation of 1, the conversion to 3:2 mixture of 9 and 10 was virtually quantitative (vpc). Irradiation of 2 under similar conditions also gave a 3:2 mixture of 9 and 10 but at a much slower rate. After 96 hr irradiation *ca.* 90% of 2 had reacted. In addition some polymer was formed.

B. **Photoaddition of MTHF to DMAD.**—Irradiation of a solution of 0.1 g (0.7 mmol) of DMAD in 2 ml of MTHF under the conditions described previously gave initially a 6:2:1:1 mixture of the products 3, 4, 5, and 6 (vpc).

C. **Photoaddition of Oxetane to DMAD.**—A solution of 0.5 g (3.5 mmol) of DMAD in 10 ml (0.15 mol) of oxetane was irradiated in a Pyrex vessel in a Rayonet photoreactor equipped with 3000-Å lamps. The reaction was followed by vpc, which showed initial formation of the two primary products 7 and 8 in a ratio of *ca.* 2:1. These were subsequently transformed into two new products, 11 and 12 (ratio 6:2, 46 hr irradiation). After evaporation of excess oxetane, the mixture of 11 and 12 was separated from the product mixture by preparative vpc. 11 and 12 were not easily separated by preparative vpc, but samples which were enriched in both isomers could be obtained. The structural assignments of 11 and 12 are based on comparison of the nmr spectra of these enriched mixtures with the nmr spectra of 9 and 10. Total yield was *ca.* 80%.

Similar irradiations of tetrahydropyran and oxepane solutions of DMAD gave no adduct formation.

Isomerization of the Adducts 1 and 2.—A 50-mg (0.235 mmol) portion of 1 in 1 ml of benzene was treated with 10 mg (0.09 mmol) of thiophenol and exposed to sunlight. Vpc analysis at different intervals showed slow isomerization of 1 to a mixture of 1 and 2. After 1 week, the ratio of 1 and 2 was 50:50 and did not change further. The same result was obtained when 2 was treated similarly.

Isolation of the Cis Isomers 2, 4, and 6.—The product mixtures from the additions of DMAD to THF and MTHF, respectively, were hydrolyzed by refluxing in NaOH–methanol solution overnight. After acidification and extraction with ether and water, the ether layer was evaporated and the residue was distilled. At 80–90° (0.1 mm), tetrahydro-2-furylmaleic anhydride was collected: ir C=O 1840, 1770, -C=C- 1650 cm^{-1}; nmr δ 2.0 (m, 4 H), 4.0 (m, 3 H), 4.8 (t, J = 6 Hz, 1 H), 6.8 (d, J = 1 Hz, 1 H). This material was refluxed overnight in methanol solution with a trace of sulfuric acid. Usual work-up gave pure 2. In a similar way, a mixture of 4 and 6 was isolated from the mixture of 3, 4, 5, and 6. The ratio of 4 and 6 was shown to be 8:2 in the mixture obtained from the thermal addition.

Registry No.—1, 33536-59-3; 2, 28864-83-7; 3, 33536-63-9; 4, 33536-64-0; 5, 33522-13-3; 7, 38229-58-2; 8, 38229-59-3; 9, 38229-60-6; 10, 38229-61-7; 11, 38229-62-8; 12, 38229-63-9; THF, 109-99-9; MTHF, 96-47-9; DMAD, 762-42-5; oxetone, 503-30-0.

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The Kinetics of Epimerization of Dimethyl *cis*- and *trans*-1,2-Cycloalkanedicarboxylates[1]

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The kinetics, position of equilibrium, and related thermodynamic parameters have been determined for epimerization of a series of 1,2-dimethyl esters of cycloalkanes varying from cyclopropane through cycloheptane and for the related 1-methylcyclohexane, 1-methylcyclohex-4-ene systems. The trans isomer is always favored, with K (trans/cis) varying from 99 (cyclopropane) to 1.6 (1-methylcyclohexene). Insertion of a Δ^4 double bond in cyclohexane increases the amount of cis isomer (K changes from 11.7 to 2.8), but decreases the trans isomer in the 1-methyl derivative (K changes from 1.8 to 1.6). All of the equilibrium effects are accounted for in terms of decreased configurational or steric strain in the more stable isomer. The rate effects ($3 < 6 < 4 \simeq 7 < 5$) are explained in terms of steric strain or its relief in a trigonal transition state and relative ease of removal of the enolizable proton.

The relations between conformation, steric factors, and chemical reactivity have long posed problems of theoretical interest. Substituents in axial positions are more crowded, which is a principal factor controlling their reactivity. Thus reactions which proceed with relief of strain are generally facilitated, while those with transition states involving increase in strain are hindered.[3] Examples of this effect include the rates of hydrolysis of esters of cyclohexanol, cyclohexanecarboxylic acid, and *cis*- and *trans*-4-*tert*-butylcyclohexyl acetates.[4] In cases where a common intermediate is found the difference in reactivity becomes the difference between the free energies of the two ground states.[5]

Studies of the effect of ring size on solvolysis reactions have been conducted by several workers.[6-8] The configuration of cyclohexanedicarboxylic, cycloheptanedicarboxylic, and cyclopentanedicarboxylic esters greatly affects the rate of both acid- and base-catalyzed hydrolysis.[9-11]

Systems containing a carbonyl group and at least one α proton undergo enolization with either acidic or basic catalysts, a process which is greatly influenced by both steric and polar effects. In general the enols that are stronger acids are formed more rapidly than those that are weaker.[12]

Ring size plays an important role in the rate of enolization of alicyclic ketones and cycloalkyl phenyl ketones. Schechter concluded from data on base-catalyzed enolization that the rates are related to the amount of s character in the carbon orbital directed toward the enolizable hydrogen.[13a] In a later paper, describing the results of deuterium exchange studies on phenyl cyclopropyl ketone, it was pointed out that s character alone cannot account for exchange or lack of it.[13b]

The carbonyls of ester groups are, in general, not as effective in enolization reactions as are those of ketones. However, reactions such as the Claisen-type condensation do involve anions which are at least partially stabilized by ester carbonyl participation in enolization.[14] Base-catalyzed equilibrations of cyclic esters yield an equilibrium mixture which reflects the relative stabilities of the cis and trans isomers.[15-19]

In order to examine the combined effects of ring size, conformation, steric factors, and chemical reactivity, we initiated a combined kinetic and equilibration study of several dimethyl 1,2-cycloalkanedicarboxylates. This approach was chosen for several reasons: (i) relative ease of synthesis; (ii) simple analytical method (glc); (iii) synthetic value of the reaction; (iv) convenient rates of epimerization; (v) a minimum of side reactions.

Experimental Section

All melting points and boiling points are uncorrected. Gas chromatographic analyses were conducted on a MicroTek GC-1600 instrument with a flame ionization detector. Separations were made on stainless steel columns 3.2 mm o.d. and 3.3 m long packed with 20% Carbowax 20M or 20% QF-1 on Anakrom ABS (80–100 mesh) and operated isothermally at temperatures between 115 and 140° with helium as the carrier gas. Known mixtures were prepared from gas chromatographically pure esters and analyzed. The gas chromatographically determined percentages corresponded within experimental error (±1%) to those of known analytical samples, and no correction factors for the relative responses were necessary. The relative percentages of epimers were calculated using the method of half peak heights. Samples of dimethyl 1,2-cyclohexanedicarboxylate which contained less than 12% of the cis ester were determined by the ratio of peak heights, which were compared with the relative heights of known samples.

The syntheses, appropriate physical constants, and gas–liquid chromatographic data for the substrates used in this study are summarized in Table I.

Preparation of Samples for Kinetic Determinations.—Solutions of the esters were prepared to be 0.25 M, by weighing the required amount of ester into a previously tared volumetric

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TABLE I

THE SYNTHESES AND SEPARATION OF DICARBOXYLIC ESTERS FOR THE EPIMERIZATION STUDIES

Registry no.	Dicarboxylate (dimethyl)	Yield, %[a]	n_D (°C)	Lit. n_D (°C)	Ref	Bp, °C (mm)	Lit. bp, °C (mm)	Ref	Retention time, min (temp,[g] °C)
826-34-6	*cis*-1,2-Cyclopropane-	97.5[b,i]	1.4434 (27)			59 (0.6)	200-202	*t*	4.0 (180)[e]
826-35-7	*trans*-1,2-Cyclopropane-	64.0[d,i]	1.4523 (26)	1.4472 (18)	*w*	61-63 (0.5)	219-220	*w*	2.4 (180)[e]
2607-03-6	*cis*-1,2-Cyclobutane-	88.5[b,k]	1.4453 (27)	1.4430 (18)	*q*	56 (0.5)	85 (3)	*k*	7.4 (160)[f]
7371-67-7	*trans*-1,2-Cyclobutane-	58.0[d,k]	1.4430 (25)			53 (0.4)	114 (20)	*q*	5.8 (160)[f]
4841-91-2	*cis*-1,2-Cyclopentane-	91.5[b,l]	1.4512 (27)	1.4528 (21)	*r*	68-70 (0.7)	116-117 (12)	*y*	11.3 (150)[f]
941-75-3	*trans*-1,2-Cyclopentane-	54.0[d,l,m]	1.4482 (25)	1.4491 (20)	*r*	59 (0.7)	119-120 (16)	*y*	8.3 (150)[f]
1687-29-2	*cis*-1,2-Cyclohexane-	64.0[c,d]	1.4578 (25)	1.4570 (25)	*s*	73-75 (1.3)	136.2 (18)	*z*	12.6 (170)[f]
3205-35-4	*trans*-1,2-Cyclohexane-	80.0[d,z]	1.4518 (25)	1.4539 (24)	*v*	58 (1.3) Mp 33.5-35	72-75 (0.5-0.8) Mp 33°	*v* *x*	11.6 (170)[f]
38312-27-5	*cis*-1,2-Cycloheptane-	82.0[b,p]	1.4651 (26)	1.4659 (20)	*i*	85 (0.4)	143-144 (15)	*i*	8.3 (150)[f]
38312-28-6	*trans*-1,2-Cycloheptane-	*b*, *p*	1.4546 (28)	1.4630 (20)	*i*	110-120 (3.5)	140-141 (10 mm)	*i*	7.0 (150)[f]
14679-33-5	*cis*-1-Methyl-1,2-cyclohexane-	90.0[b,o]	1.4588 (27)	1.4635 (20)	*n*	69-71 (0.5)	95 (2)	*n*	21.4 (130)[e]
38312-30-0	*trans*-Methyl-1,2-cyclohexane-	92.5[b,o]	1.4594 (25)	1.4636 (20)	*n*	54-55 (0.2)	95 (2)	*n*	23.7 (130)[e]
2305-26-2	*cis*-1,2-Cyclohex-4-ene-	94.0[b,c]	1.4708 (26)	1.4700 (25)	*s*	77 (0.7)	110-113 (3)	*u*	13.3 (165)[f]
17673-68-6	*trans*-1,2-Cyclohex-4-ene-	*h*, *o*							11.8 (165)[f]
14679-33-5	*cis*-1-Methyl-1,2-cyclohex-4-ene-	*h*, *n*, *o*							18.8 (115)[e]
38312-30-0	*trans*-1-Methyl-1,2-cyclohex-4-ene-	*h*, *n*, *o*							20.3 (115)[e]

[a] References are to syntheses of the acids or anhydrides. [b] Acids esterified by diazomethane. [c] Anhydride obtained commercially. [d] Acids esterified by Fischer method. [e] On QF-1 column. [f] On Carbowax 20M column. [g] See experimental conditions. [h] Ester prepared as described in ref *o*; all physical constants identical with those reported there. [i] J. Sicher, F. Sipos, and J. Jonas, *Collect. Czech. Chem. Commun.*, **26**, 262 (1961). [j] L. L. McCoy, *J. Amer. Chem. Soc.*, **80**, 6568 (1958). [k] E. R. Buchman, A. O. Reims, T. Skei, and M. J. Schlatter, *ibid.*, **64**, 2696 (1942). [l] S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, **20**, 1178 (1955). [m] W. J. Bailey and W. R. Sorenson, *J. Amer. Chem. Soc.*, **76**, 5421 (1954). [n] I. N. Nazarov and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 289 (1952); *Chem. Abstr.*, **47**, 5363c (1953). [o] J. J. Bloomfield and S. L. Lee, *J. Org. Chem.*, **32**, 3919 (1967). [p] K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, **28**, 1464 (1963). [q] W. A. Roth and G. J. Östling, *Chem. Ber.*, **46**, 309 (1913). [r] L. N. Owen and A. G. Peto, *J. Chem. Soc.*, 2383 (1955). [s] A. C. Cope and E. C. Herrick, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 306. [t] H. von Pechman, *Chem. Ber.*, **27**, 1888 (1894). [u] F. V. Brutcher, Jr., and D. D. Rosenfeld, *J. Org. Chem.*, **29**, 3154 (1964). [v] L. Bauer and C. N. V. Nambury, *ibid.*, **26**, 1106 (1961). [w] G. J. Östling, *J. Chem. Soc.*, **101**, 457 (1912). [x] A. von Baeyer, *Justus Liebigs Ann. Chem.*, **258**, 145 (1890). [y] Reference 10. [z] Reference 11.

flask. The solution was made to volume with methanol. All methanol used in the kinetic studies was specially dried by reaction with magnesium followed by distillation, and was stored over molecular sieve (3A) under a drying tube.

Sodium methoxide solutions were prepared approximately 0.25 *M* by dissolving hexane-washed sodium metal in methanol, treated as above, in a dried volumetric flask. The solution was made to volume by addition of methanol. Each solution was standardized by titration of weighed portions of potassium acid phthalate dissolved in water, using phenolphthalein as indicator. These stock solutions were prepared several times in the course of the work to avoid the use of sodium methoxide samples contaminated with sodium hydroxide.

Aliquots of the standard ester and base solutions necessary to prepare the desired concentrations were pipetted into dried volumetric flasks. These flasks were filled to volume with methanol and a septum was placed in the neck of the flask. The solution was agitated and placed in a constant-temperature bath. In cases where the reaction was reasonably fast the ester solution and methanol were added and the mixture was allowed to reach temperature equilibrium. The base solution was then added and the solution quickly agitated.

Duplicate kinetic samples were run in each case and equilibrium was approached with both cis and trans samples at 50 ± 0.02°, 35 ± 0.05°, and 25 ± 0.05°.

Removal of Samples and Work-up for Kinetic Runs.—Samples (1 ml) were removed with a syringe and quenched with 0.1 *N* hydrochloric acid. Saturated sodium chloride solution (1 ml) and ether (1 ml) were added to the quenched sample in a 3-in. test tube. The tube was shaken and the phases were allowed to separate. The ethereal phase was removed and dried with anhydrous magnesium sulfate. Samples prepared in this manner were used for gas chromatography directly. Each sample was analyzed three times and the average of the three values of relative percentages was used in subsequent calculations. The relative percentages of samples of known ester composition worked up in the above manner showed no significant deviations from the known values.

The kinetics of a first-order reversible reaction of the type

$$A \underset{k_t}{\overset{k_c}{\rightleftharpoons}} B$$

where $K = k_c/k_t$, may be expressed as[20]

$$\ln (AK - B) = \ln (A_0K - B_0) - (k_t + k_c)t \qquad (1)$$

(20) S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill, New York, N. Y., 1960, p 96.

where A_0 and B_0 are the initial concentrations of the cis and trans esters, respectively. The rates of the base-catalyzed epimerization reactions of *cis*- and *trans*-1,2-cycloalkanedicarboxylates were observed to obey this equation and to have pseudo-first-order, reversible kinetics. The values of the equilibrium constants, K, were measured from analysis of the equilibrium concentrations. Dimethyl *cis*- and *trans*-1,2-cyclopropanedicarboxylate did not attain equilibrium in a reasonable time; so the values reported by Shiengthong were used.[19] The concentration of the esters, A and B, was calculated from the relative percentages a and b, which were measured by gas chromatography and the initial concentration, A_0, by the relations

$$A = aA_0(0.01)$$

$$B = bA_0(0.01)$$

Equation 1 is linear; therefore plots of ln $(AK - B) = Y_i$ *vs.* t (time) have a slope of $-(k_t + k_c)$ and a y intercept of ln $(A_0K - B_0)$.

The least squares equations for the slope, S, and the y intercept are as follows.

$$S = -(k_c + k_t) = \frac{N\Sigma t_iY_i - \Sigma t_i\Sigma Y_i}{N\Sigma t_i^2 - (\Sigma t_i)^2}$$

$$\ln (A_0K - B_0) = \frac{\Sigma t_i^2Y_i - \Sigma t_i\Sigma t_iY_i}{N\Sigma t_i^2 - (\Sigma t_i)^2}$$

Because the reliability of the data decreases as equilibrium is approached, the above equations were modified so that a weighted least squares treatment could be used to calculate the rate constant. The data were weighted in the following manner: the deviation of each value of Y [ln $(AK - B)$] was calculated from the least squares line by the equation.

$$DY = [K(DA) - DB]/AK - B$$

where DA and DB are the errors in A and B, respectively. The error in A is assumed to be the same for all values with a corresponding relative percentage greater than 97.0% and for B with a value less than 3.0%.

The weighting factors, w_i, were calculated by the following arbitrary relation.

$$w_i = 1.0/[DY]$$

The factors were then normalized so that $\Sigma w_i = 1.0$. With the inclusion of weighting factors the least squares equations become[21]

$$S = \frac{\Sigma w_it_iY_i - \Sigma w_it_i\Sigma w_iY_i}{\Sigma(w_it_i)^2 - (\Sigma w_it_i)^2}$$

and

$$\ln (A_0K - B_0) = \frac{\Sigma w_iY_i\Sigma(w_it_i)^2 - \Sigma w_it_iY_i\Sigma w_it_i}{\Sigma(w_it_i)^2 - (\Sigma w_it_i)^2}$$

The pseudo-first-order rate constants obtained were corrected for base concentration by the relation

$$k_c = k_c \text{ (pseudo)/base concentration}$$

The free energy of each reaction was calculated by the relation

$$\Delta G^\circ = -RT \ln K$$

The activation parameters $\Delta H^\ddagger$, $\Delta G^\ddagger$, and $\Delta S^\ddagger$ were calculated by standard relationships.[22]

The rate calculations described above were executed on an IBM 1410 computer. The program used calculated the least squares slope, the rate constants, and their associated errors, as well as a statistical analysis of the equilibrium constant values.[23] Values for the standard deviations and related error functions have been tabulated.[23]

Discussion

Our kinetic and equilibration study of the base-catalyzed epimerization of an homologous series of *cis*- and *trans*-1,2-cycloalkanedicarboxylates, from three to seven carbon rings, also included the 1-methylcyclohex-4-ene and cyclohex-4-ene systems. Dimethyl *cis*- and *trans*-1,2-cycloalkanedicarboxylates were equilibrated from both directions with sodium methoxide in methanol. By measurements of the relative percentages of each pair of esters at equilibrium, the equilibrium constant and the free energy value may be calculated for the epimerization reaction (Table III, columns 1 and 2). The effect of ring size on the equilibrium position in epimerization reactions of the preceding type has been studied by Fonken and Shiengthong.[18,19]

The rates of epimerization, k_c and k_t, were measured for the epimerizations of both cis and trans esters (Table II). As the trans runs involve small changes of concentration, in most cases the data derived from them is less accurate. Plots of log k_c *vs.* ring size for the homologous series of esters, Figure 1, resemble those for solvolysis reactions.[8,9,23]

The effect of ring size in reactions of various types has been the subject of many studies. In small rings (3, 4) the principal rate-determining factor is angular strain. In normal rings (5, 6, 7) bond opposition strains play a large role but angular strain is still

TABLE II

EQUILIBRIUM AND KINETIC DATA FOR THE EPIMERIZATION OF ESTERS

Temp, °C	K (trans/cis)[a]	k_c, l. sec^{-1} mol^{-1}[b]	k_t, l. sec^{-1} mol^{-1}[b]
	Dimethyl *cis*-1,2-Cyclopropanedicarboxylate		
25	99[c]	7.06×10^{-8}	7.11×10^{-10}
35	99[c]	2.42×10^{-7}	2.44×10^{-9}
50	99[c]	2.09×10^{-6}	2.12×10^{-8}
	Dimethyl *cis*-1,2-Cyclobutanedicarboxylate		
25	8.40	1.32×10^{-4}	1.57×10^{-5}
35	7.67	3.00×10^{-4}	3.92×10^{-5}
50	8.58	1.71×10^{-3}	2.42×10^{-4}
	Dimethyl *cis*-1,2-Cyclopentanedicarboxylate		
25	9.53	1.76×10^{-4}	1.84×10^{-5}
35	7.37	5.72×10^{-4}	7.78×10^{-5}
50	6.08	2.55×10^{-3}	4.17×10^{-4}
	Dimethyl *cis*-1,2-Cyclohexanedicarboxylate		
25	13.5	6.72×10^{-6}	4.97×10^{-7}
35	9.71	2.36×10^{-5}	2.43×10^{-6}
50	11.7	1.41×10^{-4}	1.20×10^{-5}
	Dimethyl *cis*-1,2-Cycloheptanedicarboxylate		
25	3.74	6.06×10^{-5}	1.61×10^{-5}
35	4.51	2.02×10^{-4}	4.78×10^{-5}
50	3.90	9.11×10^{-4}	2.33×10^{-5}
	Dimethyl *cis*-1-Methyl-1,2-cyclohexanedicarboxylate		
25	1.84	4.42×10^{-7}	2.41×10^{-7}
35	1.84	1.26×10^{-6}	6.83×10^{-7}
50	1.75	7.00×10^{-6}	3.81×10^{-6}
	Dimethyl *cis*-1,2-Cyclohex-4-enedicarboxylate		
25	2.68	2.42×10^{-7}	9.06×10^{-6}
35	3.19	5.50×10^{-5}	1.72×10^{-5}
50	2.82	2.47×10^{-4}	8.78×10^{-5}
	Dimethyl *cis*-1-Methyl-1,2-cyclohex-4-enedicarboxylate		
25	1.60	1.35×10^{-6}	8.44×10^{-7}
35	1.60	4.33×10^{-6}	2.71×10^{-6}
50	1.70	1.76×10^{-5}	1.03×10^{-5}

[a] Equilibrium constants, unless otherwise noted, are obtained by measuring percentages of equilibrated mixtures. [b] The second-order rate constants k_c and k_t are all taken from runs with a base concentration of 0.05 M. [c] Values taken from ref 18 and 19.

(21) H. D. Young, "Statistical Treatment of Experimental Data," McGraw-Hill, New York, N. Y., 1962.

(22) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1961.

(23) D. S. Seigler, Ph.D. Dissertation (Chemistry), The University of Oklahoma, Norman, Okla., 1967.

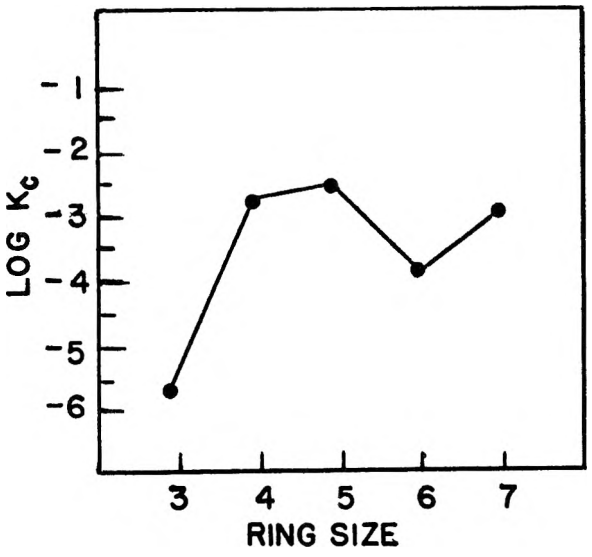

Figure 1.—Log K_c *vs.* ring size for epimerization of *cis*-1,2-cycloalkanedicarboxylates at 50°.

important. In seven-membered rings transannular effects become a factor to be considered.

The epimerization must involve a change from one tetrahedral configuration to another *via* trigonal bonding. Solvolyses of cycloalkyl tosylates[8] and halides[9] show similar trends of reactivity, and similar effects of ring size are observed.

The equilibrium percentages for the different esters are rather similar, except for the cyclopropane case, where the trans epimer is overwhelmingly preferred. This is not unexpected, for in the cis epimer the carbomethoxy groups are eclipsed and this strain is relieved in the trans epimer. The rate of epimerization is slow because the reaction involves change from an already distorted tetrahedral angle (60°) to a trigonal angle (120°) which introduces even more strain into the ring (*cf.* ref 13b).

The position of equilibrium for the cyclobutane system is similar to those of the cyclopentane and cyclohexane systems. This provides evidence for the nonplanarity of the cyclobutane ring. If this ring were planar the *cis*-carbomethoxy groups would be eclipsed as in the *cis*-cyclopropane ester and a substantially different position of equilibrium would be observed. The epimerization of planar cyclobutyl esters should be rather slow by the same assumptions. However, the cyclobutyl system is nonplanar,[24] and the rates more closely resemble those observed for the cyclopentane system.

The cyclopentane esters also exist in a nonplanar form, allowing a partial relief of interactions in the cis epimer. This is again reflected in the equilibrium constant for the epimerization reaction.

Formation of a trigonal carbon atom is facilitated by the relief of bond eclipsing. This relief of bond opposition strains is easily enough to offset the change from a tetrahedral to a trigonal configuration.

Similar considerations apply to the cycloheptyl system, which contains many bond oppositions, and this epimerization is also observed to be rapid. The cis diester in this system is stabilized relative to that of the corresponding cyclohexane system (see below) because of a degree of flexibility in the ring which allows the substituents to decrease 1,3-diaxial and gauche butane interactions. The trans ester is affected less by this flexibility, although some gauche butane interactions are undoubtedly relieved.

In cyclohexane systems a much greater amount of puckering exists than in cyclopentane and other factors, such as 1,3-axial interactions, become important. The position of equilibrium for 1,2-cyclohexanedicarboxylates indicates a destabilization of the cis epimer with respect to the trans. The situation is made more complex by the possibility of conformers of each of the epimeric esters. Dimethyl *cis*-1,2-cyclohexanedicarboxylate must contain one equatorial and one axial carbomethoxy group. The corresponding trans ester, by analogy with 1,2-dimethylcyclohexane, should largely exist in the diequatorial conformation.[20]

The rate is slower in cyclohexane systems because the ground state has no angle strains and no bond opposition strains. Any attempt to change the hybridization of a ring atom is resisted, as it increases eclipsings (and introduces some angular strain, although in this case angle strain is probably a minor factor).

Comparison of 1,2-disubstituted cyclohexanes with 1,2-disubstituted cyclohex-4-ene shows that an axial position for a substituent is relatively more stable in the olefin because of loss of a 1,3 interaction[25] Therefore the cis ester should be more stable in cyclohexene than in cyclohexane. This stabilization is observed, with a decrease in the trans/cis ratio from 11.7 to 2.8.

The rate of epimerization of dimethyl *cis*-1,2-cyclohex-4-enedicarboxylate is 1.8 times faster than that of the corresponding saturated compound. The approach to the hydrogen atom is easier, as there are less steric effects, *i.e.*, less crowding in the unsaturated systems.

The introduction of a methyl group into the 1 position of 1,2-cyclohexanedicarboxylates produces an appreciable effect on the relative stabilities of the two epimers. In dimethyl *trans*-1-methyl-1,2-cyclohexanedicarboxylate the diequatorial conformation (carbomethoxy groups) should again be preferred. The cis ester may exist in two conformations. The carbomethoxy groups are axial and equatorial and the methyl group may be either axial or equatorial. Examination of all possible 1,3 and gauche butane interactions indicates that the preferred conformation has the methyl group in an equatorial position. Similar conformational analysis reveals that the cis and trans isomers will differ only slightly. There is a difference of two 1,3 interactions and two gauche butane interactions with the methyl group in the trans isomer, whereas in the cis isomer these interactions are with a carbomethoxy group. As the interactions of a carbomethoxy group and a methyl group are similar,[16] the cis isomer should be stabilized relative to the trans in this system (when compared to cyclohexanedicarboxylate). Again the prediction is borne out by the experimental results, as K is the lowest for any of the saturated systems studied.

If a double bond is introduced into the system at the 4 position the trans-diequatorial conformer becomes

(24) See J. J. Bloomfield and R. Fuchs, *J. Chem. Soc., B*, 363 (1970), and references cited therein.

(25) *Cf.* H. Peters, R. A. Archer, and H. S. Moser, *J. Org. Chem.*, **32**, 1382 (1967).

TABLE III

FREE ENERGY AND ACTIVATION PARAMETERS FOR THE EPIMERIZATION OF DIMETHYL 1,2-CYCLOALKANEDICARBOXYLATES AT 50°

Ester	K (trans/cis)[a]	$\Delta G°$, kcal/mol[a]	$\Delta H^{\ddagger}$, kcal/mol	$\Delta G^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$ eu
Cyclopropane	99 (99)[b]	−2.62 (−3.1)[b]	20.2 (±0.3)	27.1 (±0.1)	−23 (±0.1)
Cyclobutane	8.58 (8.1)[b]	−1.27 (−1.5)[b]	81.7	22.7	−10
Cyclopentane	6.08 (8.8)[b]	−1.06 (−1.5)[b]	19.4	22.5	−10
Cyclohexane	11.7 (13.7)[b]	−1.45 (1.7)[b]	21.7	28.6	−23
Cycloheptane	3.99	−0.82	19.8	23.1	−11
1-Methylcyclohexane	1.84	−0.36	20.2	26.0	−20
Cyclohex-4-ene	2.82	−0.61	19.3	23.7	−15
1-Methylcyclohex-4-ene	1.60	−0.30	23.7	25.4	−6

[a] This work, measured at 50°. [b] Fonken and Shiengthong (ref 18, 19), measured at 67°.

stabilized with respect to that of the saturated 1-methyl ester by a factor of one methyl/ring gauche butane interaction and one 1,3-carbomethoxy–hydrogen interaction. Since the interactions of carbomethoxy groups are only slightly different from those of methyl groups, the effect should be small. In fact, a very slight decrease in the trans/cis ratio is observed to produce the lowest ratio found in this study.

The rates of the 1-methylcyclohexyl and 1-methylcyclohexenyl dicarboxylates are more difficult to explain. Even assuming that a statistical factor (only one acidic proton) will decrease the rate of epimerization by one-half, the 1-methyl ester is still slower by a factor of ten than the unsubstituted ester. This effect may be partially related to the added steric effects of the methyl group.

Variations in the equilibrium constants were observed for changes in temperature and concentration. The equilibrium is generally shifted toward the less stable cis isomer by an increase in temperature (Table II). Changes produced by concentration were also observed. This effect increased the cis isomer in some systems and reduced it in others.

The mechanism of the epimerization reaction has not been examined closely. The removal of an acidic proton may be the rate-controlling step and involves enolization. A similar mechanism has been proposed by Shechter for the base-catalyzed enolization of cycloalkanones and phenyl cycloalkyl ketones.[13] The transition states are fairly close to the enolate ion in character, and it is of interest to note that the energies of activation of this reaction are all nearly the same (±2 kcal). In the epimerization reaction of 1,2-cycloalkanedicarboxylates a similar situation is observed. The activation parameters are given in Table III. Large negative entropies of activation are observed in both Shechter's and the present study.

A negative entropy of activation is predicted for a reaction in which two substrates are brought together in the rate-controlling step. However, the rather large differences between some of the esters indicate a decided increase in ordering necessary in the transition state for certain esters.

The combination of a constant enthalpy of activation (or energy of activation) reflects a balance of the entropy and free energy factors, which may be expressed as

$$\text{constant} = \Delta H^{\ddagger} = \Delta(\Delta G^{\ddagger}) + T\Delta(\Delta S^{\ddagger})$$

Based on these assumptions, the rates will be chiefly determined by the entropy factor. A plot of $\Delta S^{\ddagger}$ *vs.*

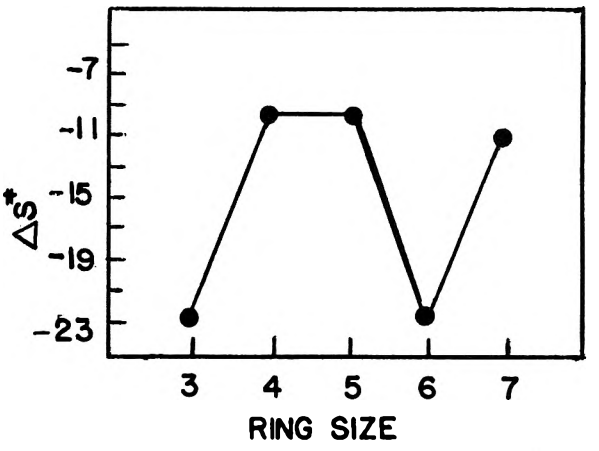

Figure 2.—$\Delta S^{\ddagger}$ *vs.* ring size for epimerization of 1,2-cycloalkanedicarboxylates at 50°.

ring size, (Figure 2) is quite similar to the plot of log k_c *vs.* ring size (*cf.* Figure 1).

A New Route to Cyclopentene-1-carboxaldehydes by Rearrangement of 2,3-Epoxycyclohexanols

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Cyclopentene-1-carboxaldehyde and the *gem*-dimethyl substituted homologs have been synthesized in high yield by LiBr–HMPA-catalyzed rearrangement of the appropriate *cis*-2,3-epoxycyclohexanols. Extensive physical data, including ^{13}C parameters, are reported.

During structure elucidation work on sesquiterpenoids we needed *gem*-dimethyl substituted cyclopentene-1-carboxaldehydes for synthesis of expected degradation products. Cyclopentene-1-carboxaldehydes have been synthesized by various methods,[1-5] almost all of which have used adipic aldehyde derivatives as precursors or intermediates in aldol-like cyclization reactions. Since substituted adipic aldehydes are not easily accessible and because unsymmetrical aldehydes could lead to mixtures that would not be easily separated, we decided to investigate the possibility of making an acid-catalyzed ring contraction of epoxyalcohols.

When boron trifluoride, acetic acid, or sulfuric acid were used as catalysts for ring contraction only traces of the desired aldehyde were obtained. Rickborn and Gerkin[6] later published a synthesis of cyclopentanecarboxaldehydes by ring contraction of epoxycyclohexanes in anhydrous benzene with a lithium bromide–hexamethylphosphoric triamide (HMPA) complex as catalyst. In spite of formation of water in our reaction, we decided to test the equimolar LiBr–HMPA catalyst used by Rickborn and Gerkin. An exploratory study of the reaction variables showed that reaction temperature and the total amount of LiBr–HMPA had a significant effect on the yield (Table I).

TABLE I

YIELDS (VPC) IN THE REARRANGEMENT OF *cis*-5,5-DIMETHYL-2,3-EPOXYCYCLOHEXANOL (**5**) TO 4,4-DIMETHYLCYCLOPENTENE-1-CARBOXALDEHYDE (**13**) IN REFLUXING SOLVENT AS A FUNCTION OF SOLVENT BOILING POINT AND MOLAR RATIO OF CATALYST (LiBr:HMPA 1:1) TO EPOXYALCOHOL

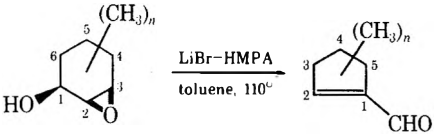
Solvent (temp, °C)	LiBr–HMPA: Epoxyalcohol	Yield, %
Benzene (80)	2.2	60
Toluene (110)	0.2	21
Toluene (110)	0.5	67
Toluene (110)	1.0	70
Toluene (110)	1.5	72
Toluene (110)	2.2	85
Xylene (139)	2.2	85

The following general procedure was found satisfactory. A toluene solution of the cis epoxyalcohol was added dropwise to a refluxing toluene solution of LiBr–HMPA under nitrogen. The reaction mixture was cooled and poured into a double volume of ether to precipitate the LiBr–HMPA complex. This gave a solution of almost pure aldehyde.

To obtain some idea of the mechanism and the limitations of the reaction, the epoxy alcohols shown in Table II were synthesized and submitted to the reaction conditions cited above.

TABLE II

PRODUCTS AND YIELDS IN THE REACTION



Epoxyalcohol Compd	Epoxyalcohol n^a	Product aldehyde(s) Compd	Product aldehyde(s) n^a	Product ratio, %	Total yield, % Vpc	Total yield, % Distn
1	0	10	0	100	98	43
2	1 [3]	*b*			0	
3	3 [3,5,5]	*b*			0	
4	2 [4,4]	11	2 [5,5]	80	92	70
		12	2 [3,3]	20		
5	2 [5,5]	13	2 [4,4]	100	85	76
6[d]	2 [6,6]	11	2 [5,5]	20	83	68
		12	2 [3,3]	80		
7	3 [1,5,5]	*b*			0	
8	1 [1]	*b*			0	
9	2,3-Epoxyhexan-4-ol	*c*			0	

[a] *n* is the number of methyl groups and position (in brackets). [b] No aldehyde formed. [c] No reaction. [d] Contains 15% of the trans isomer.

The product mixtures obtained from **4** and **6** were characterized by vpc and ^1H nmr spectroscopy. The ^1H nmr spectra of the mixtures showed a pair of unequal triplets in the vinyl region with J = 1.6 and 2.6 Hz (Figure 1). Presumably the smallest of the coupling constants is due to long-range trans coupling to the allylic methylene protons in **12**.[7] The larger coupling constant then results from vicinal coupling to the allylic methylene protons in **11**. Although the value seems to be rather small for vicinal coupling, it is well documented that olefinic protons in cyclopentene systems couple to allylic protons with coupling constants of 2–3 Hz.[7-9] To determine the product distribution unequivocally, bromine was added directly to the aldehyde mixtures in the nmr tubes. The vinyl signals at approximately 6.7 ppm disappeared completely and new signals appeared at approximately 4.5 ppm.

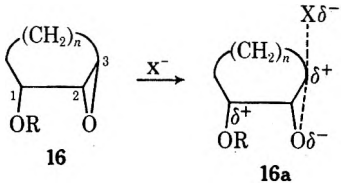
(1) J. English, Jr., and G. W. Barber, *J. Amer. Chem. Soc.*, **71**, 3310 (1949).
(2) J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 3634 (1950).
(3) F. Korte, K. H. Büchel, and A. Zschocke, *Ber.*, **94**, 1952 (1961).
(4) J. Chuche and J. Wiemann, *Bull. Soc. Chim. Fr.*, 1491 (1968).
(5) H. Favre and J. P. Lapointe, *Can. J. Chem.*, **49**, 3851 (1971).
(6) B. Rickborn and R. M. Gerkin, *J. Amer. Chem. Soc.*, **93**, 1693 (1971).
(7) G. V. Smith and H. Kriloff, *ibid.*, **85**, 2016 (1963).
(8) T. Okuda and T. Yoshida, *Tetrahedron Lett.*, 439 (1964).
(9) N. S. Bhacca and D. H. Williams in "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 87.

Obviously the singlet just upfield from 4.5 ppm belongs to **15** and the pair of doublets to **14**, thus establishing the product distribution shown in Table II (see Figure 1). These conclusions are also supported by ^{13}C nmr measurements (vinyl carbon shifts of **11** and **12**. See Table III).

For the rearrangement of alkyl-substituted cyclohexane epoxides, Rickborn and Gerkin[6] proposed a mechanism starting with a reversible epoxide ring opening by nucleophilic attack of a bromide ion. A lithium ion, solubilized by HMPA, was thought to polarize the C–O bond, thus facilitating the ring opening leading to intermediate halohydrin salts.

Several workers[10] have studied extensively epoxide ring opening in cyclic compounds such as **16** with an electron-attracting substituent in an α position to the epoxide ring. A close analogy of these systems with the present starting materials is quite obvious. Different nucleophiles (*e.g.*, OH^-, MeO^-, Br^-, Cl^-) were used under acidic and basic conditions.

In these kinetically controlled reactions, polar effects have been found to dominate steric effects[10] and appear to favor transition states like **16a**, which explain the nearly exclusive nucleophilic attack at position 3 in **16**.

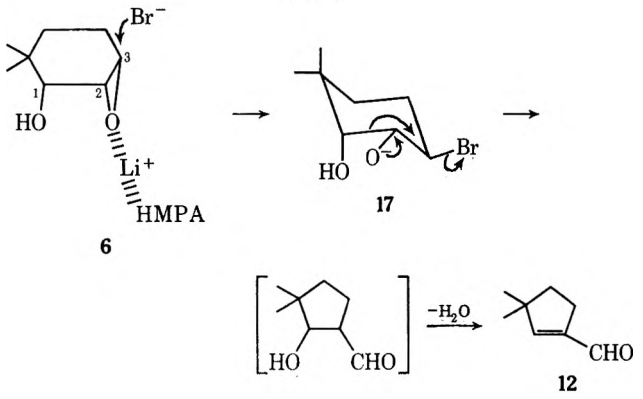


16 **16a**

R = H, CH_3
n = 1, 2

By analogy with these well-known interpretations, a mechanism for the reaction, exemplified with **6**, is suggested in Scheme I which involves epoxide ring

SCHEME I



opening to give the intermediate **17**. In the most stable conformation of **17** the bonds between the carbons carrying oxygen and between carbon and bromine lie in a trans-coplanar arrangement suitable for ring contraction with expulsion of bromide ion.

Because significant amounts of isomeric aldehydes are formed in the rearrangements of **4** and **6** (Figure 1), other mechanisms must therefore also be involved. Expulsion of OH^- in **17** would lead to the observed by-product **11**, but OH^- is a poor leaving group, and steric

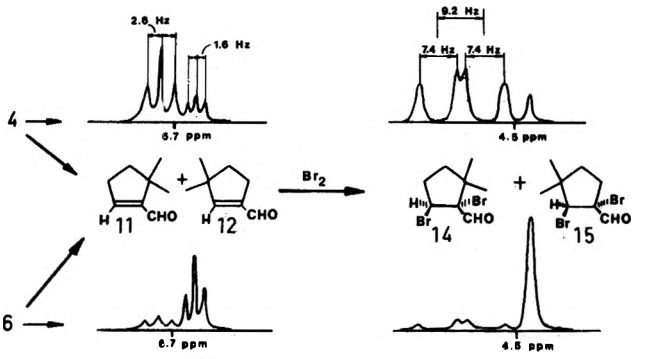
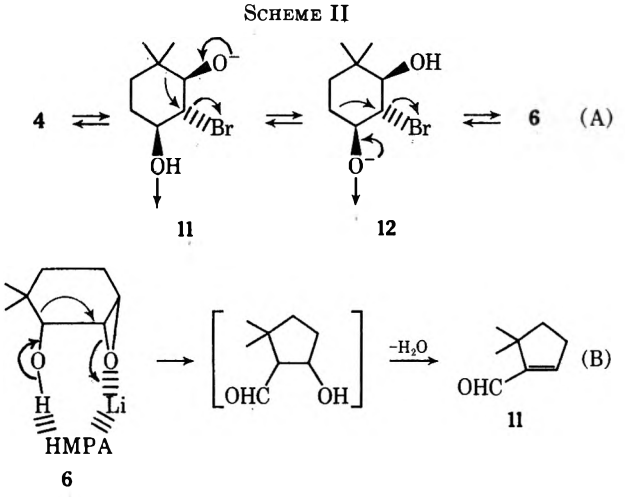


Figure 1.—Product distribution on rearrangement of epoxyalcohols **4** and **6** determined from ^1H nmr spectra.

conditions for OH^- loss are also unfavorable. A direct base-catalyzed isomerization of **6** to **4** should also lead to **11** but would require a trans arrangement of the epoxyalcohol. There remain two reasonable alternatives for the formation of the minor isomeric aldehydes: A, bromide ion attack at position 2 in **6** followed by a proton shift in the intermediate halohydrin salts[10,11] and ring contraction; or B, a concerted mechanism as depicted in Scheme II. Further mechanistic studies on these reactions are in progress.

SCHEME II



As can be seen in Table II, cyclic epoxyalcohols with a methyl group on carbon 1 or 3 gave no aldehyde, although the starting material was consumed during the reaction. In the case of the open-chain epoxyalcohol **9**, almost all of the starting material was recovered after the reaction and no aldehyde was formed.

The epoxyalcohols were easily prepared from the corresponding allylic alcohols with *m*-chloroperbenzoic acid. Epoxidations with perbenzoic acid are known to show good selectivity for cis addition (cis:trans *ca.* 9:1),[12] but *m*-chloroperbenzoic acid proved to be even more selective, giving less than 5% trans addition except with 6,6-dimethylcyclohex-2-enol (**31**), where 15% of the trans isomer of **6** was found (quantitative vpc and ^{13}C nmr). The cyclic allylic alcohols were readily obtained from the corresponding α,β-unsaturated ketones by aluminum hydride reduction[13] or by hy-

(10) J. G. Buchanan and H. Z. Sable in "Selective Organic Transformations," Vol. 2, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N Y., 1972, and references cited therein.

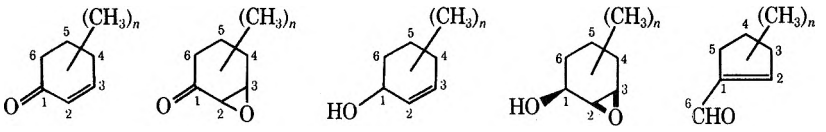
(11) G. B. Payne, *J. Org. Chem.*, **27**, 3819 (1962).

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

(13) M. J. Jorgenson, *Tetrahedron Lett.*, 559 (1962).

TABLE III

^{13}C NMR CHEMICAL SHIFTS[a] AND ^{13}C–^{1}H COUPLING CONSTANTS[b]



Compd (position of methyl groups)	C-1	C-2	C-3	C-4	C-5	C-6	CH_3
			α,β-Unsaturated Ketones				
18	199.1	129.2	150.4	25.6	22.3	37.6	
19 (3)	199.4	126.1	162.7	30.7	22.3	36.7	24.3
20 (3,5,5)	198.7	124.9	159.4	44.8	33.1	50.4	23.9, 27.9
		(160)		(130)		(130)	(130) (130)
21 (4,4)	198.8	126.3	159.2	32.6	35.8*[c]	34.2*	27.5
22 (5,5)	198.6	128.2	147.6	39.2	33.0	51.1	27.6
			Epoxyketones				
23 (3)	205.8	61.6	61.2	27.4	16.2	34.7	21.2
24 (3,5,5)	207.1	61.1	64.0	42.4	35.7	47.6	30.4, 27.4, 23.5
		(180)		(135)		(132)	(130) (130) (130)
25 (4,4)	205.1	56.3*	64.4*	31.0	30.0**	33.4**	27.6, 23.0
			Allylic Alcohols				
26	65.0	129.9	129.9	24.5	18.6	31.5	
	(145)	(159)	(159)	(130)	(130)	(130)	
27 (3)	65.5	124.1	137.1	29.9*	18.8	31.3*	23.2
28 (3,5,5)	66.4	123.6	135.3	43.8*	31.0	44.8*	30.7, 25.3, 23.1
29 (4,4)	65.6	127.5	140.1	31.5	33.2	28.7	28.7
	(145)	(155)	(155)		(130)	(130)	(130)
30 (5,5)	65.8	129.3	127.6	38.8	30.5	44.8	31.1, 25.5
	(140)	(155)	(155)	(130)		(130)	(130) (130)
31 (6,6)	73.6	128.4*	128.9*	22.4	32.4	33.4	26.1, 21.3
32 (1)	67.7	133.5	128.3	25.0	19.4	37.8	29.3
33 (1,5,5)	68.6	132.3	126.5	38.7	29.3	50.2	30.9, 30.5, 27.7
34 (hex-2-en-4-ol)	17.2	133.9*	125.9*	73.9	28.7	9.3	
	(128)	(150)	(150)	(140)	(130)	(130)	
			Epoxyalcohols				
1	67.0	55.1*	55.3*	22.6	18.3	28.1	
	(140)	(175)	(175)	(130)	(130)	(130)	
2 (3)	66.5	62.2	61.0	27.9	17.6	27.9	23.2
3 (3,5,5)	66.2	62.0	60.6	42.1	30.9	39.7	30.9, 26.2, 24.4
4 (4,4)	66.4	56.3	63.2	25.7	32.4	28.6	26.3, 25.2
	(142)	(178)	(175)		(130)	(130)	(120) (120)
5 (5,5)	66.2	54.9*	54.1*	36.3	30.9	40.1	30.9, 26.4
6 (6,6)	70.7	55.3*	53.7*	20.6	25.9	32.4	24.7, 23.9
	(145)	(175)	(178)	(130)	(130)		(130) (130)
trans							
6 (6,6)	73.9	56.3*	52.9*	27.6	29.3	32.3	25.9, 18.0
7 (1)	67.5	59.0	55.5	22.9	16.2	35.3	25.3
8 (1,5,5)	68.4	58.3	56.3	36.7	30.4	48.9	30.6, 27.5
9 (2,3-epoxyhexan-4-ol)	16.6	52.3*	62.3*	72.4	26.7	9.0	
			Aldehydes				
10	147.7	152.3	27.7*	22.1	33.1*	189.0	
		(160)	(135)	(135)	(135)	(170)	
12 (3,3)	144.2	161.4	45.8	38.2	38.2	190.0	26.9
		(160)		(130)	(130)	(172)	(130)
13 (4,4)	146.1	151.2	42.8*	38.5	48.2*	189.9	29.0
11 (5,5)	153.4	152.7	30.3	40.8	43.6	189.2	25.9
		(165)	(130)	(130)		(170)	(130)

[a] Parts per million downfield from TMS. [b] Coupling constants (hertz) in parentheses. [c] Chemical shifts with * are probable but tentative.

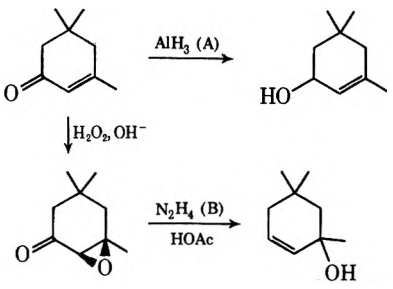
drazine reduction of the corresponding epoxyketone,[14] exemplified with isophorone in Scheme III. The epoxyketones and the α,β-unsaturated ketones were prepared by standard procedures.

^{13}C nmr data are collected in Table III. The off-resonance decoupling technique and substituent effect parameters[15] were used in making assignments of ^{13}C chemical shifts.

(14) P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961).

(15) P. S. Pregosin and E. W. Randall in "Determination of Organic Structures by Physical Methods," Vol. 4, F. C. Nachod and J. J. Zuckerman, Ed., Academic Press, New York, N. Y., 1971.

SCHEME III



Experimental Section

Qualitative vpc measurements were run on a 1.5 m × 0.125 in. steel column packed with silicone XE-60 (2% on Chromosorb G, 100–120 mesh) at 180°. Quantitative vpc measurements were run on a 50 m × 0.5 mm capillary steel column (silicone GE SF 96) at 85°. Melting points are uncorrected. The ^{1}H nmr spectra were recorded on a Varian T-60 instrument and the ^{13}C nmr spectra on a Varian XL-100-15 instrument equipped with a Fourier transform unit. The ir spectra were run as liquid films.

Commerical cyclohex-2-enone (**18**) and 3,5,5-trimethylcyclohex-2-enone (**20**) (isophorone) were used. 3-Methylcyclohex-2-enone (**19**) was prepared according to Natelson and Gottfried,[16] 4,4-dimethylcyclohex-2-enone (**21**) according to Conia and Le Craz,[17] and 5,5-dimethylcyclohex-2-enone (**22**) according to Frank and Hall.[18]

3,5,5-Trimethyl-2,3-epoxycyclohexanone (**24**) was obtained by epoxidation of isophorone.[19]

4,4-Dimethyl-2,3-epoxycyclohexanone (**25**) was prepared by epoxidation of **21** as for the epoxidation of isophorone:[19] yield 47%; bp 82–83° (11 mm); n^{24}D 1.4614; ir 1718 cm^{-1}; nmr ($CDCl_3$) δ 3.18 (s, 2), 1.22 (s, 3), 1.10 (s, 3).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.5; H, 8.6. Found: C, 68.5; H, 8.7.

3-Methyl-2,3-epoxycyclohexanone (**23**) was prepared from **19** applying the same oxidation technique:[19] yield 30%; bp 85° (15 mm); n^{22}D 1.4643; ir 1715 cm^{-1}; nmr ($CDCl_3$) δ 3.02 (s, 1), 1.43 (s, 3).

Anal. Calcd for $C_7H_{10}O_2$: C, 66.7; H, 8.0. Found: C, 66.7; H, 8.0.

For ^{13}C nmr data of the ketones see Table III.

The cyclohexenols were prepared by two different procedures: by AlH_3 reduction of the appropriate α,β-unsaturated ketones (A)[13] or by N_2H_4 reduction of the α,β-epoxyketones (B)[14] as exemplified with isophorone in Scheme III.

A. Aluminum Hydride Reduction of Cyclohex-2-enones.[13]—$AlCl_3$ (16.6 g) was added to an ice-cold suspension of $LiAlH_4$ (14.4 g) in dry ether (2 l.). The resulting mixture was stirred mechanically until it had reached room temperature. Separation under nitrogen pressure through a Fiberglas plug yielded a *ca.* 0.25 *M* ethereal solution of AlH_3. Part of this solution (500 ml) was transferred under nitrogen into a 1-l., three-necked flask. The ketone (0.25 mol) dissolved in ether (50 ml) was added dropwise to the stirred AlH_3 solution over 15 min (ice cooling). The stirring was continued for another 30 min and the resulting aluminum complex was hydrolyzed with $Na_2SO_4 \cdot 10H_2O$ and finally with water. Filtration, after the addition of 2 *M* NaOH (2 ml), gave a colorless filtrate which was washed with water (2 × 50 ml) and dried over Na_2SO_4. Evaporation of the solvent and distillation through a 20-cm Vigreux column gave the allylic alcohol.

B. Hydrazine Reduction of 2,3-Epoxycyclohexanones.[14]—The epoxyketone (0.1 mol) was added to a stirred, ice-cooled solution of hydrazine hydrate (12.5 ml, *ca.* 2.5 equiv) and acetic acid (1.2 ml) in methanol (100 ml). Cooling and stirring were maintained for 30 min and the reaction mixture was then allowed to warm to room temperature. The bulk of the methanol was evaporated under reduced pressure through a 30-cm Vigreux column. Water (200 ml) was added to the residue and the water phase was extracted with ether (2 × 200 ml). The ether solution was then washed with water (100 ml), dried (Na_2SO_4), and evaporated. Distillation of the residue gave the allylic alcohol.

Cyclohex-2-enol (**26**) (by method A, yield 75%) had bp 61–62° (11 mm); n^{23}D 1.4859; ir 1655, 1055, 965 cm^{-1}; nmr ($CDCl_3$) δ 5.80 (s, 2), 4.20 (m, 1).

Anal. Calcd for $C_6H_{10}O_2$: C, 73.4; H, 10.3. Found: C, 73.5; H, 10.3.

The *p*-nitrobenzoate had mp 77–78° from hexane.

3-Methylcyclohex-2-enol (**27**) (by method A, yield 80%) had bp 74–75° (11 mm); n^{23}D 1.4832; ir 1675, 1038, 960 cm^{-1}; nmr ($CDCl_3$) δ 5.50 (m, 1), 4.15 (s broad, 1), 1.65 (s, 3).

Anal. Calcd for $C_7H_{12}O$: C, 75.0; H, 10.8. Found: C, 75.0; H, 10.7. The *p*-nitrobenzoate had mp 69–70° from hexane.

1-Methylcyclohex-2-enol (**32**) (by method B, yield 56%) had bp 60–61° (15 mm); n^{22}D 1.4757; ir 1655, 1130 cm^{-1}; nmr ($CDCl_3$) δ 5.68 (s, 2), 1.26 (s, 3).

Anal. Calcd for $C_{14}H_{15}NO_4$ (*p*-nitrobenzoate): C, 64.4; H, 5.8; N, 5.4. Found: C, 64.3; H, 5.5; N, 5.3.

The *p*-nitrobenzoate had mp 101–102° from hexane.

4,4-Dimethylcyclohex-2-enol (**29**) (by method A, yield 67%) had bp 74–77° (11 mm); n^{23}D 1.4694; ir 1655, 1050 cm^{-1}; nmr ($CDCl_3$) δ 5.55 (s, 2), 4.00–4.30 (m, 1), 1.00 (s, 3), 0.95 (s, 3).

Anal. Calcd for $C_{15}H_{17}NO_4$ (*p*-nitrobenzoate): C, 65.4; H, 6.2; N, 5.1. Found: C, 65.1; H, 6.2; N, 5.0.

The *p*-nitrobenzoate had mp 40–41° from hexane.

5,5-Dimethylcyclohex-2-enol (**30**) (by method A, yield 74%) had bp 76–77° (11 mm); n^{26}D 1.4677; ir 1655, 1040, 940 cm^{-1}; nmr ($CDCl_3$) δ 5.63 (s, 2), 4.00–4.50 (m, 1), 0.98 (s, 3), 0.88 (s, 3).

Anal. Calcd for $C_8H_{14}O$: C, 76.1; H, 11.2. Found: C, 76.2; H, 11.2.

The *p*-nitrobenzoate had mp 41–42° from hexane.

6,6-Dimethylcyclohex-2-enol (**31**) (by method B, yield 55%) had bp 67–68° (11 mm); n^{22}D 1.4758; ir 1655, 1060 cm^{-1}; nmr ($CDCl_3$) δ 5.72 (s, 2), 3.65–3.80 (m, 1), 0.98 (s, 3), 0.92 (s, 3).

Anal. Calcd for $C_{15}H_{17}NO_4$ (*p*-nitrobenzoate): C, 65.4; H, 6.2; N, 5.1. Found: C, 65.3; H, 6.1; N, 5.1.

The *p*-nitrobenzoate had mp 107–108° from hexane.

1,5,5-Trimethylcyclohex-2-enol (**33**) (by method B, yield 43%, *cf.* ref 14, 66%) had bp 69–72° (13 mm); n^{22}D 1.4666; ir 1655, 1063, 905 cm^{-1}; nmr ($CDCl_3$) δ 5.67 (s, 1), 1.27 (s, 3), 1.05 (s, 3), 0.97 (s, 3).

Anal. Calcd for $C_{16}H_{19}NO_4$ (*p*-nitrobenzoate): C, 66.4; H, 6.6; N, 4.8. Found: C, 66.3; H, 6.6; N, 4.8.

The *p*-nitrobenzoate had mp 84–85° from hexane.

3,5,5-Trimethylcyclohex-2-enol (**28**) (by method A, yield 66%) had bp 87–88° (11 mm); n^{23}D 1.4723; ir 1665, 1023 cm^{-1}; nmr ($CDCl_3$) δ 5.45 (s, 1), 4.00–4.50 (m, 1), 1.66 (s, 3), 1.02 (s, 3), 0.89 (s, 3).

Anal. Calcd for $C_9H_{16}O$: C, 77.1; H, 11.5. Found: C, 77.1; H, 11.4.

The *p*-nitrobenzoate had mp 71–73° from hexane.

Hex-2-en-4-ol (**34**) was prepared by standard Grignard reaction of crotonaldehyde with ethylmagnesium bromide, yield 67%. The *trans*-hexenol was contaminated with minor amounts of the cis isomer (^{13}C nmr). For ^{13}C nmr data of the allylic alcohols, see Table III.

Oxidation of the Allylic Alcohols with *m*-Chloroperbenzoic Acid.—A solution of the allylic alcohol (0.1 mol) and *m*-chloroperbenzoic acid[20] (0.1 mol) in dry methylene chloride (150 ml) was stirred under anhydrous conditions for 2 hr at 0°. The precipitated *m*-chlorobenzoic acid was filtered off and the filtrate was dried (Na_2SO_4, 5 g) for 1 hr. After anhydrous $Ca(OH)_2$ (10 g) was added to precipitate the remaining acids, the mixture was filtered, the solvent was evaporated, and the residue was distilled to obtain the cis epoxyalcohol containing less than 5% of the trans isomer (quantitative vpc) except for compound **6** where the trans isomer amounts to 15% (quantitative vpc and ^{13}C nmr).

cis-**2,3-Epoxycyclohexanol** (**1**) (yield 84%) had bp 46° (0.3 mm); n^{23}D 1.4857; ir 3000, 1070, 855 cm^{-1}; nmr ($CDCl_3$) δ 3.80–4.25 (m, 1), 3.37 (s, 2).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.1; H, 8.8. Found: C, 63.2; H, 8.8.

The α-naphthylurethane had mp 173.5–174.0° (lit.[21] mp 173.5–175.0°).

1-Methyl-*cis*-2,3-epoxycyclohexanol (**7**) (yield 80%) had bp

(16) S. Natelson and S. P. Gottfried, *J. Amer. Chem. Soc.*, **61**, 1001 (1939).

(17) J. M. Conia and A. Le Craz, *Bull. Soc. Chim. Fr.*, 1937 (1960).

(18) R. L. Frank and H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **72**, 1645 (1950).

(19) R. L. Wasson and H. O. House, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 552.

(20) Large amounts of the peracid were conveniently prepared by standard synthetic reactions from inexpensive commercially available *m*-aminobenzoic acid. (AB Bofors Nobelkrut, Bofors, Sweden.)

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

80–83° (11 mm); $n^{23}D$ 1.4734; ir 940, 827 cm^{-1}; nmr ($CDCl_3$) δ 3.40 (s broad, 1), 3.08 (d, 1, J = 4.0 Hz), 1.35 (s, 3).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.6; H, 9.4. Found: C, 65.6; H, 9.3.

3-Methyl-*cis*-2,3-epoxycyclohexanol (2) (yield 79%) had bp 39° (0.3 mm); $n^{22}D$ 1.4727; ir 1045, 848 cm^{-1}; nmr ($CDCl_3$) δ 4.00 (m, 1), 3.20 (d, 1, J = 3.0 Hz), 1.40 (s, 3).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.6; H, 9.4. Found: C, 65.8; H, 9.4.

4,4-Dimethyl-*cis*-2,3-epoxycyclohexanol (4) (yield 89%) had bp 51° (0.4 mm); $n^{22}D$ 1.4691; ir 1068, 862 cm^{-1}; nmr ($CDCl_3$) δ 3.85–4.20 (m, 1), 3.40 (t, 1, J = 4.0 Hz), 2.92 (d, 1, J = 4.0 Hz), 1.09 (s, 3), 1.02 (s, 3).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.6; H, 9.9. Found: C, 67.4; H, 9.9.

5,5-Dimethyl-*cis*-2,3-epoxycyclohexanol (5) (yield 89%) had bp 53° (0.4 mm); $n^{23}D$ 1.4706; ir 1053, 832 cm^{-1}; nmr ($CDCl_3$) δ 3.90–4.35 (m, 1), 3.36 (s, 2), 0.92 (s, 6).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.6; H, 9.9. Found: C, 67.5; H, 9.8.

6,6-Dimethyl-*cis*-2,3-epoxycyclohexanol (6) (yield 86%) had bp 35° (0.3 mm); $n^{23}D$ 1.4760; ir 1068, 815 cm^{-1}; nmr ($CDCl_3$) δ 3.30–3.60 (m, 3), 1.00 (s, 3), 0.88 (s, 3). The product contained 15% of the trans isomer (^{13}C nmr, quantitative vpc).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.6; H, 9.9. Found: C, 67.3; H, 9.9.

1,5,5-Trimethyl-*cis*-2,3-epoxycyclohexanol (8) (yield 78%) had bp 96–97° (12 mm); $n^{23}D$ 1.4661; ir 1020, 840 cm^{-1}; nmr ($CDCl_3$) δ 3.39 (m, 1), 3.02 (d, 1, J = 4.0 Hz), 1.38 (s, 3), 0.99 (s, 3), 0.96 (s, 3).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.2; H, 10.3. Found: C, 69.2; H, 10.3.

3,5,5-Trimethyl-*cis*-2,3-epoxycyclohexanol (3) (yield 72%) had bp 46° (0.3 mm); $n^{23}D$ 1.4635; ir 1030, 823 cm^{-1}; nmr ($CDCl_3$) δ 4.10 (m, 1), 3.18 (d, 1, J = 2.0 Hz), 1.40 (s, 3), 0.94 (s, 3), 0.92 (s, 3).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.2; H, 10.3. Found: C, 69.6; H, 10.2.

2,3-Epoxyhexan-4-ol (9) (yield 74%) had bp 63–66° (10 mm); $n^{24}D$ 1.4281; ir 870 cm^{-1}; nmr ($CDCl_3$) δ 1.33 (d, 3, J = 5.0 Hz), 0.98 (t, 3, J = 6.0 Hz). The product was contaminated with the epoxyalcohol originating from the cis allylic alcohol (^{13}C nmr).

Anal. Calcd for $C_6H_{12}O_2$: C, 62.0; H, 10.4. Found: C, 61.8; H, 10.4. For ^{13}C nmr data of the epoxyalcohols see Table III.

Ring Contraction of 2,3-Epoxycyclohexanols to Cyclopentene-1-carboxaldehydes.—The epoxyalcohol (0.045 mol) dissolved in dry toluene (50 ml) was added under nitrogen to a refluxing solution of LiBr (0.1 mol) and HMPA (0.1 mol) in dry toluene (50 ml) over 30 min. About 2 min after the addition was finished the reaction mixture was cooled in an ice bath and poured into ether (200 ml). The LiBr–HMPA complex that separated as a heavy oil was discarded. The ethereal solution was washed with water (3 × 15 ml) and dried (Na_2SO_4). Yields were estimated by vpc with decalin as internal standard. Solvent was removed through an efficient column at atmospheric pressure and the residue was fractionally distilled to give the pure aldehyde. The toluene solution of the aldehyde can be used directly for further reaction, thus avoiding distillation losses. Distilled yields are given in parentheses.

Cyclopentene-1-carboxaldehyde (10) [yield 98% (43%)] had bp 42–44° (10 mm); $n^{23}D$ 1.4874 [lit.[2] bp 52° (20 mm); $n^{17}D$ 1.4892]; uv max (99.5% EtOH) 236 nm (ε 10,800); ir 3045, 2720, 1685, 1620 cm^{-1}; nmr ($CDCl_3$) δ 9.85 (s, 1), 6.95 (m, 1).

Anal. Calcd for C_6H_8O: C, 75.0; H, 8.4. Found: C, 74.9; H, 8.4.

The dinitrophenylhydrazone had mp 216–217° from ethanol (lit.[22] mp 211–215°).

3,3-Dimethylcyclopentene-1-carboxaldehyde (12) [yield 83% (68%); product mixture, see Table II] had bp 58° (12 mm); $n^{23}D$ 1.4697; uv max (99.5% EtOH) 236 nm (ε 11,300); ir 3040, 2720, 1685, 1622, 1368, 1353 cm^{-1}; nmr ($CDCl_3$) δ 9.83 (s, 1), 6.62 (t, 1, J = 1.6 Hz), 1.18 (s, 6).

Anal. Calcd for $C_{14}H_{16}N_4O_4$ (dinitrophenylhydrazone): C, 55.3; H, 5.3; N, 18.4. Found: C, 55.3; H, 5.3; N, 18.3.

The dinitrophenylhydrazone had mp 213.5–214.5° from ethanol.

4,4-Dimethylcyclopentene-1-carboxaldehyde (13) [yield 85% (76%)] had bp 52° (10 mm); $n^{23}D$ 1.4663; uv max (99.5% EtOH) 237.5 nm (ε 12,600); ir 3050, 2720, 1685, 1620, 1370, 1360 cm^{-1}; nmr ($CDCl_3$) δ 9.76 (s, 1), 6.72 (s broad, 1), 2.25–2.52 (m, 4), 1.12 (s, 6).

Anal. Calcd for $C_8H_{12}O$: C, 77.4; H, 9.7. Found: C, 77.1; H, 9.8.

The dinitrophenylhydrazone had mp 227–228° from ethanol.

5,5-Dimethylcyclopentene-1-carboxaldehyde (11) [yield 92% (70%); product mixture, see Table II] had bp 53° (11 mm); $n^{23}D$ 1.4697; uv max (99.5% EtOH) 235 nm (ε 9700); ir 3050, 2720, 1685, 1618, 1365, 1350 cm^{-1}; nmr ($CDCl_3$) δ 9.82 (s, 1), 6.78 (t, 1, J = 2.6 Hz), 2.30–2.70 (m, 2), 1.65–2.00 (m, 2), 1.26 (s, 6).

Anal. Calcd for $C_8H_{12}O$: C, 77.4; H, 9.7. Found: C, 77.5; H, 9.7.

The dinitrophenylhydrazone had mp 167–170° from ethanol. For ^{13}C nmr data of the aldehydes see Table III.

Registry No.—**1,** 26828-72-8; **2,** 38309-43-2; **3,** 38309-44-3; **4,** 38309-45-4; **5,** 38309-46-5; *cis*-**6,** 38309-47-6; *trans*-**6,** 38309-48-7; **7,** 38309-49-8; **8,** 38309-50-1; **9,** 1193-06-2; **10,** 6140-65-4; **11,** 38312-90-2; **11** DNP, 38312-91-3; **12,** 38312-92-4; **12** DNP, 38312-93-5; **13,** 38312-94-6; **13** DNP, 38312-95-7; **18,** 930-68-7; **19,** 1193-18-6; **20,** 78-59-1; **21,** 1073-13-8; **22,** 4694-17-1; **23,** 21889-89-4; **24,** 10276-21-8; **25,** 1074-26-6; **26,** 822-67-3; **26** *p*-nitrobenzoate, 38313-01-8; **27,** 21378-21-2; **27** *p*-nitrobenzoate, 38313-03-0; **28,** 470-99-5; **28** *p*-nitrobenzoate, 38313-05-2; **29,** 5020-09-7; **29** *p*-nitrobenzoate, 38313-07-4; **30,** 25866-56-2; **30** *p*-nitrobenzoate, 38313-09-6; **31,** 38313-10-9; **31** *p*-nitrobenzoate, 38313-11-0; **32,** 23758-27-2; **32** *p*-nitrobenzoate, 38313-13-2; **33,** 3779-25-2; **33** *p*-nitrobenzoate, 38313-15-4.

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Synthesis and Characterization of *cis*- and *trans*-1,4-Dimethylenecyclohexane Diepoxide

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Convenient procedures for the synthesis of *cis*- and *trans*-1,4-dimethylenecyclohexane diepoxide are described. Reaction of 1,4-dimethylenecyclohexane (1) with *m*-chloroperbenzoic acid in benzene or tetrahydrofuran yields *trans*-1,4-dimethylenecyclohexane diepoxide (2), mp 106–108°, in 97–100% purity and in high yield. Reaction of 1 with aqueous *N*-bromoacetamide or *N*-bromosuccinimide yields *cis*-1,4-dihydroxy-1,4-bis(bromomethyl)cyclohexane (3), mp 163–164°, in 30% yield as a water-insoluble solid. The trans dibromohydrin 4, mp 139–141°, can be recovered from the aqueous portion of the reaction mixture. Reaction of 3 with aqueous KOH yields *cis*-1,4-dimethylenecyclohexane diepoxide (5), mp 79–81°, in nearly quantitative yield. The structures of 2 and 5 were established by dipole moment and nmr measurements. Reduction of 2 or 5 with $NaAlH_2(OCH_2CH_2OCH_3)_2$ in THF yields the corresponding cis and trans isomers of 1,4-dihydroxy-1,4-dimethylcyclohexane.

During the course of studies on the polymerization of difunctional cyclohexane derivatives, we had occasion to develop convenient syntheses of *cis*- and *trans*-1,4-dimethylenecyclohexane diepoxide.[1] We report these procedures in this paper because the diepoxides are useful intermediaes for the synthesis of a variety of cis and trans 1,1,4,4-tetrasubstituted cyclohexane derivatives.

The reaction of 1,4-dimethylenecyclohexane[4,5] (1) with *m*-chloroperbenzoic acid[6] was found to be stereospecific when conducted in benzene or tetrahydrofuran, yielding *trans*-1,4-dimethylenecyclohexane diepoxide (2), mp 106–107°, in 97–100% purity. When conducted in $CHCl_3$ at 0°, the reaction yields product that is at least 90% trans. A single recrystallization from hexane affords the pure trans isomer. Mixtures of cis and trans isomers are obtained when other solvents or peracids are used. The results of an extensive study on the influence of reaction conditions in the course of the reaction are summarized in Table I.

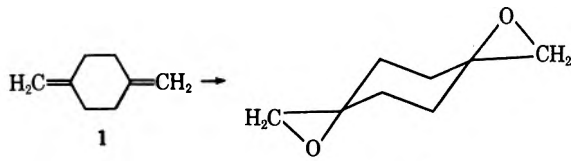

Table I
STUDIES ON THE REACTIONS OF 1,4-DIMETHYLENECYCLOHEXANE WITH PERACIDS

Solvent	ε (solvent)	Temp, °C	Time, hr	Yield of diepoxide, %	Trans[a] content (±2%), %
m-Chloroperbenzoic Acid					
Benzene	2.28	22	4	66	97
Chloroform	4.81	0	2	76	90
Chloroform	4.81	22	2	75	85
Tetrahydrofuran	7.6	22	34	44	100
Methylene chloride	9.1	40	48	79	70
Ethylene chloride	10.7	22	3	68	70
tert-Butyl alcohol	11.7	22	48	68	73
Acetonitrile	37.5	22	10	52	70
Monoperphthalic Acid					
Diethyl ether	4.34	22	40	20	93
Peroxybenzimidic Acid[b]					
Methanol	33.6	22	22	32	55
Peracetic Acid					
Ethyl acetate	6.02	0	>48	25	85

[a] Determined by nmr. [b] Formed *in situ* from the reaction of hydrogen peroxide with benzonitrile.

Although formation of the trans diepoxide is favored when conventional peracids are used, it is stereospecific only when the reactions are conducted in solvents with low dielectric constants. This suggests that polar contributions[7-9] to the transition state leading to the cis diepoxide cause cis diepoxidation to be less favorable than trans diepoxidation, particularly in nonpolar solvents. As has been observed in other olefin–peracid reactions,[6,10] longer reactions times were required when solvents capable of disrupting the intramolecular hydrogen bonding of the peracid were used.

It is interesting that approximatly equal amounts of cis and trans diepoxides are obtained when "peroxybenzimidic acid,"[11,12] formed *in situ* from benzonitrile in methanol at pH 8, is the oxidant. Carlson and Behn[13] have also noted that "peroxybenzimidic acid" acts differently from conventional peracids in olefin epoxidation reactions, and their results show that the presence of methanol is not responsible for the results obtained. It would seem that a species other than a peracid is the active reagent in "peroxybenzimidic acid" oxidations.

(1) We are pleased to acknowledge preliminary work in our laboratories by Dr. F. D. Shannon.[2] Dr. F. Lautenschlaeger, of the Dunlop Research Center, Toronto, Canada, has informed us privately that he has also prepared a mixture of the diepoxides and has separated them by fractional crystallization. The trans isomer seems to have been obtained previously[3] from the reaction of diazomethane with 1,4-cyclohexanedione.

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(6) N. N. Schwartz and J. M. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).

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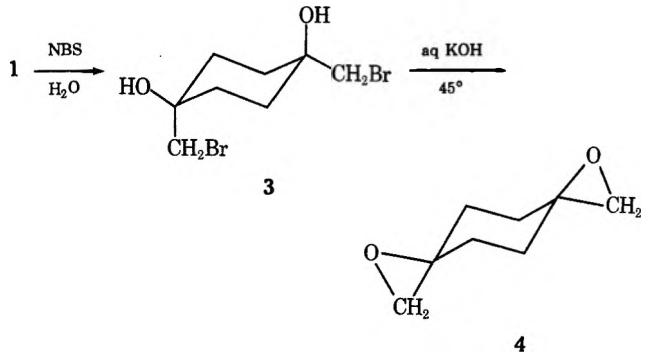
trans-1,4-Dimethylenecyclohexane diepoxide was characterized by its low dipole moment (0.1 ± 0.1 D), by the fact that it could be reduced to *trans*-1,4-dihydroxy-1,4-dimethylcyclohexane[14] with $NaAlH_2(OCH_2CH_2OCH_3)_2$, and by its nmr spectrum, details of which will be discussed later. It should be noted that *trans*-1,4-dihydroxy-1,4-dimethylcyclohexane has been difficult to obtain in pure form in reasonable yield hitherto, but that it can now be prepared easily in two steps from dimethylenecyclohexane.

Although *cis*- and *trans*-1,4-dimethylenecyclohexane diepoxide can be separated by fractional crystallization from hexane, the separation is tedious and an efficient route to the cis diepoxide was sought. Work by Schultz[15] and Morales[16] has shown that the reaction of 1,4-dimethylenecylcohexane with aqueous *N*-bromoacetamide or *N*-bromosuccinimide yields *cis*-1,4-dihydroxy-1,4-bis(bromomethyl)cyclohexane (**3**) in 20–30% yield. This material is the only easily isolated product formed in the reaction. It separates from the reaction mixture as an oily solid and can be purified by recrystallization from benzene–ethanol or benzene–methanol. Reaction of **3** with aqueous KOH afforded *cis*-1,4-dimethylenecyclohexane diepoxide (**4**),



mp 79–81°, in 90% yield. Although the formation of **3** is a low-yield process, the material is easy to isolate and the sequence **1** → **3** → **4** provides a convenient route to the cis diepoxide.

The cis diepoxide was characterized by its high dipole moment (4.2 ± 0.5 D), by the fact that it is lower melting than the trans isomer, by the fact that it can be reduced to *cis*-1,4-dihydroxy-1,4-dimethylcyclohexane,[14] and by its nmr spectrum, details of which will be considered next. In addition, its infrared spectrum was more complex than that of the trans isomer, in keeping with the lower symmetry of the cis isomer.

The nmr spectra of the cis and trans diepoxides provided evidence supporting their configurational assignments. The nmr spectrum of the trans isomer at room temperature consisted of a singlet at 2.57 ppm (oxirane CH_2) and an AA′BB′ pattern (cyclohexane CH_2), the strongest signals of which occurred at 2.18, 2.02, 1.40, and 1.26 ppm. The resonance of the oxirane methylene protons was observed as a singlet at −100°, the half-width of which was comparable to that of TMS resonance. At elevated temperatures, the AA′BB′ multiplet peaks shifted only slightly toward the center of the pattern. These results suggest that the trans isomer has a preferred conformation at room temperature.

The nmr spectrum of the cis isomer at room temperature consists of a sharp singlet at 2.54 ppm (oxirane CH_2) and a broad resonance centered at 1.72 ppm (cyclohexane CH_2). At −100°, the oxirane methylene proton resonance is observed as a pair of resonances of equal intensity, separated by 4 Hz. In addition, the resonance of the cyclohexane protons at −100° becomes similar to that of the trans isomer. These results indicate that the cis isomer readily undergoes conformational interconversion at room temperature, but that the rate of this process becomes slow on the nmr time scale at −100°.

The relative chemical shifts of the oxirane methylene protons are also in accord with the configurational assignments. The trans isomer can be expected to favor the conformation having equatorial oxirane methylene groups,[17] whereas the oxirane methylene groups must be in both axial and equatorial positions in the cis isomer. Since the resonance of oxirane methylene protons in an equatorial position occurs at lower field than when they have an axial position,[13,17] it is reasonable that the oxirane proton resonance of the trans isomer occurs at lower field than that of the cis isomer.

Experimental Section[18]

***trans*-1,4-Dimethylenecyclohexane Diepoxide.**—A solution of *m*-chloroperbenzoic acid (8.90 g of 85.4% active material, 44 mmol) in chloroform (100 ml) was added slowly (20 min) to a solution of 1,4-dimethylenecyclohexane[4,5] (2.37 g, 22 mmol) in $CHCl_3$ (50 ml) at 0°. The reaction mixture was stirred until it showed a negative reaction to starch–iodide paper. The mixture was filtered and then washed with 10% $NaHCO_3$ solution and with distilled water. The $CHCl_3$ solution was then dried over Na_2SO_4 and evaporated to dryness in a stream of nitrogen. The solid residue, 2.34 g (76%), mp 90–101°, was shown by thin layer chromatography to consist of two species, presumably the cis and trans isomers. *Anal.* Calcd for $C_8H_{12}O_2$ (140): C, 68.54; H, 8.63. Found: C, 68.78; H, 8.80.

The product was recrystallized from *n*-hexane to obtain 1.8 g (60%) pure *trans*-1,4-dimethylenecyclohexane diepoxide: mp 106–108° (white needles); ir 3.29, 7.69, 10.1, 10.89, and 11.96 μ (single bands, oxirane ring[22,23]); near-ir 2.213 and 2.223 (terminal epoxide[24]) and 2.355 μ (cyclohexane CH_2); nmr (CCl_4) δ 2.18, 2.02, 1.40, and 1.26 (strongest lines in AA′BB′ pattern, 8, cyclohexane CH_2), 2.57 (s, 4, oxirane CH_2). The material can be further purified by sublimation. *Anal.* Found: C, 68.49; H, 8.71.

When the reaction was conducted in other solvents, the procedure used was essentially the same as that described above, although the amount of solvent employed sometimes had to be adjusted to dissolve the peracid.

In those cases where *m*-chlorobenzoic acid was soluble in the reaction mixture, it was evaporated to dryness *in vacuo* and the

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(18) Nmr spectra of the materials were recorded using Varian A-60 and T-60 spectrometers. CCl_4 was used as a solvent for most nmr and ir studies. Tetramethylsilane was used as an internal standard.

Dipole moments were determined by the procedure of Hedestrand,[19,20] using apparatus assembled by Dr. G. Corsaro. Benzene was used as a solvent and measurements were made at room temperature. $P_{0_{2\epsilon}}$ values were estimated from molecular refractivities calculated[21] for the diepoxides.

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diepoxide was extracted from the residue with $CHCl_3$. The results obtained are summarized in Table I.

Reaction of 1,4-Dimethylenecyclohexane with Monoperphthalic Acid.—1,4-Dimethylenecyclohexane was added dropwise to an ethereal solution of monoperphthalic acid[25] (2 mol of peracid to 1 mol of diene) and the solution was allowed to stand for 40 hr at room temperature. Phthalic acid which precipitated was filtered and the filtrate was washed with 10% $NaHCO_3$ and with distilled water. The ether solution was then dried over anhydrous Na_2SO_4 and evaporated to dryness under nitrogen. The solid residue (20% yield) was shown by nmr analysis to contain 93% of the trans isomer.

Reaction of 1,4-Dimethylenecyclohexane with *in Situ* Peroxybenzimidic Acid.[11,12]—Thirty per cent hydrogen peroxide (10.6 g, 93 mmol) was slowly added to a stirred solution of 1,4-dimethylenecyclohexane (4.75 g, 44 mmol), benzonitrile (9.60 g, 93 mmol), and $KHCO_3$ (1.50 g) in methanol (50 ml). The mixture was stirred at room temperature for 18 hr and was then heated for 4 hr at 45–50°. The resulting solution was diluted with water (75 ml) and thoroughly extracted with 25-ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with water and dried over anhydrous Na_2SO_4. The $CHCl_3$ was allowed to evaporate and the solid obtained was extracted with boiling hexane and filtered to remove benzamide. Evaporation of the hexane filtrate yielded the diepoxide mixture (1.96 g, 32%, mp 72–95°), which was shown by nmr analysis to contain 55% of the trans isomer.

Reaction of 1,4-Dimethylenecyclohexane with Peracetic Acid.[26,27]—A calculated amount of a solution of peracetic acid in ethyl acetate (13.40 g of solution, 44 mmol of CH_3CO_3H) was added slowly at 0° to a solution of 1,4-dimethylenecyclohexane (2.375 g, 22 mmol) in ethyl acetate (50 ml) containing *ca.* 1 g of anhydrous Na_2CO_3. The mixture was vigorously stirred so that the Na_2CO_3 remained suspended.

After 48 hr, the mixture showed a positive reaction to starch–iodide paper. The unreacted peracid was decomposed with 10% Na_2SO_3 and the mixture was then washed thoroughly with water and dried over anhydrous Na_2SO_4. Evaporation of the ethyl acetate under reduced pressure yielded a mixed diepoxide (25% yield) that was shown by nmr analysis to contain 85% of the trans isomer.

***cis*-1,4-Dihydroxy-1,4-bis(bromomethyl)cyclohexane**[15,16] **(3).**—A mixture of 1,4-dimethylenecyclohexane (3.56 g, 33 mmol), *N*-bromosuccinimide (11.8 g, 66 mol), and water was vigorously shaken for about 35 min, and was then allowed to stand in the dark for 1 hr. The mixture was then filtered. The oily solid collected was washed with ether, dried, and recrystallized from benzene–ethanol mixtures to obtain *cis*-1,4-dihydroxy-1,4-bis(bromomethyl)cyclohexane, 2.0 g, as white needles: mp 163–164°; nmr (DMSO-d_6) δ 3.52 (s, 2, CH_2Br), ~4.6 (s, temperature and concentration dependent, 1, OH), 1.55 (m, 4, ring CH_2); mass spectrum *m/e* 221 and 223 (parent − CH_2Br). *Anal.* Calcd for $C_8H_{14}Br_2O_2$ (302.1): C, 31.80; H, 4.67; Br, 53.00. Found: C, 31.73; H, 4.51; Br, 53.18; mol wt (Rast), 341.

Saturation of the aqueous phase with NaCl caused an additional quantity of the cis bromohydrin to precipitate. The total yield obtainable is about 30%.

Ether-soluble products isolated from the reaction mixture by chromatography on alumina include a brominated dibromohydrin (7%), mp 110–112° (*Anal.* Calcd for $C_8H_{13}Br_3O_2$: C, 25.16; H, 3.41; Br, 62.99; O, 8.44. Found: C, 26.19; H, 3.62; Br, 60.55; O, 8.39); *p*-xylylene dibromide (2%), mp and mmp 144–145°, and a large amount of uncharacterized oil.

In addition, *trans*-1,4-dihydroxy-1,4-bis(bromomethyl)cyclohexane (5%) was obtained by allowing the aqueous phase to concentrate by evaporation: mp 139–141°; nmr (DMSO-d_6) δ 3.42 (s, 2, $-CH_2Br$), 1.32, 1.46, 1.56 (b), 1.65, 1.82 (part of AA'BB' pattern, 4, ring CH_2).

Anal. Calcd for $C_8H_{14}BrO_2$: C, 31.78; H, 4.63; Br, 52.98; O, 10.59. Found: C, 31.82; H, 4.63; Br, 53.99; O, 9.56.

***cis*-1,4-Dimethylenecyclohexane Diepoxide.**—One gram of *cis*-1,4-dihydroxy-1,4-bis(bromomethyl)cyclohexane was added slowly, as a solid, to a stirred solution of KOH (450 mg of 85% material) in water (60 ml) at 40°. The mixture was maintained at this temperature for 1 hr after the dibromohydrin had completely dissolved. The reaction mixture was then saturated with NaCl and extracted with five portions of ether. The ether extracts were combined, dried over anhydrous $MgSO_4$, and evaporated under nitrogen to obtain 441 mg (95%) of *cis*-1,4-dimethylenecyclohexane diepoxide: mp 79–81°; nmr (CCl_4) δ 2.54 (s, 4, oxirane CH_2), 1.72 (b m, 8, cyclohexane CH_2); ir 3.29 (oxirane CH), 7.69 + 7.94, 9.13 + 9.82, 7.69 + 7.94, 10.87 + 11.11,[28] 11.84 + 12.43, no band at 10.1 μ; near ir 2.218 (terminal oxirane), 2.355, and 2.339 μ (cyclohexane CH_2).

The compound can be further purified by sublimation. *Anal.* Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.46; H, 8.62.

The trans diepoxide can also be prepared by dehydrohalogenation of *trans*-1,4-dihydroxy-1,4-bis(bromomethyl)cyclohexane with aqueous KOH.

Reduction of *cis*-1,4-Dimethylenecyclohexane Diepoxide with $NaAlH_2(OCH_2CH_2OCH_3)_2$.—VITRIDE reducing agent[29] (2.5 ml) was added to a solution of *cis*-1,4-dimethylenecyclohexane diepoxide (0.577 g) in THF (20 ml) during 15 min. The reaction mixture was allowed to stand for 1 hr and was then poured into a small volume of water. The mixture was then evaporated to dryness and the residue was extracted with dry acetone. Evaporation of the acetone extract yielded 0.41 g (72%) of crude diol, mp 135–158°. This was purified by sublimation to obtain *cis*-1,4-dihydroxy-1,4-dimethylcyclohexane, mp 164–165° (reported[14] mp 166–167°).

Reduction of *trans*-1,4-Dimethylenecyclohexane Diepoxide with $NaAlH_2(OCH_2CH_2OCH_3)_2$.—A solution of VITRIDE reducing agent[29] (2.8 ml) in 5 ml of THF was added to a solution of the trans diepoxide (0.68 g) in 25 ml of THF with stirring. After 2 hr, the reaction mixture was worked up as is described for the reduction of the cis isomer. The crude product (0.53 g) yielded 0.23 g (33%) of *trans*-1,4-dihydroxy-1,4-dimethylcyclohexane, mp 196–198°, after recrystallization from acetone. Courtot, *et al.*,[14] report a melting point of 199–200° for the trans diol.

Registry No.—**1**, 4982-20-1; **2**, 28250-09-1; ***cis*-3**, 38312-48-0; ***trans*-3**, 38312-49-1; **4**, 28250-28-4; *m*-chloroperbenzoic acid, 937-14-4; monoperphthalic acid, 2311-91-3; peroxybenzimidic acid, 20996-66-1; peroxyacetic acid, 79-21-0.

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(28) The band at 11.1 μ was used to determine the cis-isomer content of diepoxide mixtures. Nmr analyses were obtained by comparing the relative intensities of cyclohexane or oxirane methylene proton resonances due to the cis and trans isomers. The results of both techniques were in good agreement.

(29) VITRIDE reducing agent is a 70% solution of $NaAlH_2(OCH_2CH_2OCH_3)_2$ in benzene that is available from Eastman Kodak Company, Eastman Organic Chemicals, Rochester, N. Y. 14650.

New Friedel–Crafts Chemistry. XXVIII. Cyclialkylation and Bicyclialkylation of Some Diastereomeric Diphenylalkyl Chlorides and Diphenylalkanols[1]

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The diastereomeric isomers of 1-chloro-2-methyl-4,5-diphenylpentane (**5a** and **5b**) and of 1-hydroxy-2-methyl-4,5-diphenylpentane (**4a** and **4b**) were obtained separately by stereoselective syntheses. Reaction of both diastereomeric chlorides with $AlCl_3$ gave the same products, 1-benzyl-3-methyltetralin (**10**), 1,1-dimethyl-3-phenyltetralin (**15**), 1-benzyl-3,3-dimethylindan (**16**), 1-methyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**9**), 2-methyl-1,5-diphenylpentane (**12**), and 2-methyl-4,5-diphenylpentane (**14**), but the relative amounts of the components of the reaction mixtures from the isomeric chlorides were significantly different. These differences were attributable to steric effects on cyclialkylation and bicyclialkylation processes in competition with other carbonium ion reactions such as 1,2 shifts and hydride exchanges. With $AlCl_3/CH_3NO_2$ catalyst, it was shown that the rate of cyclialkylation of **5a** was about three times that of **5b**. Neither **5a** nor **5b** gave any bicyclialkylation with the modified catalyst, and neither did the alcohols **4a** and **4b** in reaction with H_3PO_4, confirming the theory that bicyclialkylation involves hydride abstraction from an intermediate tetralin and this requires the strong catalyst $AlCl_3$. The differences in the yields of bicyclialkylation products from the diastereomeric chlorides suggests that hydride abstraction is assisted by back-side phenyl participation.

In recent years, we have directed part of our effort toward a systematic study of Friedel–Crafts cyclialkylation reactions with the aim of clarifying certain aspects of their mechanisms, including electronic, steric, and ring-strain effects.[3-6] Our most recent report on this subject[6] was concerned with the cyclialkylation of 1-chloro-4,5-diphenylpentane and 1-chloro-2-methyl-4,5-diphenylpentane in the presence of aluminum chloride. We reported that treatment of the latter chloride with aluminum chloride in petroleum ether or in carbon disulfide at room temperature gave a complex mixture which was comprised of 1-benzyl-3-methyltetralin, 2-methyl-1,5-dimethylpentane, 1-benzyl-3,3-dimethylindan, 1,1-dimethyl-3-phenyltetralin, and 1-methyl-2,3:6,7-dibenzobicyclo-[3.3.1]nona-2,6-diene.

In conducting the aforementioned preliminary work on the cyclization of 1-chloro-2-methyl-4,5-diphenylpentane, we were aware of the fact that this molecule and the alcohol from which it was derived have two asymmetric centers in them, and hence there are two diastereomeric pairs of enantiomers for each compound. We were equally aware of the fact that the synthetic procedure applied for the preparation of these compounds was not stereoselective and undoubtedly yielded mixtures of the diastereomeric pairs of each compound. In fact, the appearance of the nmr spectra of the alcohol and chloride were indicative of the presence of both diastereomers in each case.

Although we were unable to obtain the pure diastereomeric alcohols and chlorides at that time, we recognized that the individual diastereomers might give quite different results in cyclialkylation reactions. The present paper describes the stereoselective synthesis of the individual diastereomeric alcohols and chlorides and their behavior when subjected to cyclialkylation reactions.

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

(2) On leave of absence from the Chemistry Department, Assiut University, Assiut, U. A. R.

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

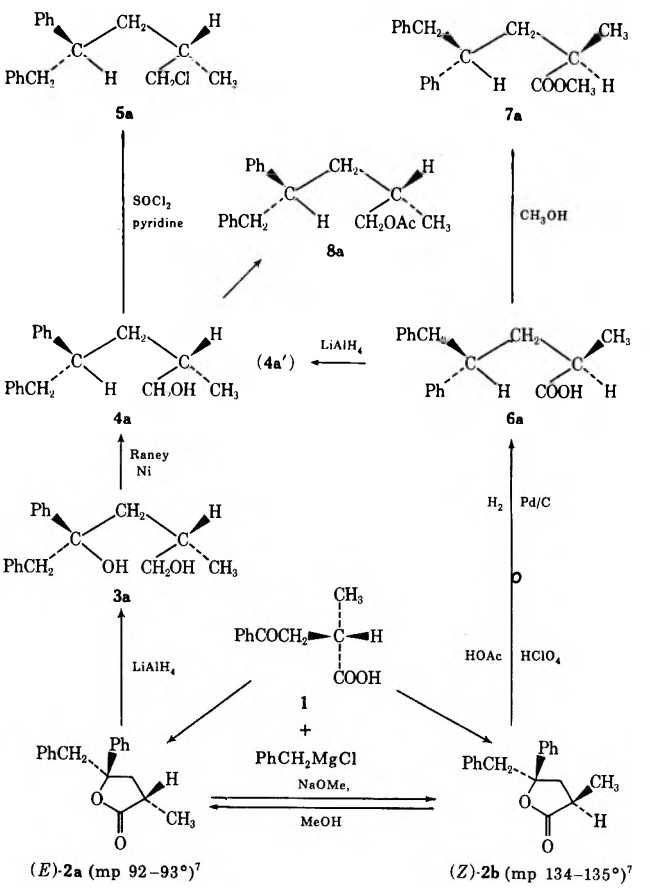
(4) A. A. Khalaf and R. M. Roberts, *ibid.*, **34**, 3571 (1969).

(5) A. A. Khalaf and R. M. Roberts, *ibid.*, **36**, 1040 (1971).

(6) R. M. Roberts, G. P. Anderson, Jr., A. A. Khalaf, and Chow-Eng Low, *ibid.*, **36**, 3342 (1971).

Synthesis and Structural Assignments of Starting Materials.—A diagrammatic representation of the various steps involved in the stereoselective synthesis of the two diastereomeric alcohols **4a** and **4b** and the chlorides **5a** and **5b** is given in Schemes I. It is to be

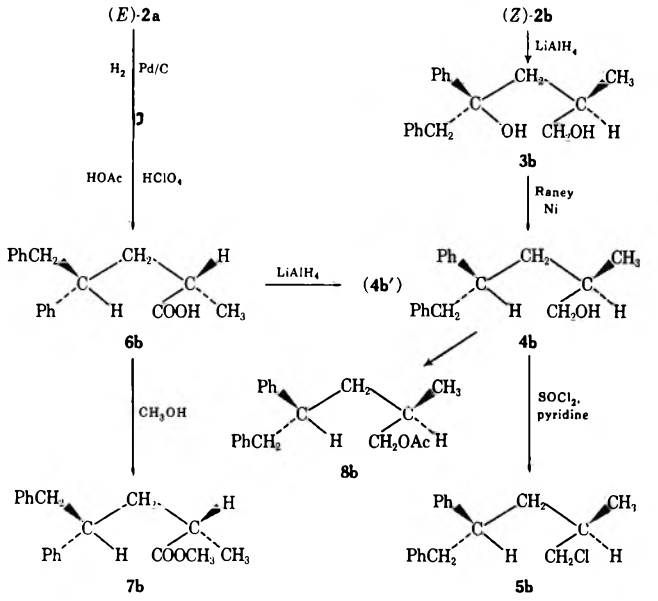
SCHEME IA



noted, however, that, although all of the steps yield mixtures of the two possible enantiomers, for the sake of simplicity we have drawn only one of the two enantiomers produced in each step.

As outlined in Scheme IA, the reaction of benzylmagnesium chloride with β-benzoyl-α-methylpropionic acid (1) gave a cis:trans mixture of γ-benzyl-α-methyl-γ-

SCHEME IB



phenyl-γ-butyrolactones, mp 92–93 and 134–135°. On the basis of the chemical properties of the diastereoisomeric chlorides (**5a** and **5b**) and alcohols (**4a** and **4b**) obtained from them by stereoselective syntheses, the isomeric lactones are assigned the *E* and *Z* configurations shown in Scheme IA. However, it must be emphasized that these assignments are deductive and could not be established definitely by means of physical data.[7]

With the isomeric lactones **2a** and **2b** in hand, two alternative routes were developed to convert them to alcohols **4a** and **4b**. One of these involved reduction with $LiAlH_4$ to the diols **3a** and **3b**, followed by Raney nickel reduction to the alcohols. Both the $LiAlH_4$[8] and the Raney nickel[9] reduction methods are known to be stereoselective and to proceed with complete retention of configuration. The alternative procedure involved the catalytic reduction of lactones **2a** and **2b** with hydrogen and palladium on carbon in glacial acetic acid containing a little perchloric acid to yield the two diastereomeric acids **6b** and **6a**, respectively. Reduction of acids **6b** and **6a** by $LiAlH_4$ gave alcohols **4b'** and **4a'**, respectively, which were identical in properties with their enantiomers, **4b** and **4a**, obtained by the former route. It is obvious from the stereochemical outcome of the latter route that, in accordance with literature reports, the palladium on carbon catalyzed hydrogenation proceeded with inversion at the benzylic carbon center.[9b-d] It is also important to mention at this point that the differentiation between the two diastereomeric alcohols **4a** and **4b** was conveniently achieved by nmr analysis of their acetate esters (**8a**, **8b**). The former (**8a**) showed the singlet for the $OCOCH_3$ at δ 1.82, but the latter (**8b**) showed the corresponding signal at 1.87.

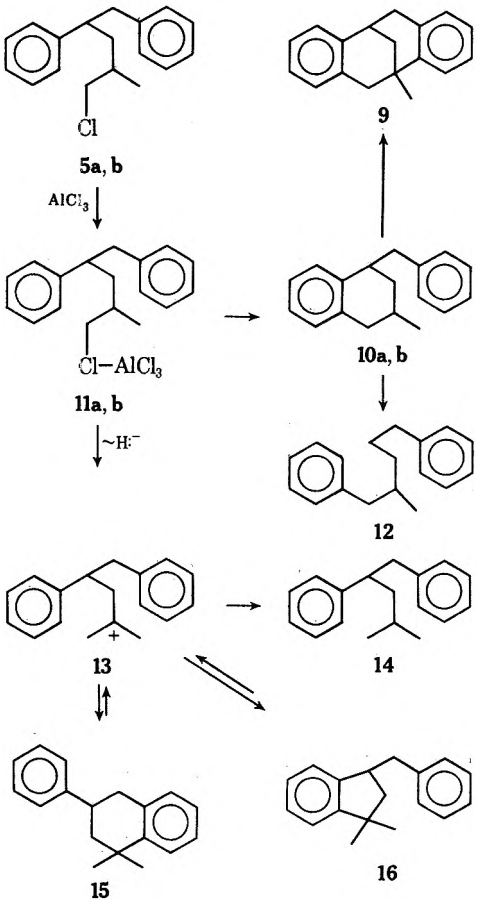
Owing to the difficulty encountered in the separation and purification of the required amounts of lactone **2a**, in large-scale preparations of alcohols **4a** and **4b** it was found advantageous to utilize lactone **2b** as a common precursor, converting it to alcohol **4b** *via* diol **3b** and to alcohol **4a** *via* acid **6a**. Once the alcohols were available, they were converted to the corresponding chlorides by treatment with thionyl chloride in pyridine.

Results and Discussion

The results of the $AlCl_3$- and $AlCl_3/CH_3NO_2$-catalyzed cyclialkylation of chlorides **5a** and **5b** and of the phosphoric acid catalyzed cyclialkylation of alcohols **4a** and **4b** are summarized in Table I.

By examining Table I, it can be seen that, in accord with our former report,[6] both chlorides **5a** and **5b** gave with $AlCl_3$ product mixtures composed of 1-benzyl-3-methyltetralin (**10**, Scheme II), 1,1-dimethyl-3-phenyltetralin (**15**), 1-benzyl-3,3-dimethylindan (**16**), 1-methyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene (**9**), and 2-methyl-1,5-diphenylpentane (**12**). An additional product found was 2-methyl-4,5-diphenylpentane (**14**). However, the relative yields of these components in the product mixture from chloride **5a** were significantly different from those in the product mixture from chloride **5b**.

SCHEME II



(7) Extensive nmr data of different kinds were gathered with the goal of assigning definite configurations to the lactones. These included benzene-induced solvent shift studies, decoupling experiments, and Eu and Pr shift reagent studies. Although these experiments could be interpreted as supporting the assignments shown in Scheme IA, we do not consider the data to be definitive. The major difficulty in interpretation of the data resides in the uncertainty as to the orientation of the flexible benzyl group.

(8) (a) H. L. Goering and C. Serres, Jr., *J. Amer. Chem. Soc.*, **74**, 5908 (1952); (b) M. Hinder and M. Stoll, *Helv. Chim. Acta*, **33**, 1308 (1950).

(9) (a) D. J. Cram and J. Allinger, *J. Amer. Chem. Soc.*, **76**, 4516 (1954); (b) S. Mitsui and S. Imaizumi, *Bull. Chem. Soc. Jap.*, **34**, 744 (1961), and references cited therein; (c) S. Mitsui, Y. Senda, and K. Konno, *Chem. Ind. (London)*, 1354 (1963); (d) S. Mitsui and Y. Kudo, *ibid.*, 381 (1965), and references cited therein.

TABLE I

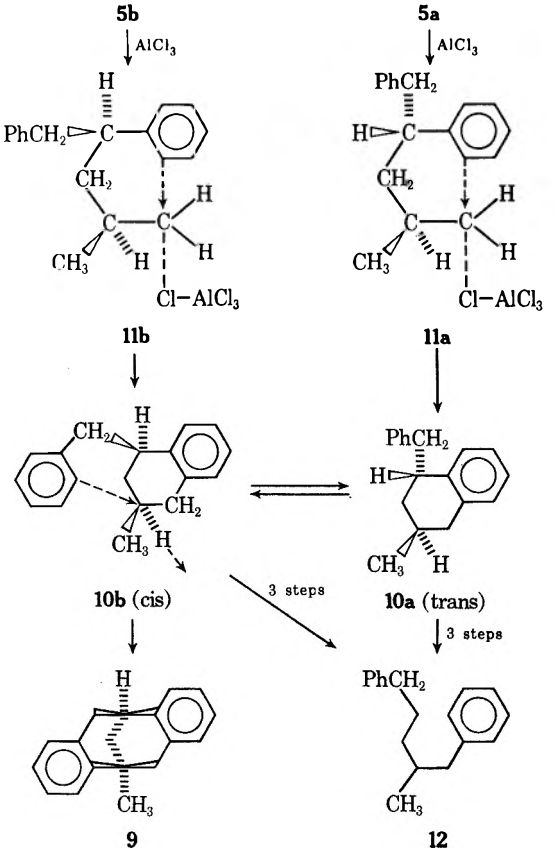
PRODUCTS FROM CYCLIALKYLATION AND BICYCLIALKYLATION OF DIASTEREOMERIC 1-CHLORO- AND 1-HYDROXY-2-METHYL-4,5-DIPHENYLPENTANES

Starting compd	Catalyst	Time, hr	Products,[a-d] % 14	16	12	10a (trans)	10b (cis)	15	9	Starting compd
Chloride **5a**	$AlCl_3$	2.5	1	10	4	43	12	16	10	
Chloride **5b**	$AlCl_3$	2.5	2	21	4	3		29	38	
Chloride **5a**	$AlCl_3$/	4		Tr		18	Tr	20		62
	CH_3NO_2	9		Tr		20	Tr	30		50
		24		Tr		25	Tr	35		40
Chloride **5b**	$AlCl_3$/	4		Tr		Tr	4	14		82
	CH_3NO_2	9		Tr		Tr	7	22		71
		24		Tr		Tr	10	30		60
Alcohol **4a**	H_3PO_4	0.25		7		31		62		
Alcohol **4b**	H_3PO_4	0.25		5		6		85		

[a] Products were analyzed using three columns: (3) a 6 ft × 0.125 in. silicone gum rubber, methyl type, SE-30 (5%) on 60–80 mesh Chromosorb W column operated at 190° with nitrogen carrier gas at 5 psi; (2) a 16 ft × 0.125 in. DEGA (25%) on 45–60 mesh Chromosorb W column operated at 210° with nitrogen carrier gas at 30 psi; (1) a 10 ft × 0.125 in. Bentone-34 (5%) and silicone gum rubber, SE-52 (5%) on 60–80 mesh column operated at 190° with nitrogen carrier gas at 40–50 psi. [b] Products are arranged in order of increasing glpc retention times on the 16 ft × 0.125 in. DEGA column. [c] Relative amounts of products distilling in the diphenylalkane range; about 15–20% of the reaction products were in the monophenylalkane range as a result of dephenylation. The "monophenylalkanes" produced consisted chiefly of 1,1-dimethylindan and 2-methyl-5-phenylhexane with minor amounts of 1,3-dimethyltetralin. [d] The relative amounts were determined by glpc; totals do not add up to 100% because small amounts of unidentified products are not included in the table.

In the first place, the yields of the tertiary cyclialkylation products **15** and **16** were twice as great from chloride **5b** as from chloride **5a**. This may be explained as follows. Inspection of models of chlorides **5a** and **5b** (or their enantiomers) indicates that **5a** should cyclize with no difficulty to *trans*-1-benzyl-3-methyltetralin (**10a**, Scheme III), whereas **5b** should

SCHEME III



give *cis*-1-benzyl-3-methyltetralin (**10b**), but with considerable steric opposition exerted by the developing 1,3-benzyl–methyl interaction. This steric hindrance to cyclialkylation by the primary complex **11b** may allow rearrangement to the tertiary carbonium ion **13** to compete significantly, resulting in higher yields of the tertiary cyclialkylation products **15** and **16** from **5b** than from **5a**.

The other major product from **5b** was **9**, resulting from hydride abstraction at the tertiary C-3 carbon atom of **10b** concerted with phenyl participation in the cyclialkylation. Apparently, most of the *cis*-1-benzyl-3-methyltetralin (**10b**) formed by primary cyclialkylation of **11b** (in competition with rearrangement to **13** as mentioned above) undergoes facile bicyclialkylation; no **10b** remained in the reaction mixture. By contrast, *trans*-1-benzyl-3-methyltetralin (**10a**) is the major product (43%) from **5a**. Although it is produced more easily by primary cyclialkylation than the cis isomer, it does not undergo bicyclialkylation readily. In **10a** the C-3 hydrogen is on the same side of the tetralin ring as the C-1 benzyl group, so that the phenyl group cannot assist in the hydride abstraction.[10] The 10% of **9** found in the reaction mixture from **5a** probably comes from bicyclialkylation of **10b**, which is produced by isomerization of **10a**.[11]

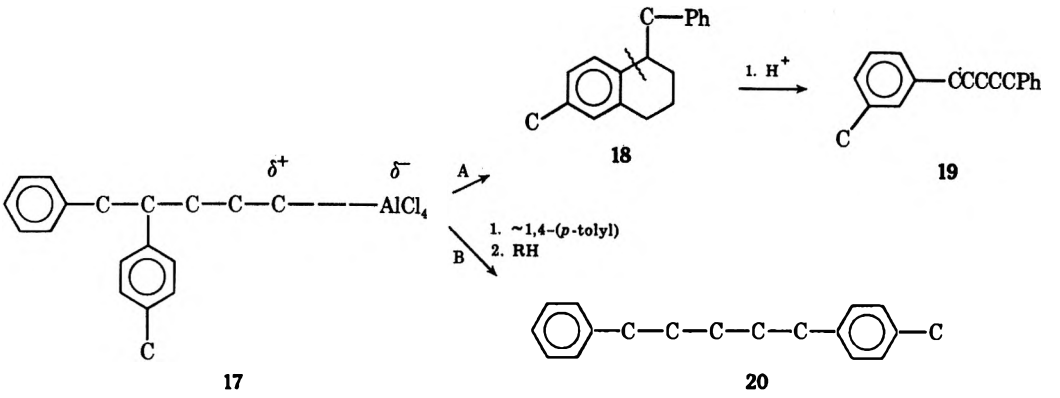
In order to obtain additional information on the stereochemical course of cyclialkylation reactions, with less complication from side reactions such as dealkylations and bicyclialkylations, we studied the cyclialkylation of chlorides **5a** and **5b** in the presence of nitromethane-moderated aluminum chloride, and the reactions of alcohols **4a** and **4b** in the presence of phosphoric acid. Moreover, we followed the progress of the $AlCl_3/CH_3NO_2$-catalyzed reaction by analyzing samples taken from the reaction mixture after various time intervals. The results of these reactions are also included in Table I.

Examination of these results indicates that they not only confirm our previous conclusions about the

(10) For example see (a) C. J. Kim and H. C. Brown, *J. Amer. Chem. Soc.*, **91**, 4286, 4287, 4289 (1969); (b) P. v. R. Schleyer, *et al.*, *ibid.*, **91**, 4291, 4298, 4296, 4297 (1969); (c) A. F. Diaz and S. Winstein, *ibid.*, **91**, 4300 (1969); (d) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **35**, 3717 (1970).

(11) Unpublished data by R. M. Roberts and K.-H. Bantel showed that **10a** and **10b** can be interconverted under the influence of $AlCl_3$.

SCHEME IV



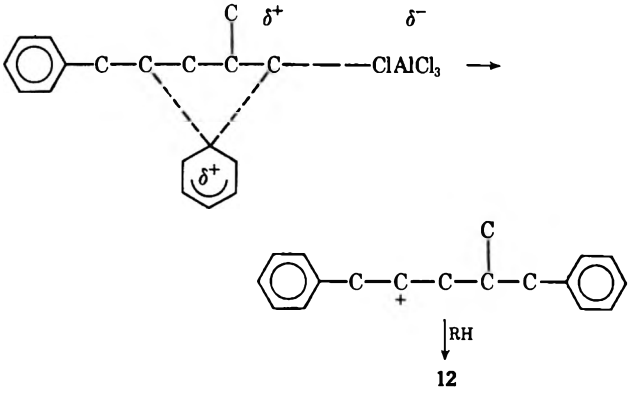
stereochemical behavior of chlorides **5a** and **5b**, but also provide two more interesting pieces of information that are in good agreement with our present theories. First, from a comparison of the rates of primary cyclialkylation (to form **10a** and **10b**) of chlorides **5a** and **5b**, determined after similar durations, it can be judged that chloride **5a** reacts roughly three times as fast as does chloride **5b**. This difference in reactivity can be explained simply by recalling the severe benzyl–methyl interactions experienced by chloride **5b** upon cyclialkylation to **10b**.

Secondly, the data from both the $AlCl_3/CH_3NO_2$- and H_3PO_4-catalyzed reactions indicate that 1,1-dimethyl-3-phenyltetralin (**15**) is the chief tertiary cyclialkylation product resulting from the closure of cation **13**. This is not unexpected on the basis of the fact that six-membered ring formation, when possible, is the most favored in terms of both entropy and strain factors.[12] Furthermore, this finding is in accord with the observation that **15** was the sole product obtained when 2,4-dimethyl-5-phenyl-2-pentene was subjected to the action of 85% sulfuric acid.[13]

No bicyclialkylation product (**9**) was found in any of the reactions of the chlorides **5a** and **5b** with $AlCl_3/CH_3NO_2$ or of the alcohols **4a** and **4b** with phosphoric acid. This is understandable in terms of the known fact that these catalysts are much poorer hydride-abstracting agents than unmodified $AlCl_3$, and it is the abstraction of hydride from the tertiary C-3 carbon of **10** that is essential to the bicyclialkylation.

The above result, together with the finding that in the $AlCl_3$-catalyzed reactions both chlorides **5a** and **5b** gave **15** and **16** in an apparent equilibrium ratio of about 1.2–1.4:1, directed our attention to the possibility that the latter ratio may be the result of a secondary process involving the isomerization of **15** to **16**. To examine this possibiility, we decided to investigate the behavior of both **15** and **16** in the presence of $AlCl_3$ under conditions comparable to those of the alkylation reactions. We found that both hydrocarbons gave isomerization mixtures in which the ratios of **15** to **16** were indeed very similar to those observed in the alkylation mixture, thus substantiating the proposition that **16** is formed mainly by intramolecular isomerization of **15** by $AlCl_3$.

The presence of 2-methyl-1,5-diphenylpentane (**12**) among the products of reaction of **5a** and/or **5b** with $AlCl_3$ was indicated previously, and was also confirmed by our present results. However, the mode of formation of **12** from the methyldiphenylpentyl chloride was not exactly understood. In our previous paper we assumed that **12** was formed by dealkylation at the C-1 position of 1-benzyl-3-methyltetralin (**10**) as indicated in Scheme II. However, this does not exclude the possibility that some of the **12** could have been formed *via* another route involving 1,4-phenyl migration, as illustrated in the following equation.



To test the latter alternative, we investigated the diaryl open-chain product resulting from the action of $AlCl_3$ on the related (methyl-labeled) 1-chloro-5-phenyl-4-(*p*-tolyl)pentane (**17**).

As is evident from Scheme IV, the structure of the diaryl open-chain product would be determined by the path responsible for its formation; path A would yield 1-phenyl-5-(*m*-tolyl)pentane (**19**) and path B 1-phenyl-5-(*p*-tolyl)pentane (**20**). If both paths are operating, the diaryl open-chain product would be a mixture of **19** and **20**.

When the above reaction was carried out, we found **19** to be the only diaryl open-chain compound produced, with no detectable amounts of **20** (Table II). In addition, **18** was shown separately to produce **19** upon treatment with $AlCl_3$. These results appear to exclude the involvement of 1,4-aryl migration as a possible route for the production of diaryl open-chain products in such reactions.[14]

(12) (a) See ref 2–6; (b) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1964, p 198.

(13) Unpublished data by the authors which is being prepared for publication.

(14) Although no 1-methyl-3-(*p*-tolyl)tetralin was detected in this reaction, it seems reasonable to assume that a small amount of it may have been produced but underwent dealkylation to give toluene and 1-methyltetralin under the reaction conditions. The fact that both toluene and 1-methyltetralin were present among the products of cyclialkylation of chloride **17** with $AlCl_3$ supports the above assumption.

The small amounts of **14** detected in the reaction mixtures from **5a** and **5b** and $AlCl_3$ are assumed to come from hydride exchange with the intermediate **13**. The alternative of dealkylation of **10a,b** is unlikely in view of the fact that dealkylation of a primary carbon atom would be required. Separate treatment of **10a,b** with $AlCl_3$ gives **12**, but no **14**.[15]

In summary, we may conclude on the basis of this and other earlier work[3-6] that cyclialkylations (intramolecular alkylations) in general are more rapid than intermolecular alkylations and occur at rates comparable to those of 1,2-hydride shifts. When two aromatic nuclei are present in the same molecule with one of them at a position suitable for direct closure to a six-membered ring, then cyclialkylations occur at rates faster than those of competing 1,2-hydride shifts, provided steric retardations are not encountered. The significant differences in the extent of bicyclialkylation which we observed to result from reactions of diastereomeric diphenylalkyl chlorides indicate that hydride abstraction from an intermediate tetralin is assisted by back-side phenyl participation.

Expermental Section[16]

The purity (unless specified, 95% or higher) and identity of the starting materials and of the final products were determined by glpc, ir, nmr, and in some cases, also by mass spectrometric analysis. Except where otherwise specified yields in each step were not less than 70%.

β-Benzoyl-α-methylpropionic acid (1) was prepared by a modified procedure involving the addition of a solution of methylsuccinic (pyrotartaric) anhydride (1.0 mol) in benzene (700 ml) to a solution made from $AlCl_3$ (2.2 mol), CH_3NO_2 (4.0 mol), and benzene (500 ml) over a period of 0.5 hr. After addition was complete, the reaction mixture was allowed to stir at room temperature for 2 hr. The reaction mixture was then decomposed by pouring into a 5-l. beaker containing 1000 ml of ice-cold 4 *N* hydrochloric acid. When the resulting mixture was left under the hood, most of the solvents evaporated, leaving a solid product which was filtered and repeatedly recrystallized from benzene to give an 86% yield of β-benzoyl-α-methylpropionic acid (1), mp 142–144° (undepressed when mixed with a sample of the same acid available from previous preparation).[3] The nmr and ir spectra were consistent with the formation of the compound.

(*E*)- (2a) and (*Z*)- (2b) γ-Benzyl-α-methyl-γ-phenyl-γ-butyrolactones.—In a typical experiment, benzylmagnesium chloride[18] (0.7 mol) was inversely added over a period of 30 min to a stirred solution of β-benzoyl-α-methylpropionic acid (0.23 mol) in a dry ether–benzene mixture.[19] After addition was complete, the reaction mixture was stirred at reflux temperature for 1 hr and at room temperature for 3 hr, then decomposed by cold dilute hydrochloric acid. Separation of the organic layer and evaporation of the solvents gave about 41 g of solidified crude product which melted over a wide range (70–110°). This was shown by combined glpc, ir, and nmr analysis to be a mixture consisting of two isomeric β-benzyl-α-methyl-γ-phenyl-γ-butyrolactones in a ratio of 3:2. Careful fractional crystallization of the above mixture from ethanol gave 20 g of one lactone isomer that melted at 134–135°, 3 g of another lactone isomer that melted at 92–93°, and 12 g of a mixture containing *ca.* 80% of the higher melting isomer. Based on the starting acid, the overall yield of crude lactone was about 90%.

Interconversion between Lactones 2a and 2b.—To a solution of the lactone (**2a** or **2b**) in 20 ml of ethanol was added 1 g of sodium methoxide and the resulting mixture was stirred at room temperature. After the desired reaction time, a 1-ml aliquot was withdrawn, acidified in a vial containing dilute hydrochloric acid, and extracted with a little ether, and the ether layer was then placed in another vial containing some anhydrous sodium sulfate. The ether layer was analyzed by glpc using a 6 ft × 0.25 in. cyanosilicone column at 190° with helium pressure adjusted to 30 psi. On this column, lactone **2a** has a shorter retention time than lactone **2b**.

Starting with **2b**, samples taken after 4, 24, 48, 72, and 120 hr showed 40, 49, 46, 49, and 54%, respectively, isomerization to lactone **2a**. After the same times, lactone **2a** underwent 51, 45, 52, 52, and 51%, respectively, isomerization to lactone **2b**.

(*E*)-γ-Benzyl-α-methyl-γ-phenyl-γ-butyrolactone (2a)[7] had the following properties: colorless crystals; mp 92–93°; ir (Nujol) 1775 cm^{-1} (C=O); nmr (determined with a Varian HA-100 spectrometer in $CDCl_3$ solvent) δ 7.40–6.90 (m with sharp singlet at 7.26, 10, aromatic), 3.36–3.02 (AB pattern of four lines centered about 3.19, 2, $PhCH_2$), 2.91–1.80 (complex ABC multiplet, 3, $C_\alpha HC_\beta H_2$), and 1.06 ppm (d, 3, J = 3.2 Hz, CH_3).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.20; H, 6.77. Found: C, 81.08; H, 7.00.

(*Z*)-γ-Benzyl-α-methyl-γ-phenyl-γ-butyrolactone (2b)[7] had the following properties: colorless crystals; mp 134–135°; ir (Nujol) 1760 cm^{-1} (C=O); nmr (determined with a Varian HA-100 spectrometer in $CDCl_3$ solvent) δ 7.36–6.98 (m with sharp singlet at 7.29, 10, aromatic), 3.27–2.96 (AB pattern of four lines centered about 3.12, 2, $PhCH_2$), 2.94–1.70 (complex ABC multiplet, 3, $C_\alpha HC_\beta H_2$), and 1.05 ppm (d, 3, J = 3.5 Hz, CH_3).

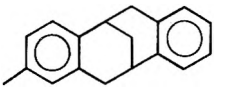
Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.20; H, 6.77. Found: C, 81.05; H, 6.60.

TABLE II

PRODUCTS OF TREATMENT OF 1-CHLORO-5-PHENYL-4-(*p*-TOLYL)PENTANE (17) WITH $AlCl_3$ AT 25°

Reaction time	Reaction products, %[a]					
	Toluene	1-Methyltetralin	17	18	19	Unidentified[b]
5 min	Tr	Tr	41	50	6	3
15 min	Tr	Tr	35	37	18	10
30 min	Tr	Tr	23	28	36	13
1 hr	2	2	18	21	36	21
2 hr	4	3	8	8	38	39
8 hr	9	11	4	5	24	47

[a] The relative amounts were determined by glpc using two different columns: (1) a 6 ft × 0.125 in. DEGA (25%) on 40–60 mesh Chromosorb W column operated at 210° with nitrogen carrier gas to 50 psi, and (2) a 6 ft × 0.25 in. Cyanosilicone (30%) on 60–80 mesh firebrick operated at 160–190° with helium carrier gas at 30 psi. [b] Consisting chiefly of a high-boiling product which, by analogy with other cases, is believed to be a bicyclialkylation product having the following structure.



(15) R. M. Roberts and coworkers, results to be published.

(16) Melting points and boiling points were not corrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The nmr spectra were determined in the solvent specified on a Varian A-60 nmr spectrometer unless mentioned otherwise.[17] High-resolution mass spectra were determined by means of a Du Pont Instruments, Inc., mass spectrometer, Model No. 21-110-C.[17] A Beckman IR-5A spectrophotometer was used to record the ir spectra. The glpc analysis was carried out using a Varian Aerograph Hy-Fi Model 600-D and a Beckman GC-2A instrument. Preparative glpc separations were made with a Wilkens A-700 (Autoprep) instrument. The following columns were used: (1) a 16 ft × 0.125 in. DEGA (25%) on 45/60 Chromosorb W operated at 200° with nitrogen carried gas at 22–25 psi; (2) a 10 ft × 0.125 in. Bentone-34 (5%) and silicone gum rubber, SE-52 (5%) on 60/80 Chromosorb W at 190–200° with nitrogen carrier gas at 40–50 psi; (3) a 6 ft × 0.25 in. Cyanosilicone (30%) on 60/80 Chromosorb P at 190° with He carrier gas at 30 psi; (4) a 6 ft × 0.125 in. Carbowax 20M (30%) on 60/80 firebrick at 190° with nitrogen carrier gas at 30–40 psi; (5) a 10 ft × 0.125 in. Apiezon L (20%) on Chromosorb W 30/60 operated at 150–200° with nitrogen carrier gas at 7–9 psi. All five columns were used for purity check of hydrocarbons and for analysis of the cyclialkylation reaction products; column 3 was used to analyze lactones, esters, alcohols, and chlorides.

(17) Spectra of lactones **2a** and **2b** at 100 MHz were obtained using a Varian HA-100 spectrometer. This instrument and the high-resolution mass spectrometer were purchased with funds provided by the National Science Foundation in Grants No. GP-6940 and GP-8509, respectively.

(18) H. Gilman and W. E. Catlin, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 471.

(19) Several experiments were carried out in which the methyl ester of this acid was used instead of the acid, but these resulted in lower yields of the required lactones. A similar observation was also made by M. S. Newman and K. Naiki, *J. Org. Chem.*, **27**, 863 (1962).

1,4-Dihydroxy-2-methyl-4,5-diphenylpentanes (3a,b).—These were prepared by $LiAlH_4$ reduction of the two isomeric lactones **2a** and **2b**. In a typical experiment, a solution of the lactone (10 g) in dry ether (400 ml) was added dropwise over a period of 20 min to a stirred suspension of $LiAlH_4$ (3 g) in dry ether (200 ml). After addition was complete, the reaction mixture was stirred under reflux for 1.5 hr and at room temperature for 1 hr. Following the usual work-up, the solid residue from lactone **2b** was purified by recrystallization from ethanol and the viscous oily residue from lactone **2a** was purified by repeated trituration with *n*-pentane. Yields were over 85%.

Lactone **2a** gave **1,4-dihydroxy-2-methyl-4,5-diphenylpentane (3a)**: viscous oil; ir (film) 3308 cm^{-1}, broad band (–OH); nmr (CCl_4) δ 7.40–6.60 (multiplet with sharp singlet at 7.17, 10, aromatic), 4.85–1.10 [broad multiplets with a singlet at 2.93, 9, $-CH_2C(OH)CH_2CHCH_2OH$], and 0.67 ppm (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 80.00; H, 8.15. Found: C, 80.22; H, 8.26.

Lactone **2b** gave **1,4-dihydroxy-2-methyl-4,5-diphenylpentane (3b)**: mp 123–124°; ir (Nujol) 3310 cm^{-1}, broad band (–OH); nmr ($CDCl_3$) δ 7.40–6.60 (multiplet with sharp singlet at 7.27, 10, aromatic), 3.45–1.40 [broad multiplets with sharp singlets at 3.17 and 1.93, 9, $-CH_2C(OH)CH_2CHCH_2OH$], and 0.92 ppm (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 80.00; H. 8.15. Found: C, 79.85; H, 8.32.

1-Hydroxy-2-methyl-4,5-diphenylpentanes (4a,4b).—These were synthesized by two different methods.

Method A was by Raney nickel reduction of diols **3a** and **3b**. In a typical experiment, a solution of the diol (14 g) in absolute ethyl alcohol (250 ml) was introduced into a flask containing about 60 g of freshly prepared W_2 Raney nickel[20] and the mixture was efficiently stirred for 4 hr at room temperature. The mixture was then filtered (Celite) and the cake was rinsed with ether (200 ml) and ethanol (200 ml). Evaporation of solvents led to the product. Yields were over 90%.

After hydrogenolysis, diol **3a** with Raney nickel gave 1-hydroxy-2-methyl-4,5-diphenylpentane (**4a**): bp 163° (2.0 mm); $n^{23}D$ 1.5500; ir (film) 3300 cm^{-1} (–OH); nmr (CCl_4) δ 7.30–6.75 (m, 10, aromatic), 3.27 (d, 2, J = 5 Hz, $-CH_2OH$), 2.80 (an apparent strong singlet overlapping a weak multiplet at base, 3, $PhCH_2CH-$), 2.53 (s, 1, –OH), 2.10–1.00 (m, 3, $-CH_2CH-$), and 0.78 ppm (d, 3, J = 6 Hz, CH_3).

Anal. Calcd for $C_{18}H_{22}O$: C, 85.04; H, 8.66. Found: C, 84.83; H, 8.42.

Diol **3b** gave 1-hydroxy-2-methyl-4,5-diphenylpentane (**4b**): bp 161–163° (1.3 mm); mp 45–47°; ir (Nujol) 3300 cm^{-1} (–OH); nmr (CCl_4) δ 7.07 (a broad singlet with base extending from 7.40 to 6.70, 10, aromatic), 3.13 (d, 2, J = 5 Hz, $-CH_2OH$), 2.80 and 2.60 (a large and a small broad singlet apparently overlapping a weak multiplet, 4, $PhCH_2CH-$ and –OH), 2.20–1.00 (m, 3, $-CH_2CH-$), and 0.73 ppm (d, 3, J = 5 Hz, $-CH_3$).

Anal. Calcd for $C_{18}H_{22}O$: C, 85.04; H, 8.66. Found: C, 85.04; H, 8.72.

The above diastereomeric alcohols **4a** and **4b** were converted to the corresponding acetate esters (in over 85% yield) by treatment with glacial acetic acid in ethylene dichloride and in the presence of catalytic amounts of concentrated H_2SO_4 as described in the literature.[21]

Alcohol **4a** gave **1-acetoxy-2-methyl-4,5-diphenylpentane (8a)**: bp 157° (1.25 mm); ir (film) 1725 cm^{-1} (C=O); nmr (CCl_4) δ 7.30–6.80 (m, 10, aromatic), 3.83 (d, 2, J = 5 Hz, CH_2O), 3.10–2.60 (broad singlet at 2.82 with very weak multiplet at base, 3, $PhCH_2CH-$), 1.82 (s, 3, $OCOCH_3$), 2.00–1.20 (broad multiplet overlapping latter singlet at base, $-CH_2CH$), and 0.82 ppm (d, 3, J = 6.5 Hz, $CHCH_3$); mass 296.1774 (calcd for $C_{20}H_{24}O_2$, 296.1776).

Alcohol **4b** gave **1-acetoxy-2-methyl-4,5-diphenylpentane (8b)**: boiling point identical and ir similar to those of isomer **8a**; nmr (CCl_4) δ 7.32–6.80 (m, 10, aromatic), 3.75 (d, 2, J = 6 Hz, CH_2O), 3.20–2.60 (broad singlet centered at 2.83 with weak multiplet at base, 3, $PhCH_2CH$), 1.87 (s, 3, $OCOCH_3$), 2.00–1.00 (broad multiplet, partly overlapping latter singlet at base, 3, $-CH_2CH$), and 0.81 ppm (d, 3, J = 6 Hz, $CHCH_3$); mass 296.1780 (calcd for $C_{20}H_{24}O_2$, 297.1776).

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

(21) R. O. Clinton and S. C. Laskowski, *J. Amer. Chem. Soc.*, **70**, 3135 (1948).

Method B was by catalytic reduction of lactones **2a** and **2b** followed by $LiAlH_4$ reduction of resulting acids.

A. Reduction of Lactones 2a and 2b to Acids 6b and 6a, Respectively.—In a typical reduction, a mixture of the lactone (8.5 g), 5% palladium on carbon (3 g), and perchloric acid (0.5 ml) in 100 ml of glacial acetic acid was shaken under hydrogen (60 psi) for 8 hr. The catalyst was filtered off and the acetic acid solution was diluted with water and extracted with ether. The ether layer was washed repeatedly with water until the washing was neutral to litmus paper. After drying over anhydrous sodium sulfate, the ether was evaporated and the residue was recrystallized from hexane. The acids were obtained in over 90% yields.

Lactone **2a** gave 2-methyl-4,5-diphenylpentanoic acid (**6b**): colorless rosettes; mp 93–94°; ir (Nujol) 1702 cm^{-1} (C=O); nmr (CCl_4) δ 11.63 (s, 1, COOH), 7.30–6.70 (m, 10, aromatic), 3.10–2.60 (weak multiplet with strong singlet at 2.83, 3, $PhCH_2CH$), 2.50–1.30 (broad multiplet, 3, CH_2CH), and 1.02 ppm (d, 3, J = 6.5 Hz, CH_3); mass 268.1458 (calcd for $C_{18}H_{20}O_2$, 268.1463).

Lactone **2b** gave 2-methyl-4,5-diphenylpentanoic acid (**6a**): colorless prisms; mp 100–101°; ir (Nujol) 1700 cm^{-1} (C=O); nmr (CCl_4) δ 12.28 (s, 1, COOH), 7.35–6.75 (m, 10, aromatic), 2.87 (broad singlet, 3, $PhCH_2CH$), 2.50–1.20 (broad multiplet, 3, CH_2CH), and 1.05 ppm (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.60; H, 7.46. Found: C, 80.81; H, 7.65.

Conversion of Acids 6a and 6b to the Corresponding Methyl Esters 7a and 7b.—The acids were converted to the methyl esters using BF_3–MeOH as described in the literature.[22] The products were distilled using a microbucket still (capacity, 0.3 ml).

Acid **6a** gave the ester **7a**: bp 80–90° (0.05 mm); ir (film) 1735 cm^{-1} (C=O); nmr (CCl_4) δ 7.30–6.80 (m, 10, aromatic), 3.48 (s, 3, OCH_3), 2.83 (partially resolved doublet overlapping weak multiplet extending between 3.1 and 2.60, 3, $PhCH_2CH<$), 2.40–1.30 (m, 3, $CH_2CHCOOMe$), and 1.0 ppm (d, 3, J = 6.8 Hz, CH_3); mass 282.1615 (calcd for $C_{19}H_{22}O_2$, 282.1620).

Acid **6b** gave the ester **7b**: bp 80–90° (0.05 mm); ir (film) 1735 cm^{-1} (C=O); nmr (CCl_4) δ 7.30–6.80 (m, 10, aromatic), 3.40 (s, 3, OCH_3), 2.85 (partially resolved doublet overlapping weak multiplet at base, 3, $PhCH_2CH$), 2.50–1.20 (m, 3, $CH_3CHCOOMe$), and 1.02 ppm (d, 3, J = 6.8 Hz, CH_3); mass 282.1623 (calcd for $C_{19}H_{22}O_2$, 282.1620).

Conversion to the above esters was useful in that it provided other means of identifying and differentiating between acids **6a** and **6b**. As evident from the nmr data of the esters, the $O=COCH_3$ signal of the ester **7a** appeared at δ 3.48, while that of the ester **7b** appeared at 3.40. Moreover, glpc analysis of the two esters on the 6-ft cyanosilicone column indicated that isomer **7a** has a shorter retention time than isomer **7b**.

B. Reduction of Acids 6a and 6b to Alcohols 4a and 4b, Respectively.—The acids were reduced by $LiAlH_4$ in dry ether following standard procedures[23] to give the corresponding alcohols in more than 90% yields. Acid **6a** gave an alcohol the properties of which (as well as of its acetate ester) were identical in all respects with those of the alcohol **4a** obtained previously. On the other hand, acid **6b** gave an alcohol whose properties (and the properties of its acetate ester) were identical in all respects with those of the alcohol **4b** prepared before.

1-Chloro-2-methyl-4,5-diphenylpentanes (5a,5b).—In a typical experiment, the alcohol (7.62 g, 0.03 mol) was dissolved in pyridine (4.7 g, 0.06 mol) and, with stirring and cooling in an ice bath, pure redistilled thionyl chloride (7.2 g, 0.06 mol) was added over a period of 30 min. The reaction mixture was heated at 100° for 1 hr and that was followed by the usual work-up procedure. The chlorides were obtained in about 65% yield.

Alcohol **4a** gave 1-chloro-2-methyl-4,5-diphenylpentane (**5a**): bp 156–157° (2.3 mm); $n^{23}D$ 1.5492; nmr (CCl_4) δ 7.30–6.80 (m, 10, aromatic), 3.29 (d, 2, J = 4.5 Hz, CH_2Cl), 2.79 (singlet with weak multiplet at base, 3, $PhCH_2CH$), 2.10–1.10 (broad multiplet, 3, CH_2CH), and 0.89 ppm (d, 3, J = 6.0 Hz, CH_3).

Anal. Calcd for $C_{18}H_{21}Cl$: Cl, 13.00. Found: Cl, 12.84.

Alcohol **4b** gave 1-chloro-2-methyl-4,5-diphenylpentane (**5b**): bp 140–141° (1 mm); $n^{23}D$ 1.5535; nmr (CCl_4) δ 7.40–6.70 (m, 10, aromatic), 3.18 (d, 2, J = 5 Hz, CH_2Cl), 2.80 (a broad singlet overlapping a very weak multiplet at base, 3, $PhCH_2CH$), 2.20–

(22) G. H. Hallas, *J. Chem. Soc.*, 5770 (1965).

(23) For example, see J. Tsuji and T. Nogi, *J. Amer. Chem. Soc.*, **88**, 1289 (1966).

1.10 (broad multiplet, 3, CH_2CH), and 0.85 ppm (d, 3, J = 6 Hz, CH_3).

Anal. Calcd for $C_{18}H_{21}Cl$: Cl, 13.00. Found: Cl, 12.67.

1-Chloro-5-phenyl-4-(*p*-tolyl)pentane (17).—Reaction of γ-chlorobutyroyl chloride with excess toluene in the presence of $AlCl_3/CH_3NO_2$ catalyst followed by the usual work-up procedure gave a 90% yield of *p*-methyl-γ-chlorobutyrophenone: buff flakes from *n*-pentane; mp 33–34°; ir (Nujol) 1667 cm^{-1} (C=O); nmr (CCl_4) δ 7.81 and 7.19 (two doublets, 4, J = 9 Hz, ortho and meta aromatic protons, respectively), 3.62 (t, 2, J = 6.5 Hz, $COCH_2$), 3.07 (t, 2, J = 6.5 Hz, CH_2Cl), 2.40 (s, 3, CH_3), and 2.17 ppm (triplet with secondary splitting, 2, J = 6.5 Hz, CH_2-CH_2CH_2Cl); mass 196.0657 (calcd for $C_{11}H_{13}O^{35}Cl$, 196.0655).

Inverse addition of benzylmagnesium chloride to the latter chloro ketone gave 1-chloro-4-hydroxy-5-phenyl-4-(*p*-tolyl)-pentane (ir no C=O peak, and OH at 3320 cm^{-1}). Catalytic reduction of the latter with hydrogen and palladium on carbon in glacial acetic acid in the presence of catalytic amounts of $HClO_4$[24] gave 1-chloro-5-phenyl-4-(*p*-tolyl)pentane (17): bp 143–145° (0.3 mm); $n^{25}D$ 1.5554; nmr (CCl_4) δ 7.25–6.75 (multiplet with sharp singlet at 6.93, 9, aromatic), 3.33 (t, 2, J = 6.0 Hz, CH_2Cl), 2.80 (broad singlet with weak multiplet at base, $PhCH_2CH$), 2.28 (s, 3, CH_3), and 2.10–1.40 ppm (broad multiplet, 4, $CH_2CH_2CH_2Cl$); mass 272.1333 (calcd for $C_{18}H_{21}{}^{35}Cl$, 272.1332).

1-Phenyl-5-(*m*-tolyl)pentane (19).[25]—Reaction of 1-chloro-4-phenylbutane with magnesium in refluxing dry ether gave the corresponding Grignard reagent, which upon condensation with *m*-tolualdehyde gave 1-hydroxy-5-phenyl-1-(*m*-tolyl)pentane. Catalytic reduction of the latter with hydrogen and palladium on carbon in glacial acetic acid and a little perchloric acid[24] gave 1-phenyl-5-(*m*-tolyl)pentane (19): bp 143° (1 mm); $n^{26}D$ 1.5402; nmr (CCl_4) δ 7.25–6.70 (multiplet with sharp singlet at 7.08, 9, aromatic), 2.70–2.35 (m, 4, $2ArCH_2$), 2.27 (s, 3, CH_3), and 1.90–1.20 ppm [broad multiplet, 6, $(CH_2)_3$]; mass 238.1723 (calcd for $C_{18}H_{22}$, 238.1721).

1-Phenyl-5-(*p*-tolyl)pentane (20).[25]—Reaction of $Ph(CH_2)_4MgCl$ with *p*-tolualdehyde followed by reduction of the resulting intermediate carbinol as described in the preparation of 19 gave the title compound: bp 131° (0.4 mm); $n^{26}D$ 1.5399; nmr (CCl_4) δ 7.08 and 6.93 (two singlets, 9, aromatic), 2.80–2.33 (broad multiplet, 4, $2ArCH_2$), 2.25 (s, 3, CH_3), and 1.90–1.00 ppm [broad multiplet, 6, $(CH_2)_3$]; mass 238.1721 (calcd for $C_{18}H_{22}$, 238.1721).

1-Benzyl-6-methyltetralin (18).[25]—Reaction of succinic anhydride with excess toluene in the presence of $AlCl_3/CH_3NO_2$ catalyst gave β-*p*-(toluoyl)propionic acid: colorless needles from benzene; mp 129–130°; ir (Nujol) broad band extending from 1650 to 1750 cm^{-1} (acidic and ketonic C=O); nmr (CCl_4) δ 9.45 (s, 1, COOH), 7.88 and 7.25 (two doublets, 4, aromatic), 3.27 (t, 2, J = 6 Hz, $PhCOCH_2$), 2.79 (t, 2, J = 6 Hz, CH_2COO), and 2.40 ppm (s, 3, *p*-CH_3); mass 192.0780 (calcd for $C_{11}H_{12}O_3$, 192.0786).

Inverse addition of benzylmagnesium chloride (2 equiv) to the above keto acid (1 equiv) with efficient cooling followed by decomposition with dilute hydrochloric acid gave a product which upon recrystallization from hexane gave 50% yield of γ-benzyl-γ-tolyl-γ-butyrolactone: colorless crystals; mp 75.5–76.5°; (Nujol) 1675 cm^{-1} (C=O); nmr (CCl_4) δ 7.50 (broad s, 9, aromatic), 3.07 (s, 2, $PhCH_2$), and 2.80–1.50 ppm (broad multiplet with a singlet located at δ 2.27, 7, CH_2CH_2 and $-CH_3$); mass 266.1305 (calcd for $C_{18}H_{18}O_2$, 266.1307).

Reduction of the above lactone by H_2 using 5% Pd/C and a little $HClO_4$ as catalyst in glacial acetic acid as solvent, in a manner similar to the reduction of lactones 2 to acids 6, gave 5-phenyl-4-(*p*-tolyl)pentanoic acid: viscous oil; bp 175–190° (0.75–1.0 mm); ir (film) 1720 cm^{-1} (C=O); nmr (CCl_4) δ 11.6 (s, 1, COOH), 7.20–6.75 (m, 9, aromatic), 2.78 (broad s, 3, $PhCH_2CH$), 2.24 (s, 3, *p*-CH_3), and 2.18–1.80 ppm (broad m, 4, CH_2CH_2); mass 268.1458 (calcd for $C_{18}H_{20}O_2$, 268.1463).

Conversion of the latter acid to acid chloride using PCl_3 followed by treatment of the acid chloride with $AlCl_3/CH_3NO_2$ in CS_2 at room temperature gave 4-benzyl-7-methyl-1-tetralone: viscous oil; bp 180–181° (0.6 mm); $n^{25.5}D$ 1.5905; nmr (CCl_4) δ 8.50–7.40 (multiplet, with strong, broad singlet at 7.75, 1, C_8H), 7.35–6.75 (m, 7, remaining aromatic protons), 3.30–1.60 (complex multiplet, 7, $PhCH_2CHCH_2CH_2CO$–), and 2.28 ppm (singlet, superimposed on latter multiplet, 3, $-CH_3$); mass 250.1355 (calcd for $C_{18}H_{18}O$, 250.1358).

Reduction of the latter tetralone derivative with H_2 using Pd/C and a little $HClO_4$ as catalyst in glacial acetic acid as solvent[24] gave 1-benzyl-6-methyltetralin: bp 158–159° (1.7 mm); $n^{24.5}D$ 1.5715; nmr (CCl_4) δ 7.17 (s, 5, C_6H_5), 7.08–6.67 (m, 3, C_6H_3), 3.40–2.50 (m, 5, $PhCH_2CHCH_2CH_2CH_2$), 2.24 (s, 3, $-CH_3$), and 2.00–1.40 ppm (broad m, 4, $PhCH_2CHCH_2CH_2$); mass 236.1570 (calcd for $C_{18}H_{20}$, 236.1565).

1-Methyl-3-(*p*-tolyl)tetralin.[14,26]—Benzyl *p*-tolyl ketone was prepared in 80% yield by interaction between phenylacetyl chloride and excess toluene in the presence of $AlCl_3$, mp 107–109° (lit.[27] mp 110°). Reaction of this ketone with ethyl bromoacetate and clean, dry zinc in dry benzene under the usual Reformatsky conditions gave ethyl β-hydroxy-γ-phenyl(*p*-tolyl)-butyrate. Hydrolysis of the crude ester with alcoholic sodium hydroxide followed by reduction by hydrogen and Pd/C in glacial acetic acid containing a little perchloric acid, as previously described for reduction of lactones **2a** and **2b**, gave γ-phenyl-β-(*p*-tolyl)butyric acid in 90% overall yield, based on hydroxy ester: white crystals from petroleum ether (bp 60–70°); mp 89–91° (lit.[28] mp 105°, from ethyl alcohol); ir (Nujol) 1715 cm^{-1} (C=O); nmr (CCl_4) δ 11.84 (s, 1, COOH), 7.40–6.90 (multiplet with strong singlet at 6.99, 9, aromatic), 3.70–2.45 (m, 5, CH_2CHCH_2CO), and 2.27 ppm (s, 3, CH_3). Conversion of the above acid to the acid chloride with PCl_3 followed by cyclization with $AlCl_3/CH_3NO_2$ catalyst in CS_2 solvent gave 3-(*p*-tolyl)-1-tetralone in 78% overall yield. This ketone, which was obtained in the form of a highly viscous oil, defied crystallization from various solvents, but its nmr and ir spectra were consistent with its formulation. The infrared spectrum (film) showed the normal C=O absorption at 1685 cm^{-1} and the nmr spectrum (CCl_4) showed the following: δ 7.98 (an apparent broad doublet, 1, aromatic proton ortho to C=O), 7.40–6.90 (an apparent multiplet with strong singlet at 7.03, 7, aromatic), 3.30–2.50 (broad multiplet, 5, $-CH_2CHCH_2CO$–), and 2.28 ppm (s, 3, CH_3). Treatment of the above tetralone with 2,4-dinitrophenylhydrazine gave a hydrazone which upon recrystallization from ethanol–ethyl acetate gave reddish orange crystals, mp 213–215°, mass 416.1484 (calcd for $C_{23}H_{20}N_4O_4$, 416.1484).

Reaction of 3-(*p*-tolyl)-1-tetralone with methylmagnesium iodide gave 1-hydroxy-1-methyl-3-(*p*-tolyl)tetralin, which upon reduction by hydrogen and Pd/C in glacial acetic acid containing a little perchloric acid gave the desired 1-methyl-3-(*p*-tolyl)-tetralin: bp 160–161° (1.8 mm); nmr (CCl_4) δ 7.80–6.80 (multiplet with strong singlet at 6.99, 8, aromatic), 3.10–1.42 (m, 5, $-CH_2CHCH_2$–), 2.25 (singlet superimposed on preceding multiplet, 3, CH_3), and 1.30 ppm (d, 3, J = 6.5 Hz, $>CHCH_3$); mass 236.1570 (calcd for $C_{18}H_{20}$, 236.1565).

Cyclialkylation Procedures. A.—The cyclization of the two diastereomeric chlorides **5a** and **5b**, as well as of the isomeric chloride **17**, was carried out as described previously.[3,6] However, it is to be noted that (a) all reactions were performed at room temperature in petroleum ether as solvent; (b) in reactions catalyzed by $AlCl_3$ the proportion of the diarylalkyl chlorides: $AlCl_3$:solvent was 1 g:0.25 g:5 ml; and (c) in reactions catalyzed by $AlCl_3/CH_3NO_2$, the latter proportion was also employed, but the $AlCl_3$ was dissolved in 6 mol of CH_3NO_2. In some cases aliquots were taken and analyzed after various time intervals. The results from these reactions are depicted in Tables I and II.

B.—The cyclialkylation of the two diastereomeric alcohols **4a** and **4b** with anhydrous phosphoric acid was conducted as described before for other alcohols.[4,5]

Treatment of Hydrocarbons 15, 16, and 18 with $AlCl_3$.—All reactions were carried out at room temperature in petroleum ether as solvent. The proportion of hydrocarbons: $AlCl_3$:solvent was 1 g:0.27 g:5 ml in the cases of **15** and **16** and 1 g:0.1 g:5 ml in the case of **18**.

Starting with 1,1-dimethyl-3-phenyltetralin (**15**), a complex mixture of products was obtained in which the following proportions of **14**:**15**:**16**:unidentified components were found after the times given: 2.5 hr, 7:46:33:14; 6 hr, 7:17:25:51; 24 hr, 8:2:25:65.

Similar treatment of 1,1-dimethyl-3-benzylindan (**16**) gave the following proportions of **14**:**15**:**16**:unidentified components after

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

(25) These compounds were synthesized with the help of M. B. Abdel-Baset.

(26) The synthesis of this compound was carried out by P. R. DeShong.

(27) H. Strassmann, *Ber.*, **22**, 1229 (1889); M. A. Mailhe, *Bull. Soc. Chim. Fr.*, **15**, 325 (1914).

(28) V. Papcke, *Ber.*, **21**, 1331 (1888).

the specified times: 2.5 hr, 4:38:26:32; 6 hr, 6:42:27:25; 24 hr, 4:38:24:34.

Starting with 1-benzyl-6-methyltetralin (18), samples taken after 15, 30, and 60 min of reaction were found to contain 8, 12, and 10% 1-phenyl-5-(*m*-tolyl)pentane (19), but no 1-phenyl-5-(*p*-tolyl)pentane (20). The rest of the mixture consisted of starting material and unidentified components.

Registry No.—**1**, 1771-65-9; **2a**, 38436-23-6; **2b**, 38436-24-7; **3a**, 38436-25-8; **3b**, 38436-26-9; **4a**, 38436-27-0; **4b**, 38436-28-1; **5a**, 38436-29-2; **5b**, 38436-30-5; **6a**, 38436-31-6; **6b**, 38436-32-7; **7a**, 38436-33-8; **7b**, 38425-19-3; **8a**, 38425-20-6; **8b**, 38425-21-7; **17**, 38425-22-8; **18**, 38425-23-9; **19**, 38425-24-0; **20**, 38425-25-1; pyrotartaric anhydride, 4100-80-5; *p*-methyl-γ-chlorobutyrophenone, 38425-26-2; 1-chloro-4-hydroxy-5-phenyl-4-(*p*-tolyl)pentane, 38425-27-3; 1-hydroxy-5-phenyl-1-(*m*-tolyl)pentane, 38425-28-4; β-*p*-(toluoyl)propionic acid, 4619-20-9; γ-phenyl-γ-tolyl-γ-butyrolactone, 38425-30-8; 5-phenyl-4-(*p*-tolyl)pentanoic acid, 38425-31-9; 4-benzyl-7-methyl-1-tetralone, 38425-32-0; ethyl β-hydroxy-γ-phenyl-(*p*-tolyl)butyrate, 38425-33-1; γ-phenyl-β-(*p*-tolyl)butyric acid, 38425-34-2; 3-(*p*-tolyl)-1-tetralone, 38425-35-3; 3-(*p*-tolyl)-1-tetralone 2,4-dinitrophenylhydrazone, 38425-36-4; 1-hydroxy-1-methyl-3-(*p*-tolyl)tetralin, 38425-37-5; 1-methyl-3-(*p*-tolyl)tetralin, 38425-38-6.

Geometrical Isomerism of 1-Arylidene-2-indanone[1]

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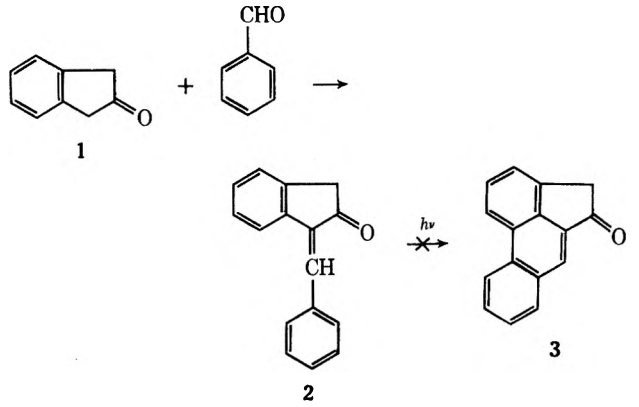
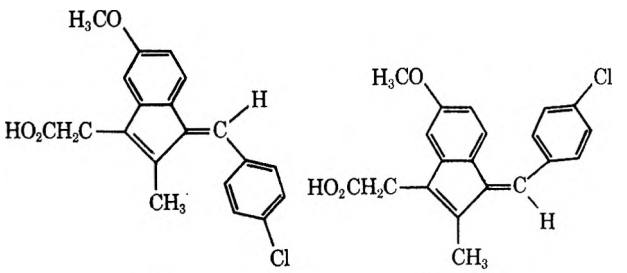
An example of geometrical isomerism in 1-(*p*-bromobenzylidene)-2-indanone is reported. Separation of the cis and trans isomers by dry column chromatography and the assignment of their structures using nmr spectroscopy and the nuclear Overhauser effect is described.

The primary objective of this investigation was to synthesize 5-acephenanthrenone (**3**),[2] an important intermediate in the synthesis of certain phenanthrene amino alcohols as potential antimalarial agents. Our initial approach involving the monocondensation of various aromatic aldehydes with 2-indanone (**1**) followed by photochemical cyclization (Scheme I) was unsuccessful.

SCHEME I



Attempts to effect the condensation of **1** using equimolar amounts of benzaldehyde in the presence of various bases such as sodium ethoxide,[3] potassium hydroxide–aqueous ethanol,[4] piperidine–benzene,[5] etc., were unsuccessful. Similarly, the use of acid catalysis (H_2SO_4–HOAc)[6] failed to give the desired compound **2**. Finally, condensation of 2-(*N*-morpholinyl)indene (**4**)[7] with *p*-bromobenzaldehyde was conducted by refluxing them in the presence of acetic acid for 4 hr.[8,9] Acid hydrolysis of the reaction mixture followed by dry column chromatography over silica gel using a fraction collector afforded a dibenzylidene compound **7** (8.7%) and two isomeric monobenzylidines, one with the *p*-bromophenyl substituent cis, compound **5** (1.3%), and the other with the *p*-bromophenyl substituent trans, compound **6** (36.6%), with respect to the C-2 oxygen (Scheme II). The assignment of **5** and **6** as cis and trans isomers is consistent with the work of Hoogsteen and Trenner[10] on the structure and conformation of the cis compound **8** and trans compound **9**, isomers of 1-(*p*-chlorobenzylidene)-2-methyl-5-methoxyindenylacetic acid. Their structural assignments were based on nmr data and single-crystal X-ray structure determination.



(1) R. E. Harmon, H. N. Subbarao, and S. K. Gupta, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, ORGN 112.

(2) R. E. Harmon, M. Mazharuddin, and S. K. Gupta, *J. Chem. Soc.*, in press.

(3) M. G. J. Beets and H. Van Essen, *Recl. Trav. Chim. Pays-Bas*, **77**, 1138 (1958).

(4) R. Baltzly, E. Lorz, P. B. Russell, and F. M. Smith, *J. Amer. Chem. Soc.*, **77**, 624 (1955).

(5) H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *ibid.*, **81**, 108 (1959).

(6) J. L. Adeltang and N. H. Cromwell, *J. Org. Chem.*, **26**, 2368 (1961).

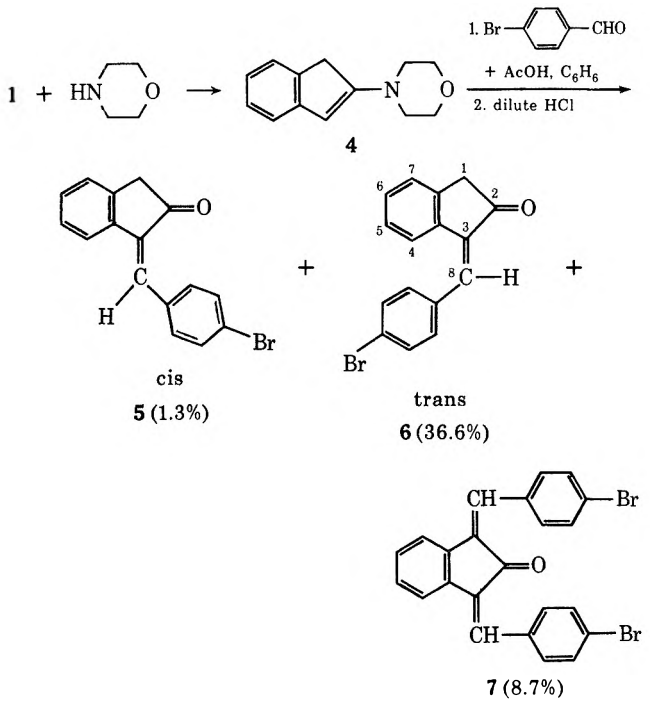
(7) A. J. Blomquist and E. J. Moriconi, *ibid.*, **26**, 3761 (1961).

(8) L. Birkofer, S. M. Kim, and H. D. Engels, *Ber.*, **95**, 1495 (1962).

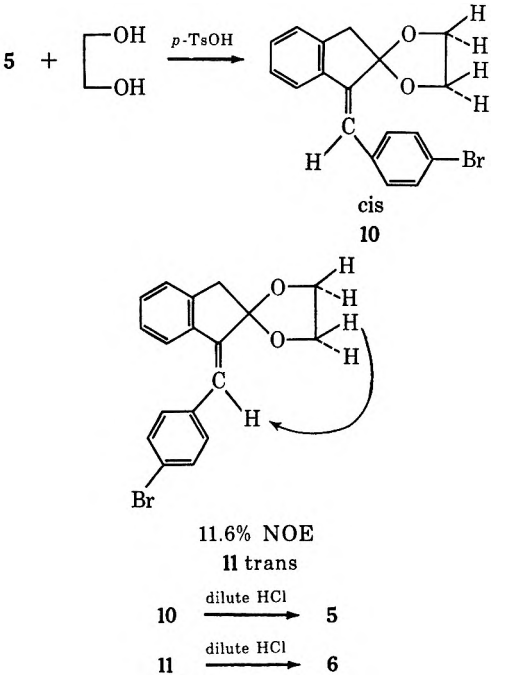
(9) K. C. Brannock, R. D. Burpit, H. E. Davis, H. S. Pridgen, and J. G. Thweatt, *J. Org. Chem.*, **29**, 2579 (1964).

(10) K. Hoogsteen and N. R. Trenner, *ibid.*, **35**, 521 (1970).

SCHEME II



SCHEME III



As compared to the excellent separations of pure cis and trans isomers **5** and **6** achieved by us using dry column chromatography, Hoogsteen and Trenner[10] were able to separate the cis and trans isomers **8** and **9** only in extremely poor yields by fractional crystallization coupled with reverse-phase partition column chromatography.

The structures of compounds **5** and **6** were established as cis and trans isomers of 1-(*p*-bromobenzylidene)-2-indanone on the basis of elemental analyses and ir, nmr, and mass spectral data. The nmr data are given in Table I. Before going into the nmr discussions, it

TABLE I

CHEMICAL SHIFTS IN THE NMR SPECTRA OF COMPOUNDS **5**, **6**, **10**, AND **11**

	Cis **5**	Trans **6**	Cis **10**	Ttrans **11**
Vinyl	7.15	7.43	7.13	6.74
Benzyl	3.55	3.57	3.17	3.20
p-Bromophenyl	7.52, 7.94	7.47, 7.56	7.42	7.33, 7.47
Ketal			3.92, 3.97	4.09, 4.21

should be mentioned that treatment of compound **6** with ethylene glycol in the presence of *p*-toluenesulfonic acid yielded two ketals, **10** (30.6%, mp 125–126°) and **11** (38.3%, mp 118–120°). On the basis of elemental analyses and nmr data discussed below, these ketals were found to be cis and trans isomers. Furthermore, each of them could be independently hydrolyzed with acid to the corresponding monobenzylidene without any significant isomerization (Scheme III).

Nmr Analysis of Compounds 5, 6, 10, and 11.— The nmr data are given in Table I. The structural assignments for compounds **5**, **6**, **10**, and **11** were based on an observed nuclear Overhauser effect (NOE) of 11.6% on the vinyl hydrogen of compound **11** when the ketal hydrogens were irradiated. Compounds **5** and **10** were therefore the cis isomers of compounds **6** and **11**, respectively. A Dreiding model of compound **11** also showed that the vinyl hydrogen in it was very close to the two α-oriented methylene hydrogens.

The NOE did not operate in the opposite direction, nor did the other isomer show an NOE because of multiple relaxation pathways. The paramagnetic shift of the vinyl hydrogen in **10** *vs.* **11** and **5** *vs.* **6** is reasonably attributed to the anisotropy in the plane of the aromatic ring. This is also in agreement with the observations of Hoogsteen and Trenner[10] from the nmr data on compounds **8** and **9**. For instance, the vinyl proton in the cis isomer **8** resonated at δ 7.47, whereas in trans isomer **9** it resonated at δ 7.00. The diamagnetic shift of the ketal hydrogens in **10** *vs.* **11** is attributed to the positive anisotropycone perpendicular to the plane of the *p*-bromophenyl ring. A Dreiding model of **10** indicated that the *p*-bromophenyl ring was rotated out of coplanarity owing to the steric hinderance of the ketal methylenes. The AA'BB' multiplets of **10** and **11** were analyzed with the LAOCN computer program.[11]

The spectrum of the trans isomer, **11**, was iterated to a fit with an RMS error of 0.353. The spectrum of the cis isomer, **10**, was fitted by adjusting the shifts but using the same coupling constants that were determined for the trans isomer. The plots of the calculated spectra were in agreement with the observed spectra. The results are summarized in Table II.

$J_{A',B'}$ (not shown in Table II) was the same as $J_{A,B}$. At first we were surprised to find $J_{A,B}$ to be -8.17 Hz instead of about -10 Hz as generally expected. To make sure that the computer did not converge to give the wrong fit, we tried to find solutions with $J_{A,B}$ around -10 Hz by varying L and keeping N constant. However, these computed spectra were significantly different from the experimental spectrum. Subsequent literature search revealed other examples of ketals showing $J_{A,B}$ in the -7.5 to -8 Hz region. For in-

(11) G. Slomp, *Appl. Spectrosc.*, **2**, 263 (1969).

TABLE II
ANALYSIS OF THE KETAL AA'BB' MULTIPLETS IN THE NMR SPECTRA OF COMPOUNDS 10 AND 11 USING LAOCN COMPUTER PROGRAM[11]

	11	10
$\delta_{A,A'}$	4.09320	3.91750
$\delta_{B,B'}$	4.21106	3.97259
$J_{A,A'}$	10.271	10.271
$J_{B,B'}$	10.271	10.271
$J_{A,B}$	−8.173	−8.173
$J_{A,B'}$	6.267	6.267

stance in 1965 Abraham[12] reported that in the A_2B_2 proton resonance spectrum of 2-methyl-1,3-dioxolane, J_{gem} was −7.5 Hz. Similarly, Fraser, *et al.*,[13] found that the nmr spectra of a series of substituted dioxolanes showed J_{gem} of −8.3 Hz.

Attempted Photochemical Cyclization of 6.—All of our attempts to achieve the photochemical cyclization of the monobenzylidene **6** to get the desired acephenanthrenone **3** failed. The reactions either yielded multicomponent mixtures or unidentifiable products. The synthesis of compound **3** has now been achieved using an entirely different approach.[2]

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are corrected. The elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. A Beckman IR-8 spectrophotometer was used for recording the ir spectra. A Cary 14 spectrophotometer was used to record the uv spectra. The nmr spectra were obtained on Varian A-60 and Varian HA-100 spectrometers using deuteriochloroform or hexadeuteriodimethyl sulfoxide as solvents using tetramethylsilane (TMS) as an internal standard. Mass spectral data were obtained on an Atlas CH-4 mass spectrometer. Silica gel G from Brinkman Instruments was used for thin layer chromatography (tlc) either on glass slides or 6 × 20 cm² glass plates. Spots on plates were detected by iodine vapor. Column chromatography was carried out on a 5 × 40 cm² glass column packed with silica gel. An Instrument Specialties Co. automatic fraction collector, Model 272, was used to collect the various fractions during column chromatography. 2-Indanone (**1**) was prepared from indene according to the procedure of Horan and Schiessler.[14] Experimental procedures used for the condensation of **1** with substituted benzaldehydes in the presence of NaOEt,[3] KOH–aqueous EtOH,[4] piperidine–benzene,[5] H_2SO_4–HOAc,[6] etc., were essentially similar to those described in the literature for similar aldol condensations. Since none of these procedures gave the desired 1-arylidene-2-indanone, it is not considered worthwhile to give the experimental details of these procedures. 2-(*N*-Morpholinyl)indene (**4**) was prepared by the reaction of **1** with morpholine using the procedure reported by Blomquist and Moriconi.[7]

Condensation of 2-(*N*-Morpholinyl)indene (4) with *p*-Bromobenzaldehyde.—A solution of *p*-bromobenzaldehyde (8.76 g, 0.06 mol) in benzene (100 ml) was added dropwise to a stirred and refluxing solution of **4** (12.06 g, 0.06 mol) in benzene (300 ml) using a Dean-Stark trap and under an atmosphere of nitrogen gas. The addition was completed in about 30 min. After that glacial acetic acid (3.6 g, 0.06 mol) was added to it and the reaction mixture was refluxed for 4 hr. The reaction mixture was hydrolyzed by adding 1:1 HCl–H_2O (100 ml) and refluxing while stirring overnight. The organic layer was separated and the solvent was evaporated under reduced pressure to give 17.4 g of a crude oil which showed several spots on a thin layer chromatogram. This crude mixture was separated into the following components using dry column chromatography over silica gel. An automatic fraction collector was used to collect the various fractions using 10:1 benzene–chloroform as solvents. The yields are based on the enamine **4**.

Combined fraction I, compound **7**, yellow crystals, 2.43 g (8.8% yield), had mp 204–205°. *Anal.* Calcd for $C_{23}H_{14}Br_2O$: C, 59.26; H, 3.02. Found: C, 59.45; H, 3.2.

Combined fraction II, compound **5**, white crystals, 0.23 g (1.3% yield), had mp 115–116°; ir ($CHCl_3$) 1710 cm⁻¹ (C=O); nmr ($CDCl_3$) is given in Table I. *Anal.* Calcd for $C_{16}H_{11}BrO$: C, 64.22; H, 3.70; Br, 26.71. Found: C, 64.11; H, 3.66; Br, 26.91.

Combined fraction III, compound **6**, yellow crystals, 6.38 g (36.6% yield), had mp 110–111°; ir ($CHCl_3$) 1725 cm⁻¹ (C=O); nmr ($CDCl_3$) is given in Table I. *Anal.* Calcd for $C_{16}H_{11}BrO$: C, 64.22; H, 3.70; Br, 26.71. Found: C, 64.47; H, 3.62; Br, 26.41.

Total yield of monocondensation products **5** and **6** was 37.9%.

Combined fraction IV, compound **1**, colorless crystals, 4.06 g, had mp 55–57°, and was identified as 2-indanone (**1**).

Treatment of 1-(*p*-Bromobenzylidene)-2-indanone (6) with Ethylene Glycol. Preparation of Ketals 10 and 11.[15]—A solution containing compound **6** (2.5 g), *p*-toluenesulfonic acid (200 mg), ethylene glycol (10 ml), and benzene (200 ml) was refluxed for 20 hr. The reaction mixture was cooled and washed first with an aqueous solution of Na_2CO_3 (10%), and then with water. The organic phase was dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residual oil was subjected to dry column chromatography over silica gel using a fraction collector. The following two fractions were separated. Fraction I, compound **11**, colorless crystals, 1.1 g (yield 38.3%), had mp 118–120°. *Anal.* Calcd for $C_{18}H_{15}BrO_2$: C, 62.99; H, 4.40; Br, 23.28. Found: C, 63.07; H, 4.24; Br, 23.21. The nmr data is given in Table I. Fraction II, compound **10**, colorless crystals, 0.87 g (yield 30.6%), had mp 125–126°. *Anal.* Calcd for $C_{18}H_{15}BrO_2$: C, 62.99; H, 4.40; Br, 23.28. Found: C, 62.95; H, 4.30; Br, 23.30.

Acid Hydrolysis of the Ketals 10 and 11.—A small amount (30 mg) of each of the ketals **10** and **11** was hydrolyzed by shaking it with a solution containing benzene (40 ml), water (10 ml), and concentrated HCl (2 ml) for 1 hr. After that the organic layer was separated and washed first with aqueous Na_2CO_3 and then with water. It was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. Using this procedure, the hydrolysis of the ketal **10** gave mainly the ketone **5**, whereas the ketal **11**, upon hydrolysis, afforded the corresponding ketone **6** exclusively. The identity of the products was established by melting point, mixture melting point, and superimposable ir spectra.

Registry No.—**1**, 615-13-4; **4**, 23929-00-2; **5**, 33611-18-6; **6**, 33611-17-5; **7**, 33500-65-1; **10**, 33611-20-0; **11**, 33611-19-7; *p*-bromobenzaldehyde, 1122-91-4; ethylene glycol, 107-21-1.

Acknowledgment.—The work at Western Michigan University was supported by the U. S. Army Medical Research and Development Command, Contract No. DADA-17-70-C-0090. The nmr analysis was performed at the Upjohn Co. This is Contribution No. 1050 to the Army Research Program on Malaria.

(12) R. J. Abraham, *J. Chem. Soc.*, 256 (1965).

(13) R. R. Fraser, R. U. Lemieux, and J. D. Stevens, *J. Amer. Chem. Soc.*, **83**, 3901 (1961).

(14) J. E. Horan and R. W. Schiessler, *Org. Syn.*, **41**, 53 (1961).

(15) Ch. R. Engel and S. Rakhit, *Can. J. Chem.*, **40**, 2153 (1962).

Perhydroindan Derivatives. XVI. The Synthesis of Racemic Epiallogibberic Acid[1]

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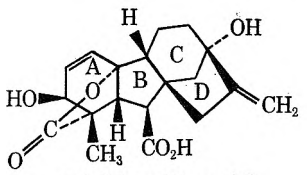
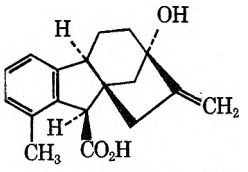
The racemic tetracyclic acetoxy olefin **4a** was subjected to oxymercuration followed by reduction and saponification to form the cis diol **5a**. Successive acetylation, reaction with dihydropyran, and selective saponification afforded the hydroxy tetrahydropyranyl ether **19b**, that was oxidized to the ketone **20**. A subsequent Wittig reaction followed by saponification afforded racemic epiallogibberic acid (**3**). The final product, racemic **3**, as well as the ester **21** and the diol derivatives **5a** and **5b**, were compared with the analogous products (+)-**3**, **12a**, **16a**, and **16b**, obtained from degradation of gibberellic acid (**1**), to establish that the structures of the synthetic and degradation products were the same.

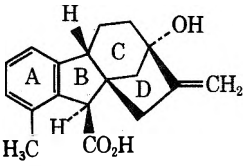
Among the early degradative studies used to establish the structure of gibberellic acid (**1**),[2] reaction of **1** with aqueous hydrazine to form allogibberic acid (**2**) and (+)-epiallogibberic acid (**3**) was especially useful



1 (gibberellic acid)



2 (allogibberic acid)

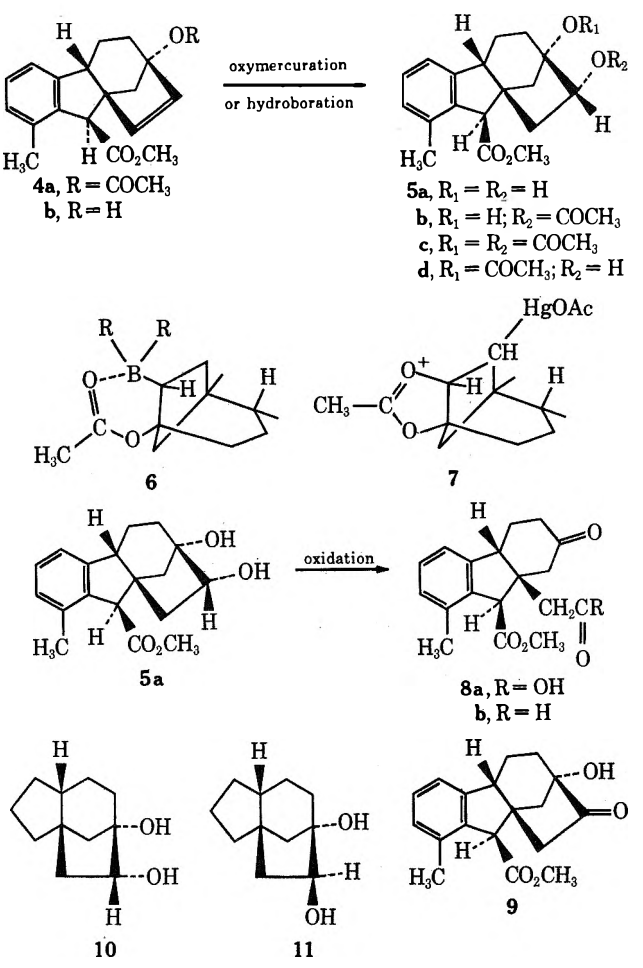


3 (epiallogibberic acid)

in providing intermediates for further structural study.[3] In seeking synthetic routes to the various gibberellins (*e.g.*, **1**) and their analogs, we were also led to consider synthetic routes to epiallogibberic acid (**3**), a substance possessing the same functional groups and stereochemical arrangement in rings B, C, and D that are present in gibberellic acid (**1**). This paper reports our synthesis of racemic epiallogibberic acid (**3**) and its comparison with (+)-epiallogibberic acid (**3**) obtained by degradation of **1**.[4]

For this synthesis, we employed the tetracyclic acetoxy olefin **4a** (Scheme I), whose preparation in synthetically useful amounts has been described in earlier papers in this series.[5] The selective hydration of this olefin **4a** to form a single product, the cis-1,2 diol **5a**, was readily accomplished either by reaction with mercury(II) acetate, followed by reduction, or by hydroboration with bis(2-methyl-2-butyl)borane, followed by oxidation. In each case we believe that the bridgehead acetoxy function plays a key role in this

SCHEME I



selectivity, either by reaction with the olefin–acetoxymercurium ion complex to form an intermediate acetoxonium ion **7** or by solvating, and hence directing, attack of the dialkylborane on the olefin to form the solvated trialkylborane **6**. In the subsequent aqueous basic reduction ($NaBH_4$ + NaOH) or oxidation (H_2O_2 + NaOH), the acetoxyl group was presumably removed by saponification. Additional evidence for the presence of an intermediate such as **7** was obtained by reduction of the organomercury intermediate in neutral aqueous solution to form the cis diol monoacetate **5b**, in which migration of the acetyl group had occurred. This same type of neighboring-group participation by the acetoxyl function has also been observed in the subsequently described degradation of (+)-epiallogibberic acid.

(1) This research has been supported by Public Health Service Grant RO1-CA-12634 from the National Cancer Institute. The execution of this research was also assisted by an Institutional Research Grant from the National Science Foundation for the purchase of a mass spectrometer.

(2) For reviews, see (a) J. F. Grove, *Quart. Rev., Chem. Soc.*, **15**, 56 (1961); (b) R. McCrindle and K. H. Overton, *Advan. Org. Chem.*, **5**, 47 (1965); (c) G. Schneider, G. Sembdner, and K. Schreiber, *Kulturpflanze*, **13**, 267 (1965).

(3) J. F. Grove and T. P. C. Mulholland, *J. Chem. Soc.*, 3007 (1960).

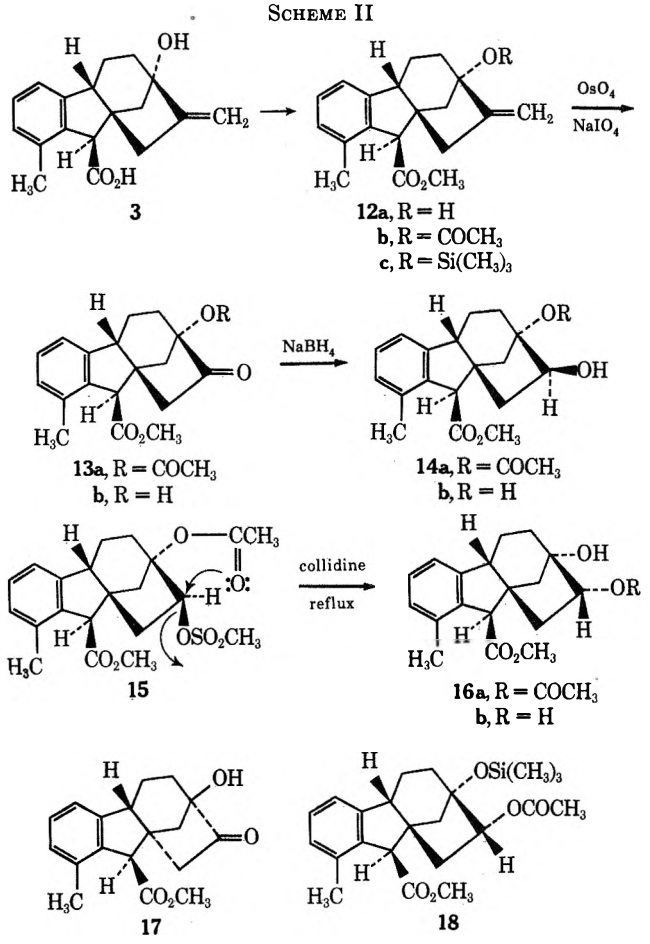
(4) For a recently completed relay synthesis of (−)-epiallogibberic acid, see K. Mori, *Tetrahedron*, **27**, 4907 (1971).

(5) H. O. House, D. G. Melillo, and F. J. Sauter, *J. Org. Chem.*, **38**, 741 (1973), and references cited therein.

Our subsequent efforts to oxidize the cis diol **5a** to the ketol **9** with a variety of oxidants (see Experimental Section) were uniformly unsatisfactory because of competing oxidative cleavage to form either the keto acid **8a** (in partially aqueous media) or the keto aldehyde **8b** (in anhydrous media). Although the successful oxidation of an analogous diol to the ketol has been reported,[6] the structurally similar trans diol **11** and, especially, the cis diol **10** have been noted to undergo oxidation cleavage.[7] Our efforts to prepare and selectively oxidize the monoacetylated diol **5b** were also unsatisfactory; a number of experimental observations suggested that the ready transfer of the acetyl group from one oxygen to the other (*i.e.*, **5b** ⇌ **5d**) was the cause of our difficulty with this approach.

At this stage in the synthesis, we concluded that it would be prudent to develop and refine further reaction conditions for the conversion of the racemic diol **5a** to racemic epiallogibberic acid (**3**) with a material that was more readily accessible than the racemic diol **5a**. For this reason, we interrupted our synthetic sequence to examine the degradation of gibberellic acid (**1**) *via* (+)-epiallogibberic acid (**3**, Scheme II) to the optically

SCHEME II

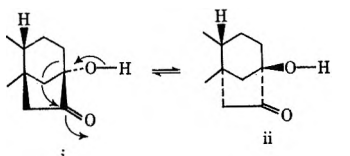


active cis diol **16b**, an ideal "model" compound for the reactions we wished to develop.

The previously reported[3,4] noncrystalline methyl (+)-epiallogibberate (**12a**) was converted to the crystalline acetate **12b** and then oxidized with a mixture of $NaIO_4$ and OsO_4.[8] Although neither the oxidation product, the keto acetate **13a**, nor the subsequent transformation products, **14**, **15**, and **16**, could be induced to crystallize, we were able to obtain satisfactory separation of the various reaction products by a combination of column chromatography and thin layer chromatography. The various spectroscopic properties of these liquid intermediates provided compelling evidence for the structural assignments indicated. Reduction of the intermediate acetoxy ketone **13a** with $NaBH_4$ formed a product believed to be the trans diol derivative **14a**, the product expected[6,9] from attack on the ketone **13a** from the less hindered exo direction. Subsequent reaction of this hydroxy acetate **14a** with methanesulfonyl chloride in pyridine followed by decomposition of the intermediate acetoxy mesylate **15** in collidine and subsequent hydrolysis produced the cis hydroxy acetate **16a**. We conclude that this transformation involves the indicated (structure **15**) displacement of the mesylate anion by the neighboring acetoxyl function and not initial elimination to form the olefin **4a**, because the olefin **4a** is stable under the conditions of this reaction.[5] Saponification of **16a** afforded the cis diol **16b**. Comparison of the ir, nmr, and mass spectra and of the tlc R_f values of both of these cis diol derivatives **16** with the racemic cis diol derivatives **5a** and **5b** provided compelling evidence that these intermediates had the same structures. Consequently, we were able to explore various transformations employing the diol **16b** with confidence that these same transformations would be applicable to the synthetic diol **5a**.

Two obstacles needed to be overcome in completing the synthesis. The first was the conversion of the cis diol **5a** to a suitable derivative of the ketol **9** (or **13b**) without serious competition from oxidative cleavage, and the second was the need to protect the hydroxyl group in the ketol **9** (or **13b**) to prevent base-catalyzed isomerization of the ketol (**13b** ⇌ **17**)[10] during introduction of the methylene group with a Wittig reagent. When the hydroxyl group was not protected in an analogous conversion of the ketol to (−)-epiallogibberic acid, the isolated yield was only 8.6%.[4] A trimethylsilyl group was used to block the ketol hydroxyl function in an analogous synthesis of steviol.[6] In the present case we found that, although a trimethylsilyl group could be selectively removed from the allylic ether **12c** to regenerate alcohol **12a**, all of our efforts to selectively remove the acetyl group from intermediate acetoxy silyl ether **18** resulted either in no reaction or in removal of both groups. Consequently,

(6) I. F. Cook and J. R. Knox, *Tetrahedron Lett.*, **No. 47**, 4091 (1970).
(7) E. J. Corey and R. L. Carney, *J. Amer. Chem. Soc.*, **93**, 7318 (1971).
(8) The use of this mixture of oxidants to cleave olefins has been described by R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).
(9) W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *J. Amer. Chem. Soc.*, **89**, 1499 (1967).
(10) Examples of this bicyclic ketol isomerization (i → ii) have been

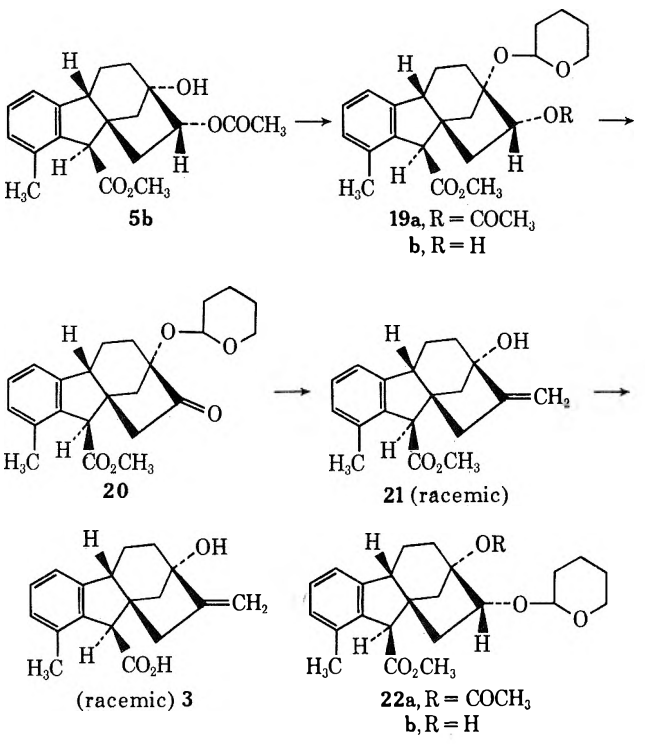


observed with a diastereoisomer of ketol **13b** (ref 4), in analogous derivatives of steviol [ref 6 and E. Mosettig, U. Beglinger, F. Dolder, H. Lichti, P. Quitt, and J. A. Waters, *J. Amer. Chem. Soc.*, **85**, 2305 (1963)], and in simple bicyclo[2.2.1]heptane derivatives [J. V. Paukstelis and D. N. Stephens, *Tetrahedron Lett.*, **No. 38**, 3549 (1971)].

we turned our attention to the tetrahydropyranyl ether blocking group.

The racemic cis diol **5a** could be selectively acetylated at the less hindered secondary hydroxyl function to form the acetoxy alcohol **5b**. Reaction with dihydropyran under carefully controlled conditions (see Experimental Section) afforded primarily the acetoxy ether **19a** (Scheme III) accompanied by a minor by-

SCHEME III



product believed to be **22a** formed by migration of the acetyl group (to form **5d**) during the acid-catalyzed ether formation. In practice, it was simplest to saponify the mixture **19a** + **22a** to the mixture of alcohols **19b** + **22b** and then to oxidize the mixture with the chromium trioxide–pyridine complex.[11] The resulting mixture of the keto ether **20** and the unchanged hydroxy ether **22b** was readily separated by chromatography. In the final stage of the synthesis we found it advantageous to treat the keto ether **20** with salt-free[12] methylenetriphenylphosphorane in order to facilitate decomposition of the intermediate betaine and, hence, minimize the reaction time. Acidic hydrolysis of the crude product cleaved the tetrahydropyranyl ether to form racemic methyl epiallogibberate (**21**), a viscous liquid product with ir, uv, nmr, and mass spectra and tlc R_f values that corresponded to those obtained with methyl (+)-epiallogibberate. Saponification with aqueous alkali afforded racemic epiallogibberic acid, mp 254–255.5° dec. Comparison of the ir, uv, nmr, and mass spectra for this sample and (+)-epiallogibberic acid, mp 243–245° dec, indicated that the two materials have the same structure.

(11) See W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969), and references cited therein.

(12) M. Schlosser, G. Müller, and K. F. Christmann, *Angew. Chem., Int. Ed. Engl.*, **5**, 667 (1966).

Experimental Section[13]

Preparation of the Racemic Cis Diol 5a. With $Hg(OAc)_2$.—To a solution of 354 mg (1.09 mmol) of the acetoxy olefin **4a** in 2.5 ml of THF was added a solution of 380 mg (1.19 mmol) of $Hg(OAc)_2$ in 2.5 ml of H_2O. The resulting yellow suspension was stirred at 25° for 10 hr and treated successively with 4 ml of aqueous 10% NaOH and 4 ml of aqueous 10% NaOH containing 2.0 mmol of $NaBH_4$. The resulting gray suspension was stirred at 25° for 30 min and then partitioned between H_2O and $CHCl_3$. The organic layer was washed with H_2O, dried, and concentrated to leave 348 mg of liquid residue. Crystallization from Et_2O separated 87 mg (27%) of the cis diol **5a** as white needles, mp 108.5–110°. Chromatography of the mother liquors on silica gel with Et_2O–hexane mixtures as the eluent separated, in order of elution, 22 mg of the starting acetoxy olefin **4a**, 55 mg of the crude hydroxy olefin **4b**, and an additional 134 mg of the diol **5a**. The hydroxy olefin **4b** crystallized from an Et_2O–hexane mixture as white needles: mp 103–104°; ir ($CHCl_3$) 3590 (OH) and 1730 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 6.8–7.4 (3 H m, aryl CH), 5.8–6.2 (2 H m, vinyl CH), 3.82 (1 H s, benzylic CH), 3.71 (3 H s, OCH_3), 3.2–3.5 (1 H m, benzylic CH), and 1.5–2.5 (10 H m, OH and aliphatic CH including an aryl CH_3 singlet at δ 2.27); mass spectrum *m/e* (rel intensity), 284 (M^+, 27), 252 (30), 227 (59), 225 (100), 197 (28), 196 (36), 195 (59), 181 (24), and 155 (19). The hydroxy olefin **4b** was reacetylated with 0.50 ml of Ac_2O in 0.75 ml of pyridine and the acetylated product was mixed with the recovered acetoxy olefin **4a** and treated with 91 mg of $Hg(OAc)_2$ in 0.5 ml of THF and 0.5 ml of H_2O. After subsequent treatment with 1.0 ml of aqueous 10% NaOH and 0.7 mmol of $NaBH_4$ in 1.4 ml of aqueous 10% NaOH, the previously described isolation procedure separated 9 mg (3% overall) of the acetoxy olefin **4a**, 29 mg (9% overall) of the hydroxy olefin **4b**, and an additional 41 mg of the cis diol **5a** (total yield 262 mg, 80%). The pure cis diol **5a** crystallized from Et_2O–hexane as white needles: mp 111.5–112.5°; ir ($CHCl_3$) 3400–3600 (broad, associated OH) and 1728 cm^{-1} (ester C=O); uv max (95% EtOH) 265 mμ (ε 291) and 273 (206); nmr ($CDCl_3$) δ 6.8–7.3 (3 H m, aryl CH), 3.6–4.0 (5 H m, CHO, benzylic CH, and CH_3O singlet at δ 3.65), 3.2–3.5 (1 H m, benzylic CH), 2.64 (2 H s, OH), and 1.5–2.9 (11 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.23); mass spectrum *m/e* (rel intensity), 302 (M^+, 2), 285 (21), 284 (100), 256 (71), 214 (25), 197 (40), 169 (33), 156 (22), 155 (30), 143 (22), 142 (21), 141 (28), 105 (29), and 43 (22).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.70; H, 7.21.

The oxymercuration was repeated without an alkaline isolation procedure with 45 mg (0.14 mmol) of the acetoxy olefin **4a**, 47 mg (0.15 mmol) of $Hg(OAc)_2$, 0.7 ml of THF, and 0.7 ml of H_2O. After a reaction period of 13 hr at 25°, the mixture was partitioned between CH_2Cl_2 and saturated aqueous NaCl and the organic layer was washed with aqueous $NaHCO_3$, dried, and concentrated. A solution of the crude organomercury intermediate (87 mg of colorless liquid) in 1.0 ml of *i*-PrOH was treated with 10 mg (0.27 mmol) of $NaBH_4$, stirred at 25° for 40 min, and then partitioned between $CHCl_3$ and H_2O. The crude product (47 mg) recovered from the organic layer was chromatographed on silica gel with Et_2O–hexane mixtures as eluents to separate 20 mg (42%) of the crude hydroxy acetate **5b**. Crystallization from Et_2O–hexane afforded the pure hydroxy acetate **5b** as white prisms, mp 103–104°, identified with a subsequently described sample by a mixture melting point determination and comparison of ir spectra.

B. With Bis(3-methyl-2-butyl)borane.—To a cold (0°) solution of the dialkylborane, prepared from 2.5 mmol of BH_3 and 366 mg (5.25 mmol) of 2-methyl-2-butene in 4.3 ml of THF, was added 258 mg (0.79 mmol) of the acetoxy olefin **4a**. The re-

(13) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 nmr spectrophotometer. The chemical shift values are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

sulting solution was stirred at 0° for 30 min and at 25° for 23 hr and then treated successively with 0.2 ml of H_2O, 4 ml of aqueous 10% NaOH, and 4 ml of aqueous 30% H_2O_2. After the resulting mixture had been stirred at 25° for 1.5 hr, it was partitioned between $CHCl_3$ and aqueous 5% $NaHCO_3$ and the organic layer was washed with H_2O, dried, and concentrated. Chromatography of the residual oil (216 mg) on silica gel with an Et_2O–hexane eluent separated 102 mg (43%) of the crude diol **5a**; recrystallization from Et_2O–hexane separated the pure cis diol **5a** as white needles, mp 109–110°.

Preparation of the Racemic Hydroxy Acetate 5b.—A solution of 290 mg (0.96 mmol) of the cis diol **5a** and 4 ml of Ac_2O in 6 ml of anhydrous pyridine was stirred at 25° for 2 hr and then partitioned between $CHCl_3$ and aqueous 2 *M* HCl. The organic layer was washed successively with aqueous $NaHCO_3$ and with H_2O and then dried and concentrated. Crystallization of the residual liquid (345 mg) from Et_2O–hexane separated 246 mg (74%) of the hydroxy acetate **5b** as white prisms: mp 103–104°; ir (CCl_4) 3590, 3480 (OH), and 1735 cm^{-1} (ester C=O); uv max (95% EtOH) 255 mμ (ε 273) and 273 (189) with intense end absorption at 210 (10,700); nmr ($CDCl_3$) δ 6.8–7.3 (3 H m, aryl CH), 4.92 (1 H d of d, J = 3.5 and 7 Hz, CHO), 3.77 (1 H s, benzylic CH), 3.65 (3 H s, OCH_3), 3.2–3.5 (1 H m, benzylic CH), and 1.5–2.7 (15 H m, OH and aliphatic CH including an aryl CH_3 singlet at δ 2.25 and a $COCH_3$ singlet at 2.11); mass spectrum *m/e* (rel intensity) 284 (10), 266 (34), 225 (25), 224 (47), 155 (44), 143 (21), 142 (23), 141 (42), 128 (22), and 43 (100).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.78; H, 7.01.

The mother liquors from this crystallization were chromatographed on silica gel with an Et_2O–hexane eluent to separate 24 mg (6%) of the crude diacetate **5c** and an additional 40 mg of the hydroxy acetate **5b** (total yield 286 mg, 87%). A solution of 26 mg (0.086 mmol) of the cis diol **5a** in 0.4 ml of Ac_2O and 0.6 ml of pyridine was stirred at 25° for 72 hr and then partitioned between $CHCl_3$ and aqueous 2 *M* HCl. The organic layer was dried and concentrated to leave 39 mg of yellow liquid that was chromatographed on silica gel with an Et_2O–hexane eluent. The fractions (27 mg, 82%) containing (tlc analysis) the diacetate **5c** were recrystallized from hexane to give the cis diacetate **5c** as white prisms: mp 122.5–123.5°; ir ($CHCl_3$) 1730 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 6.9–7.4 (3 H m, aryl CH), 5.2–5.5 (1 H m, CHO), 3.78 (1 H s, benzylic CH), 3.63 (3 H s, CH_3O), 3.1–3.5 (1 H m, benzylic CH), and 1.1–2.5 (*ca.* 17 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.23 and two CH_3CO singlets at 2.03 and 1.97).

Oxidation of the Racemic Cis Diol 5a. A. With H_2CrO_4.—A cold (0°) solution of 26 mg of the diol **5a** in 1.0 ml of acetone was treated with excess aqueous H_2CrO_4 (Jones reagent),[14] stirred at 0° for 2 min, treated with excess *i*-PrOH, and then partitioned between $CHCl_3$ and aqueous HCl. The organic layer was extracted with aqueous $NaHCO_3$ and the aqueous extract was acidified and extracted with $CHCl_3$. After the $CHCl_3$ extract had been dried and concentrated, the residual crude keto acid (10 mg) was recrystallized from Et_2O–hexane to separate 6 mg of the keto acid **8a**, mp 167–171°. This product and several comparable samples were combined and recrystallized from Et_2O–hexane to afford the pure keto acid **8a** as white needles: mp 166–169°; ir ($CHCl_3$) 2800–3500 (carboxyl OH), 1730 (ester C=O), and 1715 cm^{-1} (carboxyl and ketone C=O); uv max (95% EtOH) 264 mμ (ε 271) and 270 (221) with intense end absorption at 210 (11,900); nmr ($CDCl_3$) δ 7.0–7.8 (4 H m, OH and aryl CH, 1 H exchanged with D_2O), 4.02 (1 H s, benzylic CH), 3.68 (3 H s, OCH_3), 3.6–4.0 (1 H m, benzylic CH), and 2.0–3.1 (11 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.34); mass spectrum *m/e* (rel intensity) 316 (M^+, 3), 257 (43), 256 (100), 197 (37), 169 (29), 155 (48), 141 (20), and 55 (22).

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.04; H, 6.29.

An attempt to prevent oxidative cleavage by reaction of the diol **5a** with H_2CrO_4 in aqueous HOAc containing $Mn(NO_3)_2$[15] was not useful in this case, since oxidation of 15 mg of the diol **5a** under these conditions yielded 10 mg of the keto acid **8a**.

B. With CrO_3(pyridine)$_2$.—A solution of 28 mg (0.093 mmol) of the diol **5a** and 201 mg (0.78 mmol) of CrO_3(pyridine)$_2$[11] in 2.0 ml of CH_2Cl_2 was stirred at 25° for 30 min and then partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The crude neutral product (52 mg) from the organic layer was chromatographed on silica gel with Et_2O–hexane as an eluent. The partially purified keto aldehyde **8b** was isolated as a colorless liquid with ir and nmr spectra comparable to the spectra of the subsequently described sample obtained from degradation of gibberellic acid. Attempts to oxidize the racemic diol **5a** to a keto alcohol **9** with either *N*-bromosuccinimide or *t*-BuOCl[7] in pyridine–CH_2Cl_2 mixtures or with a modified Pfitzner–Moffatt oxidation (DMSO–pyridine·SO_3–Et_3N)[16] or Ag_2CO_3 on Celite[17] were not satisfactory in our hands.

Preparation and Transformations of (+)-Epiallogibberic Acid (3).—A solution of 18.82 g (54.4 mmol) of gibberellic acid (**1**) in 19 ml of H_2NNH_2 and 10 ml of H_2O was refluxed for 26 hr and then cooled, diluted with H_2O, and acidified with HCl to precipitate 4.18 g (27%) of (+)-epiallogibberic acid (**3**), mp 239–245° dec. Recrystallization from MeOH afforded the pure (+)-acid **3** as white prisms: mp 243–245° dec (lit.[3] mp 244°); ir (KBr pellet) 2700–3500 (OH) and 1680 cm^{-1} (carboxyl C=O); uv max (95% EtOH) 260 mμ (shoulder, ε 254), 265 (296), and 274 (204) with intense end absorption at 210 (18,650); mass spectrum *m/e* (rel intensity) 285 (20), 284 (M^+, 97), 209 (38), 195 (40), 193 (33), 181 (42), 179 (46), 178 (40), 165 (95), 155 (78), 153 (62), 152 (62), 142 (51), 141 (85), 129 (58), 128 (100), 127 (42), 115 (81), 45 (40), 43 (47), and 39 (44); nmr [$(CD_3)_2$NCDO] δ 6.8–7.3 (3 H m, aryl CH), 5.18 (1 H m, vinyl CH), 5.00 (1 H m, vinyl CH), 3.66 (1 H s, benzylic CH), 3.2–3.6 (1 H m, benzylic CH), 2.5–3.1 (*ca.* 2 H m, allylic CH), and 1.1–2.5 (9 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.27).

A cold (0°) Et_2O solution of 1.259 g (4.43 mmol) of the (+)-acid **3** was esterified with excess CH_2N_2 to yield 1.33 g of the ester **12a** as a colorless, viscous liquid (reported[3,4] as a gum): ir ($CHCl_3$) 3590 (OH), 1730 (ester C=O), and 910 cm^{-1} (C=CH_2); uv max (95% EtOH) 265 mμ (ε 317) and 273 (238) with intense end absorption at 210 (9240); nmr ($CDCl_3$) δ 6.9–7.4 (3 H m, aryl CH), 5.21 (1 H t, J = 2.5 Hz, vinyl CH), 5.08 (1 H t, J = 2.4 Hz, vinyl CH), 3.67 (4 H s, CH_3O and benzylic CH), 3.3–3.6 (1 H m, benzylic CH), 2.5–2.8 (2 H m, allylic CH_2), 2.25 (3 H s, aryl CH_3), and 1.2–2.2 (7 H m, aliphatic CH and OH at δ 1.82 exchanged with D_2O); mass spectrum *m/e* (rel intensity) 298 (M^+, 20), 239 (36), 238 (68), 155 (36), 141 (21), 119 (24), 105 (100), and 91 (20).

A solution of 980 mg (3.29 mmol) of the hydroxy ester **12a** and 10 ml of Ac_2O in 16 ml of anhydrous pyridine was stirred at 50° for 85 hr and then partitioned between $CHCl_3$ and aqueous 2 *M* HCl. The organic layer was washed successively with aqueous 2 *M* HCl, aqueous $NaHCO_3$, and H_2O and then dried and concentrated. The residual yellow liquid (1.12 g) was chromatographed on silica gel with an Et_2O–hexane eluent to separate the crude acetate **12b**. Crystallization from Et_2O–hexane afforded 1.023 g (91%) of the acetate **12b** as white needles: mp 89–91° (recrystallization sharpened the melting point to 90.5–91°); ir ($CHCl_3$) 1730 (ester C=O) and 910 cm^{-1} (C=CH_2); nmr ($CDCl_3$) δ 6.8–7.4 (3 H m, aryl CH), 5.0–5.3 (2 H m, vinyl CH), 3.72 (1 H s, benzylic CH), 3.67 (3 H s, OCH_3), 3.3–3.6 (1 H m, benzylic CH), 2.5–2.9 (2 H m, allylic CH_2), and 1.5–2.5 (12 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.23 and a CH_3CO singlet at 1.98); mass spectrum *m/e* (rel intensity) 340 (M^+, 76), 298 (29), 282 (43), 281 (100), and 221 (28).

Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.89; H, 7.10.

After a mixture of 32 mg (0.11 mmol) of the hydroxy ester **12a**, 0.25 ml of Me_3SiCl, and 0.50 ml of pyridine had been stirred at 25° for 55 hr, the mixture was concentrated under reduced pressure and partitioned between $CHCl_3$ and H_2O. The organic layer was dried and concentrated and the residual yellow liquid (36 mg) was chromatographed on silica gel with an Et_2O–hexane eluent to separate 26 mg (65%) of the trimethylsilyl ether **12c** as a colorless liquid: ir (CCl_4) 1735 (ester C=O) and 900 cm^{-1} (C=CH_2); nmr (CCl_3) δ 6.8–7.2 (3 H m, aryl CH), 4.9–5.2 (2 H m, vinyl CH), 3.2–3.7 (5 H m, two benzylic CH and CH_3O singlet at δ 3.62), 2.5–2.8 (2 H m, allylic CH_2), 2.24 (3 H s, aryl CH_3), 1.0–2.4 (6 H m, aliphatic CH), and 0.05 (9 H s, CH_3Si); mass spectrum *m/e* (rel intensity) 370 (M^+, 100), 355 (20), 75 (53), 74 (20), 73 (92), and 59 (25). When a solution of 10 mg of this silyl ether **12c** and 0.05 ml of aqueous 1 *M* HCl in 0.5 ml of

(14) E. J. Eisenbraun, *Org. Syn.*, **45**, 28 (1965).

(15) B. H. Walker, *J. Org. Chem.*, **32**, 1098 (1967).

(16) J. R. Parikh and W. von E. Doering, *J. Amer. Chem. Soc.*, **89**, 5505 (1967).

(17) M. Fétizon, M. Golfier, and J.-M. Louis, *Chem. Commun.*, 1102 (1969).

THF was stirred at 25° for 1.5 hr and then concentrated under reduced pressure, the residue was the alcohol **12a** identified with the previously described sample by comparison of ir spectra and tlc R_f values (silica gel coating).

A solution of 175 mg (0.51 mmol) of the acetoxy olefin **12b** in 6 ml of dioxane (distilled from $LiAlH_4$) and 1.7 ml of H_2O was treated with 1.2 ml of an aqueous solution containing 0.012 mmol of OsO_4. After the resulting black mixture had been stirred at 25° for 10 min, 234 mg (1.09 mmol) of powdered $NaIO_4$ was added during 10 min.[8] The resulting pale yellow solution was stirred at 25° for 17 hr and then partitioned between $CHCl_3$ and H_2O. The organic layer was dried and concentrated to leave 210 mg of yellow liquid, that was chromatographed on silica gel with an Et_2O–hexane eluent to separate 94 mg (53%) of colorless liquid fractions containing (tlc analysis) the keto acetate **13a**: ir ($CHCl_3$) 1760 (C=O in a five-membered ring) and 1730 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 6.9–7.4 (3 H m, aryl CH), 3.83 (1 H s, benzylic CH), 3.68 (3 H s, OCH_3), 3.4–3.7 (1 H m, benzylic CH), and 1.2–3.2 (14 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.27 and a CH_3CO singlet at 2.01); mass spectrum *m/e* (rel intensity) 342 (M^+, 100), 283 (21), 282 (34), 271 (65), 256 (66), 240 (28), 214 (22), 198 (20), 197 (29), 155 (31), 153 (71), 147 (23), 120 (21), and 105 (34); calcd for $C_{20}H_{22}O_5$ 342.146, found 342.14.

A solution of 401 mg (1.17 mmol) of the keto acetate **13a** and 2 ml of aqueous 3 *M* NaOH in 25 ml of MeOH was stirred at 25° for 2.5 hr and then partitioned between $CHCl_3$ and H_2O. The organic solution was dried and concentrated to leave 378 mg of liquid product with ir and nmr absorption indicating the presence of two isomeric ketols, presumably **13b** and **17**.[10]

A cold (0°) solution of 90 mg (0.26 mmol) of the keto acetate **13a** and 24 mg (0.63 mmol) of $NaBH_4$ in 3 ml of THF and 4.5 ml of MeOH was stirred for 1.5 hr and then partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic layer was washed with H_2O, dried, and concentrated to leave 90 mg of colorless liquid believed to be the crude hydroxy acetate **14a**: ir ($CHCl_3$) 3490 (OH) and 1720 cm^{-1} (broad, ester C=O); nmr ($CDCl_3$) δ 6.8–7.4 (3 H m, aryl CH), 4.1–4.5 (1 H m, CHO), 3.3–3.8 (5 H m, two benzylic CH and a CH_3O singlet at δ 3.62), and 1.2–2.9 (*ca.* 15 H m, OH and aliphatic CH including an aryl CH_3 singlet at δ 2.23 and a CH_3CO singlet at 2.00). A mixture of 30 mg (0.087 mmol) of this crude hydroxy acetate **14a**, 1 ml of aqueous 3 *M* NaOH, and 1 ml of THF was stirred at 25° for 6 hr and then partitioned between $CHCl_3$ and aqueous 0.5 *M* HCl. The organic layer was washed with H_2O, dried, concentrated, and chromatographed on silica gel. The later fractions, eluted with Et_2O, amounted to 26 mg of a colorless liquid containing (tlc analysis) a compound believed to be the trans diol **14b**: ir ($CHCl_3$) 3590, 3450 (OH), and 1725 cm^{-1} (ester C=O); nmr ($CDCl_3$) 6.8–7.3 (3 H m, aryl CH), 4.22 (1 H d of d, J = 5 and 11 Hz, CHO), 3.3–3.8 (5 H m, two benzylic CH and a CH_3O singlet at δ 3.63), and 1.2–2.8 [*ca.* 13 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.23 and OH (exchanged with D_2O)]; mass spectrum *m/e* (rel intensity) 302 (M^+, 2), 284 (100), 256 (50), 214 (45), 197 (51), 169 (37), 155 (46), 141 (33), 129 (30), 97 (30), 83 (31), 71 (30), 57 (37), 43 (36), and 41 (30). Reaction of this trans diol **14b** with excess Ac_2O in pyridine produced (tlc analysis) a new liquid product with ir and nmr spectra suggesting that it was the corresponding diacetate. Saponification of this material formed either the starting diol **14b** (ir and tlc analysis) or, under less vigorous conditions, a mixture (tlc analysis) corresponding in R_f values to the diacetate, the hydroxy acetate **14a**, and the trans diol **14b**.

A solution of 537 mg (1.56 mmol) of the crude hydroxy acetate **14a** and 1.2 ml of CH_3SO_2Cl in 12 ml of anhydrous pyridine was stirred at 25° for 4.5 hr and then partitioned between $CHCl_3$ and cold aqueous 2 *M* HCl. The organic layer was washed successively with aqueous 1 *M* HCl, aqueous $NaHCO_3$, and H_2O and then dried and concentrated to leave 688 mg of the crude mesylate **15**. A 95-mg portion of the crude product was chromatographed on silica gel with an Et_2O–hexane eluent to separate 82 mg of the mesylate **15** as a colorless liquid: ir ($CHCl_3$) 1730 (ester C=O), 1360, and 1180 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 6.9–7.4 (3 H m, aryl CH), 5.30 (1 H d of d, J = 4 and 11 Hz, CHO), 3.3–3.8 (5 H m, two benzylic CH including a singlet at δ 3.71 and a CH_3O singlet at δ 3.65), 3.08 (3 H s, CH_3SO_2), and 1.2–2.9 (14 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.23 and a CH_3CO singlet at 1.98); mass spectrum *m/e* (rel intensity), 326 (1), 266 (70), 224 (35), 197 (21), 155 (41), 141 (29), 84 (31), 83 (29), 79 (56), 55 (21), 43 (100), 42 (22), and 41 (28). A solution of 456 mg (1.08 mmol) of the crude mesylate **15** in 20 ml of collidine was refluxed for 6.5 hr and then partitioned between $CHCl_3$ and cold aqueous 2 *M* HCl. The organic layer was dried and concentrated and the residual yellow liquid (431 mg) was chromatographed on silica gel. The fractions eluted with Et_2O contained (tlc analysis) 326 mg (88%) of the hydroxy acetate **16a** as a colorless, viscous liquid that we could not induce to crystallize. Comparison of the tlc R_f values (silica gel coating), the ir spectra, and the nmr spectra of this sample **16a** and the crystalline racemic hydroxy acetate **5b** (mp 103–104°) indicated that the two samples had the same structure. A solution of 153 mg (0.45 mmol) of the hydroxy acetate **16a** and 1.0 ml of aqueous 10% NaOH in 4 ml of MeOH was stirred at 25° for 15 min and then partitioned between $CHCl_3$ and aqueous 1 *M* HCl. The organic layer was washed with H_2O, dried, and concentrated. The colorless liquid residue (156 mg) was chromatographed on silica gel and the fractions (121 mg or 91%) eluted with Et_2O contained (tlc analysis) the cis diol **16b** as a colorless liquid that again failed to crystallize. Comparison of the tlc R_f values (silica gel coating) and the ir, nmr, and mass spectra of the sample **16b** and the crystalline racemic cis diol **5a** (mp 111.5–112.5°) indicated that the two samples had the same structure.

A solution of 43 mg (0.13 mmol) of the hydroxy acetate **16a** and 0.50 ml of $(CH_3)_3SiCl$ in 1.0 ml of anhydrous pyridine was stirred at 25° for 7 hr and then concentrated under reduced pressure and partitioned between $CHCl_3$ and H_2O. The organic solution was dried, concentrated, and chromatographed on silica gel with an Et_2O–hexane eluent to separate 38 mg (73%) of the trimethylsilyl ether **18** as a colorless liquid: ir (CCl_4) 1735 cm^{-1} (ester C=O); nmr (CCl_4) δ 6.8–7.3 (3 H m, aryl CH), 4.8–5.2 (1 H m, CHO), 3.62 (4 H s, benzylic CH and CH_3O), 3.2–3.5 (1 H m, benzylic CH), 1.1–2.4 (14 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.25 and a CH_3CO singlet at 2.00), and 0.03 (9 H s, CH_3Si); mass spectrum *m/e* (rel intensity) 416 (M^+, 34), 330 (25), 329 (68), 297 (29), 283 (29), 271 (30), 270 (48), 269 (60), 268 (29), 267 (50), 266 (60), 227 (32), 226 (98), 117 (27), 75 (52), 73 (100), and 43 (63); calcd for $C_{23}H_{32}O_5Si$ 416.208, found 416.209. Attempts to saponify selectively the acetoxy function with NaOH in H_2O–THF resulted in conversion of this intermediate to the diol **16b** (tlc and ir analysis).

A cold (−60°) solution of 47 mg (0.16 mmol) of the diol **16b** and 0.2 ml of pyridine in 1 ml of CH_2Cl_2 was treated with 0.1 ml of *t*-BuOCl[7,18] and the resulting solution was stirred in the dark at −60° for 5 hr and then treated with 0.5 ml of aqueous 10% KI and 0.5 ml of aqueous 15% $Na_2S_2O_3$. After the resulting mixture had been partitioned between $CHCl_3$ and aqueous 1 *M* HCl, the organic layer was washed with H_2O, dried, concentrated, and chromatographed on silica gel. The fractions eluted with Et_2O–hexane (3:2, v/v) contained 33 mg (71%) of the crude keto aldehyde (one epimer of **8b**) as a colorless liquid that crystallized from Et_2O–hexane. Recrystallization from Et_2O–hexane separated 16 mg of the keto aldehyde (one epimer of **8b**) as white prisms: mp 97.5–98.5°; ir (CCl_4), 2820, 2720 (aldehyde CH), 1735 (ester C=O), and 1718 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.9–7.4 (3 H m, aryl CH), 4.05 (1 H s, benzylic CH), 3.4–3.8 (4 H m, benzylic CH and CH_3O singlet at δ 3.65), 2.93 (2 H broad, CH_2CO), and 1.1–2.8 (9 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.31); mass spectrum *m/e* (rel intensity) 300 (M^+, 44), 256 (100), 214 (20), 169 (22), 155 (45), and 56 (22); calcd for $C_{18}H_{20}O_4$ 300.140, found 300.14.

Preparation of Racemic Epiallogibberic Acid (Racemic 3).—After considerable experimentation, the following procedure was found most satisfactory for the formation of tetrahydropyranyl ethers. A solution of 71 mg (0.21 mmol) of the hydroxy acetate **5b** and 416 mg (4.95 mmol) of dihydropyran in 4 ml of PhH was dehydrated by distilling the solvents until approximately 1.5 ml of solution remained. The resulting solution was cooled, treated with 2 mg (0.01 mmol) of *p*-TsOH, and then stirred at 25° for 2 hr. Pyridine (0.05 ml) was added to neutralize the TsOH and then the reaction mixture was partitioned between PhH and aqueous $NaHCO_3$. The organic layer was washed with saturated aqueous NaCl, treated with several drops of pyridine, and then concentrated under reduced pressure to leave 139 mg of the crude acetoxy ether **19a** as a yellow liquid: ir (CCl_4) 1735 cm^{-1} (ester C=O); nmr (CCl_4) prominent singlets at δ 3.60 (CH_3O), 2.23 (aryl CH_3), and 2.02 (CH_3CO) attributable to the ether **19a**. A solution of the crude ester **19a** (139 mg) and 1 ml of aqueous 10% NaOH in MeOH was stirred at 25° for 1.5 hr

(18) M. J. Mintz and C. Walling, *Org. Syn.*, **49**, 9 (1969).

and then partitioned between $CHCl_3$ and H_2O. The organic solution was dried over Na_2CO_3 and concentrated to leave 126 mg of the crude hydroxy ether **19b** as a colorless liquid: ir (CCl_4) 3470 (OH) and 1735 cm^{-1} (ester C=O); nmr (CCl_4) prominent singlets at δ 3.59 (CH_3O) and 2.23 (aryl CH_3) attributable to the ether **19b**. To a solution of the crude hydroxy ether **19b** (126 mg) in 2 ml of CH_2Cl_2 was added a solution of 704 mg (2.73 mmol) of CrO_3(pyridine)$_2$ in 7 ml of CH_2Cl_2. The resulting red-brown solution was stirred at 25° for 1 hr and then partitioned between Et_2O and aqueous 5% NaOH. The organic layer was washed with H_2O, dried over Na_2CO_3, and concentrated. Chromatography of the residual yellow liquid (101 mg) on silica gel with Et_2O–hexane (1:3, v/v) separated 52 mg (66% based on the hydroxy acetate **5b**) of early fractions containing (tlc and ir analysis) the keto ether **20** as a colorless liquid: ir (CCl_4) 1765 (C=O in a five-membered ring) and 1735 cm^{-1} (ester C=O); nmr (CCl_4) δ 6.8–7.3 (3 H m, aryl CH), 4.5–5.1 (1 H m, OCHO), 3.3–3.8 (*ca.* 7 H m, CH_2O, two benzylic CH with a singlet at δ 3.74, and a CH_3O singlet at 3.61), and 1.1–2.6 (*ca.* 17 H m, aliphatic CH including an aryl CH_3 singlet at δ 2.26). Later fractions from the chromatography contained (tlc and ir analysis) a second component believed to be the isomeric hydroxy ether **22b**.

A 0.19 *M* solution of "salt-free" $Ph_3P{=}CH_2$ in benzene was prepared from $NaNH_2$ and $Ph_3PCH_3{}^+Br^-$ by the procedure of Schlosser and coworkers.[12] A solution of 52 mg (0.14 mmol) of the keto ether **20** in 0.5 ml of anhydrous PhH was treated with 0.86 ml of the PhH solution containing 0.16 mmol of $Ph_3P{=}CH_2$. After the resulting yellow solution had been refluxed for 6 hr, it was cooled, treated with 0.5 ml of aqueous 1 *M* HCl, and then partitioned between $CHCl_3$ and H_2O. The organic solution was dried and concentrated and a solution of the residual yellow oil (104 mg) in 1.0 ml of THF was treated with 0.5 ml of aqueous 1 *M* HCl and then stirred at 25° for 1 hr. The resulting mixture was again partitioned between $CHCl_3$ and H_2O and the organic layer was dried, concentrated, and chromatographed on silica gel. The early fractions, eluted with Et_2O–hexane (1:3 v/v), contained 29 mg (72%) of the hydroxy olefin **21** as a viscous, colorless liquid. This product was shown to have the same structure as the methyl (+)-epiallogibberate (**12a**) by comparison of ir (CCl_4), uv (95% EtOH), nmr ($CDCl_3$), and mass spectra and tlc R_f values (silica gel coating). The later fractions from the chromatograph, eluted with Et_2O, contained 32 mg (85%) of crystalline Ph_3PO, mp 154–156°.

A solution of 53 mg (0.18 mmol) of the hydroxy ester **21** and 1.0 ml of aqueous 4 *M* NaOH in 1.0 ml of MeOH was refluxed for 1 hr and then partitioned between $CHCl_3$ and aqueous 5% NaOH. The aqueous layer was acidified (HCl) to pH 1 and extracted with EtOAc. After the EtOAc extract had been washed with H_2O, dried, and concentrated, the white solid residue (53 mg) was recrystallized from MeOH–Et_2O to separate 40 mg (80%) of racemic epiallogibberic acid (**3**) as white prisms, mp 253–255° dec. Recrystallization from MeOH sharpened the decomposition point to 254–255.5° dec.

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.18; H, 7.11.

This product was shown to have the same structure as a sample of (+)-epiallogibberic acid by comparison of mass spectra, nmr spectra [$(CD_3)_2NCDO$], uv spectra (95% EtOH), and ir spectra ($CHCl_3$ containing 5% Et_3N).

Registry No.—**1**, 77-06-5; (±)-**3**, 28862-60-4; (+)-**3**, 13613-87-1; **4a**, 37741-45-0; **4b**, 38223-11-9; **5a**, 38229-34-4; **5b**, 38229-35-5; **5c**, 38229-36-6; **8a**, 38229-37-7; **8b**, 38229-38-8; **12a**, 34707-34-1; **12b**, 38229-40-2; **12c**, 38229-41-3; **13a**, 38229-42-4; **14a**, 38229-43-5; **14b**, 38229-44-6; **15**, 38229-45-7; **16a**, 38229-46-8; **16b**, 38229-47-9; **18**, 38229-48-0; **19a**, 38229-49-1; **19b**, 38229-50-4; **20**, 38229-51-5; **21**, 38229-52-6.

Reactivities of Polystyrene and Polypropylene toward *tert*-Butoxy Radical

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Di-*tert*-butylperoxy oxalate was decomposed at 45° under vacuum in benzene solutions of polystyrene, polypropylene, and several aromatic and aliphatic hydrocarbons. The relative reactivities of the substrates and the carbon–hydrogen bonds were measured from the ratio of *tert*-butyl alcohol and acetone formed. Both polymers were found to be less reactive than the corresponding simple model hydrocarbons: polypropylene was about one-half as reactive as calculated from 2,4-dimethylpentane and 2,2,4-trimethylpentane, and polystyrene was about one-fifth as reactive as polypropylene.

The autoxidation of polyolefins must proceed by a radical chain mechanism[1] similar to simple hydrocarbons, where hydrogen atom abstractions from the substrate by the peroxy and alkoxy radicals are among the important rate-determining steps.[2]

$$RH + ROO\cdot \longrightarrow R\cdot + ROOH$$

$$RH + RO\cdot \longrightarrow R\cdot + ROH$$

The reactivities of various hydrocarbons toward peroxy[3,4] and alkoxy[5] radicals have been determined by several investigators. Especially, those for *tert*-butoxy radical have been most extensively studied partly because the *tert*-butoxy radical can be produced rather easily from di-*tert*-butyl peroxide,[6] *tert*-butyl hypohalite,[5] di-*tert*-butylperoxy oxalate (DBPO),[7] and *tert*-butyl hyponitrite.[8]

To our knowledge, however, the reactivities of polyolefins toward the radicals have not yet been obtained. In the course of our study on the autoxidations of polyolefins, we measured the reactivities of the polymers toward oxy radicals. The objective of this work is to determine the relative reactivities of polystyrene and polypropylene toward *tert*-butoxy radical and to compare them with the simple, corresponding model hydrocarbons.

Experimental Section

Materials.—Polypropylene, kindly supplied by Mitsui Petrochemical Industries, was first soaked in benzene at room tem-

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perature for about 1 week. The insoluble fraction was separated by filtration. The soluble fraction was repeatedly precipitated from benzene solution by adding into excess methanol. It was finally dried *in vacuo* at room temperature. The intrinsic viscosity of the polypropylene determined at 45° in benzene was 0.180, and the number average molecular weight calculated by the following equation[9] was 9500.

$$[\eta] = 2.70 \times 10^{-4} M_n^{0.71}$$

The infrared spectrum of the purified polypropylene showed little absorption at 997 cm^{-1} but strong absorption at 975 cm^{-1}, indicating that little isotactic polypropylene was present.

Commercial polystyrene was purified like polypropylene using benzene and methanol as solvent and precipitant, respectively. The polystyrene solution was then washed successively with acid, water, alkali, and water. Finally its 2% solution of chloroform was introduced slowly into excess methanol while vigorously stirring to obtain white powder polystyrene. The purified polystyrene completely dissolved in methyl ethyl ketone, indicating that it is all atactic. The intrinsic viscosity of the polystyrene measured in benzene at 45° was 0.825, the calculated[10] number average molecular weight being 190,000.

$$[\eta] = 2.7 \times 10^{-4} M_n^{0.66}$$

The hydrocarbons were purified by conventional methods. The purities were higher than 99%. Di-*tert*-butylperoxy oxalate was prepared by the method of Bartlett, *et al.*[7]

Procedures.—Dried DBPO was weighed into the appropriate solution of substrate and benzene prepared beforehand. The aliquot of the solution (usually 0.5 ml) was taken into a 10-mm o.d. ampoule, which was degassed and sealed under vacuum (10^{-6} Torr). The tube was immersed into a water bath maintained at 45°, and DBPO was allowed to decompose completely in about its 10 half-lives. The half-life of DBPO at 45° was measured in several media, including viscous polymer solution, by following the rate of carbon dioxide evolution using a Toepler pump and it was obtained as 41 min, which is in good agreement with the previously reported value of 42 min in benzene solution.[7] After the decomposition, the ampoule was opened, internal standard was added by syringe, and the mixture was analyzed with glc equipped with digital integrator using a 3 mm × 7 m Carbowax 20M column. The temperature of the injection port and the column was kept below 90° to avoid the thermal decomposition of di-*tert*-butyl peroxide in glc. When the reaction mixture was too viscous to syringe directly, the ampoule was connected to the vacuum line and the volatile products and the internal standard were transferred first below 0° and finally at 50° into a trap cooled with liquid nitrogen under vacuum.

More than one run was performed in many of the solutions and the reproducibility was better than 5%. In order to minimize the effect of experimental error, k_a/k_d ratios were determined graphically from several runs rather than from one point measurement (see text).

Results and Discussion

On thermal decomposition, each molecule of DBPO quantitatively yields two *tert*-butoxy radicals and two molecules of carbon dioxide. The caged pair of *tert*-butoxy radicals either recombines to give di-*tert*-butyl peroxide (*t*-Bu_2O_2) or diffuses apart. The free *tert*-butoxy radicals may either abstract hydrogen from the substrate to give *tert*-butyl alcohol or may cleave to yield acetone and methyl radical.

$$(CH_3)_3CO\cdot + RH \xrightarrow{k_a} (CH_3)_3COH + R\cdot \quad (1)$$

$$(CH_3)_3CO\cdot \xrightarrow{k_d} CH_3COCH_3 + CH_3\cdot \quad (2)$$

Quite a small amount of isobutylene oxide was observed among the products, which must arise by the attack of *tert*-butoxy radical on the terminal hydrogen of DBPO and subsequent scission of the radical formed from DBPO.

$$(CH_3)_3CO\cdot + DBPO \rightarrow (CH_3)_3COH + (CH_3)_3COOCOCOOOC(CH_3)_2CH_2\cdot \rightarrow (CH_3)_3CO\cdot + 2CO_2 + (CH_3)_2C(\diagup O \diagdown)CH_2 \quad (3)$$

The methyl radical produced in reaction 2 presumably reacts with the substrate to yield methane and alkyl radical. The alkyl radicals are assumed to give a dimer by combination or a parent substrate and olefin by disproportionation. Under these circumstances, the relative reactivities of various hydrocarbons can be measured indirectly[11] by measuring the amount of *tert*-butyl alcohol, isobutylene oxide, and acetone formed. The *tert*-butyl alcohol produced in reaction 3 is corrected. The measurement of the substrate reactivities by the direct method[11] by following the competitive disappearance of the substrates themselves was not employed, since in this system the parent hydrocarbons are reproduced from the corresponding radical by disproportionation and the substrate may also be attacked by methyl radical formed in reaction 2.

$$\frac{[t\text{-BuOH}]}{[Me_2CO]} = \frac{k_a[RH]}{k_d} \quad (4)$$

Results of the decomposition of DBPO in benzene with added aromatic compounds and polystyrene are summarized in Table I. In neat benzene, only 88.6% of the initial *tert*-butoxy group could be accounted for. Extensive efforts were not devoted to find the missing *tert*-butoxy group, but this may be bound to the aromatic ring as, for example, *tert*-butyl phenyl ether. The amount of missing *tert*-butoxy group decreased in general with increasing concentration of the hydrogen donor. In polystyrene–benzene media, considerable *tert*-butoxy group was always unaccounted for. They may be bound to the polymer chain as *tert*-butyl ether, as was found in the decomposition of DBPO in bulk polypropylene.[1]

Table I
Decomposition of DBPO in Benzene Solution at 45°

Substrate, RH	[RH], *M*	—Products,[a] % of *t*-BuO— *t*-Bu_2O_2	Me_2CO	*t*-BuOH	*t*-BuO accounted for, %
Neat benzene		4.5	40.0	43.8	88.6
tert-Butylbenzene	1.08	5.3	31.2	60.3	97.0
tert-Butylbenzene	1.62	5.2	24.0	64.0	93.4
tert-Butylbenzene	3.23	7.9	14.8	72.5	95.2
tert-Amylbenzene	0.98	5.8	20.8	68.0	94.6
tert-Amylbenzene	1.47	6.1	16.4	74.4	96.9
tert-Amylbenzene	1.96	6.1	12.5	76.9	95.5
Cumene	0.60	5.4	11.6	76.8	93.8
Cumene	0.90	5.7	8.9	82.1	96.7
Cumene	1.44	6.4	5.4	88.7	100
Cumene	1.80	5.8	4.5	90.8	101
Polystyrene[b]	0.175	4.2	38.4	43.3	85.9
Polystyrene	0.341	4.5	40.3	46.9	92.1
Polystyrene	0.803	4.6	35.2	43.6	84.1
Polystyrene	1.356	5.1	35.7	48.0	88.8
Polystyrene	1.448	4.2	34.4	47.0	85.5

[a] [DBPO] = 0.1 *M*; 0.1–0.3% of isobutylene oxide was also found. [b] Concentrations are in monomer units.

Figure 1 shows the plots of the *tert*-butyl alcohol/acetone ratio as a function of the substrate concentration. Satisfactory straight lines are obtained and the

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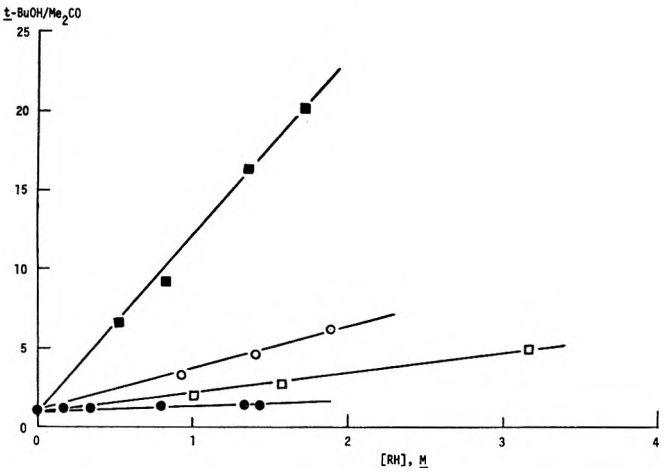

Figure 1.—Decomposition of DBPO at 45° in benzene solution of cumene (■), *tert*-amylbenzene (○), *tert*-butylbenzene (□), and polystyrene (●).

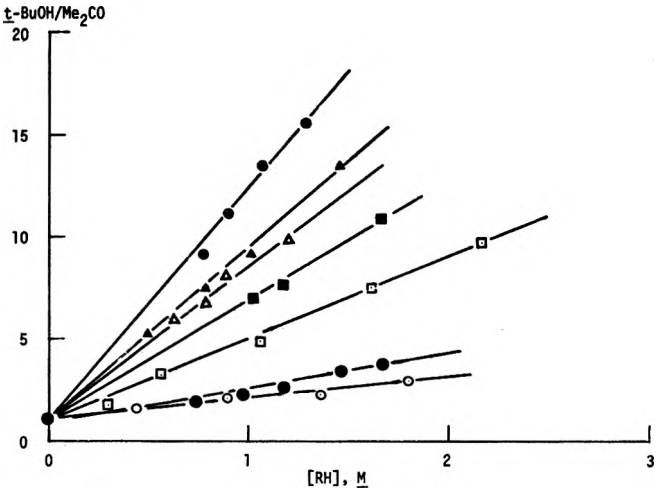

Figure 2.—Decompositions of DBPO at 45° in benzene solutions of heptane (◎), hexane (▲), 2,3-dimethylbutane (△), pentane (■), 2,4-dimethylpentane (□), 2,2,4-trimethylpentane (●), and polypropylene (⊙).

calculated k_a/k_d values from the slope are summarized in Table II. It shows that cumene is 7.1 times as reactive as *tert*-butylbenzene, which agrees well with the value of 7.3 obtained by Walling and Jacknow[5] at 40° using *tert*-butyl hypochlorite.

TABLE II

RELATIVE RATES OF HYDROGEN ABSTRACTION BY *tert*-BUTOXY RADICAL AT 45°

Substrate	k_a/k_d per molecule	Relative k_a per hydrogen
Benzene	0.098	Aromatic, 1
tert-Butylbenzene	1.40	Primary, 10.7
tert-Amylbenzene	3.07	Secondary, 54.1
Cumene	11.46	Tertiary
Polystyrene	0.186	benzylic, 656

Solvent effects on the k_a/k_d ratio have been observed and it is reported that olefinic and polar solvents give a higher value for k_d while the hydrogen atom abstraction is relatively solvent insensitive.[12] However, k_d may be assumed to be virtually constant for the present system of nonpolar aromatic hydrocarbons in excess benzene solvent. The calculated relative reactivities of the various types of carbon–hydrogen bonds are also summarized in Table II.[13] It is quite surprising that the observed k_a/k_d for polystyrene is only 0.186, 1.5% of the calculated value of 12.3.

Figure 2 shows the plots of the *tert*-butyl alcohol/acetone ratio as a function of substrate concentrations in the decomposition of DBPO in benzene solutions of polypropylene and several aliphatic hydrocarbons. More than 90% of the initial *tert*-butoxy group was always accounted for in each experiment, with less missing *tert*-butoxy group with increasing concentrations of the substrate. The calculated k_a/k_d values are summarized in Table III. Assuming that k_d is virtually constant in the present system, the relative reactivities of carbon–hydrogen bonds were calculated. The relative reactivities of the primary, secondary, and tertiary carbon–hydrogen bonds were calculated from the data for pentane, hexane, heptane, and 2,3-dimethylbutane. In Table III are also shown the values relative to aromatic hydrogen, and it gives the relative reactivity series of 1:6.9:20 for primary, secondary, and tertiary aliphatic hydrogens This is only in fair agreement with the relative reactivities of 1:10:44 obtained by Walling and Jacknow[5] at 40° for butane and 2,3-dimethylbutane. However, since the reactivity of the primary hydrogen is obtained as a small difference between large quantities, a small experimental error will produce quite a large error in the relative reactivity series. In fact, if the relative reactivities of primary, secondary, and tertiary hydrogens are 1:5:20, the relative reactivities of pentane, hexane, heptane, and 2,3-dimethylbutane are 1:1.28:1.56:1.44, whereas, if the relative reactivities of hydrogens are 1:10:40 instead, the relative reactivities of these four compounds change to 1:1.30:1.61:1.39. Thus, the relative reactivities of hydrogens change drastically with a small change in the reactivities of the substrates.

TABLE III

RELATIVE RATES OF HYDROGEN ABSTRACTION BY *tert*-BUTOXY RADICAL AT 45°

Substrate	k_a/k_d per molecule	Relative k_a per hydrogen
Benzene	0.098	Aromatic, 1
Pentane	6.68	Primary, 8.75
Hexane	8.50	Secondary, 60.6
Heptane	10.54	Tertiary, 176
2,3-Dimethylbutane	7.29	
2,4-Dimethylpentane	4.30	
2,2,4-Trimethylpentane	2.13	
Polypropylene	0.98	

The k_a/k_d ratios for 2,4-dimethylpentane and 2,2,4-trimethylpentane, relevant model compounds for polypropylene, calculated with the values in Table III are 9.24 and 6.85, respectively. Thus, the observed reactivities of 2,4-dimethylpentane and 2,2,4-trimethylpentane are about one-third to one-half the calculated reactivities. The low reactivities of these compounds toward *tert*-butoxy radical have been already reported

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(13) The data in Table II would be more useful if the contribution from aromatic abstraction were ignored in calculating k_a/H, since the removal of an aromatic hydrogen may not be direct abstraction but probably addition–abstraction and has little relationship to the other k_a's. On this basis, the relative k_a per hydrogen for primary, secondary, and tertiary benzylic hydrogens in Table II is 1:5.4:68. However, the k_a values are given relative to aromatic hydrogen so as to compare directly the primary and secondary hydrogens of aromatic and aliphatic hydrocarbons.

by Brook[14] and these have been also observed for phenyl,[15] nitrophenyl,[16] and methyl[17] radicals and hydrogen atom.[18] This is explained as being due to the preferred conformation of the substrates.[14,15,17]

The observed reactivity of polypropylene is only about 20% of the calculated reactivity from the values in Table III. Considering the structure and numbers of the primary, secondary, and tertiary hydrogens, the reactivity of polypropylene is expected to be about one-half of that of 2,4-dimethylpentane and roughly the same as that of 2,2,4-trimethylpentane. Table III indicates, however, that toward *tert*-butoxy radical polypropylene is about one-half as reactive as expected from the corresponding model compounds.

Also, polystyrene is much less reactive than expected, as shown in Table II. Metz and Mesrobian[19] suggested that the low oxidizability of polystyrene was due to the steric hindrance and steric inhibition of resonance for the attack of peroxy radical on polystyrene. As they pointed out, if the phenyl groups on alternating carbon atoms are out of plane of the polymer chain owing to their close proximity to each other, benzyl resonance (as large as 13 kcal/mol[20]) cannot occur. However, if this is the sole reason for its low reactivity, polystyrene should be at least as reactive as *tert*-amylbenzene. Table II shows that polystyrene is only $^1/_{16}$ as reactive as *tert*-amylbenzene.

The following argument shows that the polar effect is unimportant. It is known that aliphatic secondary hydrogens are more reactive than the benzylic hydrogen of toluene toward an electronegative chlorine atom (electron affinity: 3.64 eV[21]). This is explained by the inductive electron-withdrawing effect of the phenyl group. The *tert*-butoxy radical (electron affinity: 2.6 eV[22]) is also a powerful electron acceptor, preferentially attacking points of high electron availability, but not as strong as chlorine atom. Tables II and III indicate that the primary and secondary hydrogens of *tert*-butylbenzene and *tert*-amylbenzene, respectively, are about as reactive as aliphatic primary and secondary hydrogens and that benzylic hydrogen is much more reactive than the corresponding aliphatic hydrogen. Thus, the electron-withdrawing properties of the phenyl group may not be responsible for much lower reactivity of polystyrene than polypropylene.

If the reactivity of the tertiary hydrogen of polystyrene is same as that of aliphatic tertiary hydrogen, the k_a/k_d is calculated to be 5.34. Thus, the extraordinarily low reactivity of polystyrene may be ascribed mainly to the preferred conformation of the molecule: the bulky phenyl group on alternating carbon atoms must protect tertiary and also, probably, secondary hydrogens from the attack of rather bulky *tert*-butoxy radical.

However, the discussion given above does not explain why polymers are less reactive than the corresponding model compounds. One possible explanation may be that the polymers are special in having coiled configurations. Although benzene is a good solvent and polymers are expected to extend their chains in the benzene solution, only a limited fraction of the abstractable hydrogens may be exposed to the *tert*-butoxy radical.[23] The study of the effects of solvent, molecular weight, and temperature on the reactivities of polymers is now in preparation.

The preferential intramolecular propagation in the autoxidation of 2,4-dimethylpentane[24] and 2,4,6-trimethylheptane[25] may be partly because the approach of the bulky peroxy radical to the tertiary hydrogen is hindered by the methyl groups on alternating carbon atoms. This effect may be more important in the oxidations of polystyrene and polypropylene.

Registry No.—Polystyrene, 9003-53-6; polypropylene, 9003-07-0; *tert*-butoxy radical, 3141-58-0; di-*tert*-butylperoxy oxalate, 1876-22-8.

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Photostimulated Aromatic SRN1 Reactions

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Acetone enolate ion is unreactive with halobenzenes and related substrates in liquid ammonia in the dark, but reaction occurs rapidly when stimulated by near-ultraviolet light, to form phenylacetone in high yields, plus small amounts of 1,1-diphenyl-2-propanone. Phenylacetone was obtained in 57–95% yield from PhI, PhBr, PhCl, PhF, Ph_2S, $Ph_3S^+Cl^-$, Ph_2Se, and $PhNMe_3^+I^-$, and in small yield from Ph_2O and $PhOPO(OEt)_2$. An electron transfer, radical mechanism (SRN1) is indicated by the inhibitory effect of radical scavengers (O_2 and di-*tert*-butyl nitroxide).

Bromobenzene does not react with acetone enolate ion in liquid ammonia in the dark, and bromobenzene in liquid ammonia survives exposure to near-ultraviolet radiation. However, under irradiation, bromobenzene and acetone enolate ion react rapidly to form phenylacetone in high yield (eq 1). Even a 150-W

$$C_6H_5X + CH_3COCH_2^- \xrightarrow[NH_3]{h\nu} C_6H_5CH_2\overset{O}{\overset{\|}{C}}CH_3 + X^- \quad (1)$$

tungsten light bulb external to a Pyrex flask causes reaction to occur.

Several other substituted benzenes, with various nucleofugic groups, also undergo this photochemical reaction, as reported in Table I. With one minor exception, no reaction occurs without irradiation; the exception is that iodobenzene undergoes a slow dark reaction which, in two experiments, consumed about 5 and 15% of it during 3 hr. Most of the reactions of Table I were conducted in Pyrex flasks irradiated by 350-nm ultraviolet lamps in a Rayonet photochemical reactor.[2]

Rather long irradiation times were employed before the great facility of this photochemical reaction was appreciated. In later experiments, portrayed in Figure 1, samples were analyzed at frequent intervals and information as to the dependence of rate on identity of nucleofugic substituent was obtained. These experiments were all conducted in the same way, in the identical flask and with the same disposition of lamps in the reactor, but there may have been some variation of radiation intensity. Nevertheless, the results are at least qualitatively significant. They show the order of mobility: I ~ Br > SPh ≫ Cl > F ≫ OPh. Iodo- and bromobenzene were totally consumed within 5 min, the time of first observation.

Three methods for preparation of acetone enolate ion were employed. For most of the reactions of Table I, as well as for those of Figure 1, it was made by reaction of potassium metal with acetone in ammonia. This reaction,[3] which we also employed to prepare acetone enolate ion for another study,[4] has now been found to reduce about 35% of the acetone to isopropyl alcohol. Acetone enolate ion obtained by the K metal method is thus contaminated by isopropoxide ion.

For runs 11, 12, 13, 21, and 22 of Table I, the enolate ion was prepared by reaction of acetone with KNH_2 which had been formed *in situ* by iron-catalyzed reaction of K metal with the solvent. For runs 15–17, Table I, the enolate ion was made by interaction of acetone with potassium *tert*-butoxide, either supplied as such (run 17) or formed in the ammonia solvent by the remarkably slow reaction of K metal with *tert*-butyl alcohol.

Benzene was a prominent by-product of reactions with the enolate ion prepared by the K metal method, but was scarcely detectable when the enolate had been prepared by the KNH_2 or *t*-BuOK method. The implication that benzene arises from hydrogen atom abstraction from isopropoxide ion is substantiated by the fact (runs 12 and 13) that the benzene yield was increased when isopropoxide ion was intentionally added to enolate prepared by the KNH_2 method.

The virtual absence of benzene as a product from reactions with isopropoxide-free enolate ion shows that the phenyl radical is loath to abstract a hydrogen atom from ammonia.

Reactions with enolate ion prepared by the KNH_2 method were much slower than with preparations by the other methods. The reaction solutions were dark gray, probably owing to colloidal iron metal, and mere exclusion of light may have been responsible. However, it is not clear why the addition of isopropoxide ion (runs 12 and 13) enabled the reactions to occur more rapidly.

In a short series of reactions utilizing enolate prepared by the *t*-BuOK method, the time required to achieve half reaction was found to increase approximately linearly with reactant concentration. These reactions involved bromobenzene in concentrations from 0.1 to 0.6 *M*, with acetone enolate ion always in about threefold excess. One factor contributing to lower reactivity at higher reactant concentrations is the accumulation of crusts on the walls of the reaction flask above the solution; the crusts partially screen the solution from irradiation. Another may be absorption of light by substances in solution, causing a reduction of light intensity in the interior of the flask. Finally, the bimolecular termination steps of a radical chain mechanism (see below) become relatively more important at higher reagent concentrations.

When irradiation was provided by an external 150-W tungsten lamp, 1 hr was required for complete reaction of bromobenzene, in contrast to less than 5 min in the photochemical reactor. At the lower intensity of illumination, study of the effects of other substances on reaction rate was convenient. As shown in Figure 2, reaction was exceedingly slow in the presence of 4.3 mol % of di-*tert*-butyl nitroxide, a radical scavenger.[5]

(1) Grateful recipient of a fellowship from the Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina.

(2) Product of Southern New England Ultraviolet Co., Middletown, Conn.

(3) A. J. Birch, *J. Proc. Roy. Soc. New South Wales*, **83**, 245 (1949).

(4) R. A. Rossi and J. F. Bunnett, *J. Amer. Chem. Soc.*, **94**, 683 (1972).

(5) A. K. Hoffmann, A. M. Feldman, E. Gelblum, and W. G. Hodgson, *ibid.*, **86**, 639 (1964).

TABLE I

PHOTOCHEMICAL REACTIONS OF MONOSUBSTITUTED BENZENES WITH ACETONE ENOLATE ION IN LIQUID AMMONIA AT −33°

Run	Substrate	Registry no.	[Substrate], M	[$CH_3COCH_2^-$],[a] M	Time, min	Products,[b] % Substrate recovered	C_6H_6	$PhCH_2COCH_3$	$Ph_2CHCOCH_3$
1	PhI	591-50-4	0.087	Nil	180	99	1		
2			0.15	0.51	180[c]	94	2	2	
3			0.13	0.39	180[c]	83	4	8	
4			0.14	0.50	180	0	22	67	11
5			0.22	0.75	180	0	*d*	61[e]	*d*
6			0.14	0.50	5	0	20	67	10
7	PhBr	108-86-1	0.076	Nil	60	95	0.5		
8			0.076	0.43	80[c]	98	0.3		
9			0.076	0.43	80	0	22	73	6
10			0.060	0.35	5	0	27	64	5
11			0.095	0.38[f]	50	0	0.5	88	9
12			0.092	0.29[f,g]	19	0	9	78	9
13			0.089	0.23[f,h]	15	0	32	58	5
14			0.089	0.42	60[i]	0	21	65	11
15			0.095	0.24[j]	11	0	0.6	85	14
16			0.089	0.38[k]	80[i]	0	0.3	94	8
17			0.34	1.04[l]	110	<0.1	<0.1	86[m]	14
18	PhCl	108-90-7	0.063	0.44	180	0	31	61[n]	5
19	PhF	462-06-6	0.066	0.48	200	0	31	60[n]	3
20	PhSPh	139-66-2	0.063	0.44	30	0	26	66[o]	5
21	$Ph_3S^+Cl^-$	4270-70-6	0.029	0.46[f]	70	*d*	1	75[p]	2
22	PhSePh	1132-39-4	0.024	0.30[f]	30	0	1	95[q]	3
23	PhOPh	101-84-8	0.072	0.47	250	77	6	14[n,r]	0
24	$PhNMe_3^+I^-$	98-04-0	0.035	0.44	60	*d*	37	57	1
25	$PhOPO(OEt)_2$	2510-86-3	0.078	0.40	250	*d*	11	13[s]	0

[a] Prepared from acetone and K metal unless otherwise noted; concentration listed assumes quantitative conversion of acetone to enolate ion. [b] Yield by glpc unless otherwise noted. [c] Dark. [d] Not determined. [e] Isolated and weighed. [f] Prepared from acetone and KNH_2. [g] $(CH_3)_2CHO^-K^+$ (0.13 *M*) also present. [h] $(CH_3)_2CHO^-K^+$ (0.23 *M*) also present. [i] Irradiation by 150-W tungsten bulb. [j] From acetone and *t*-BuOK (0.39 *M*). [k] From acetone and *t*-BuOK (0.47 *M*). [l] From acetone and commercial *t*-BuOK (1.18 *M*). [m] Yield of isolated and weighed phenylacetone, 73%. [n] *Ca.* 1% 1-phenyl-2-propanol also detected. [o] C_6H_5SH (97%) also determined. [p] From 10.2 mmol of $Ph_3S^+Cl^-$, 0.11 mmol of C_6H_6, 7.66 mmol of phenylacetone, 0.10 mmol of diphenylacetone, 2.22 mmol of PhSPh, and 5.28 mmol of PhSH were obtained. [q] PhSeH (83%) also formed, isolated as PhSeSePh. [r] Phenol (20%) also determined. [s] Phenol (71%) also determined.

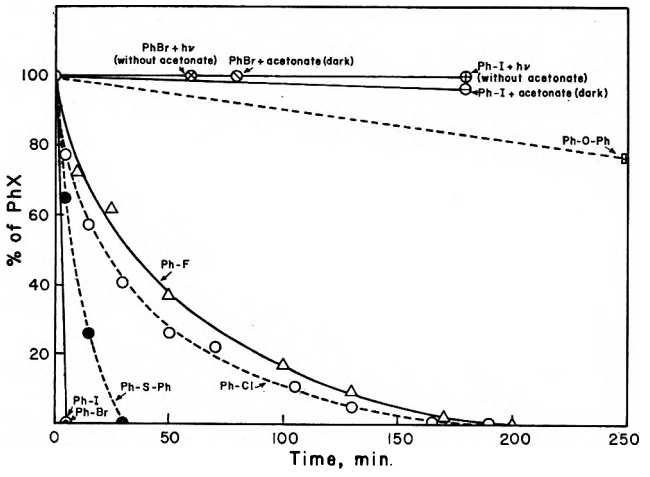

Figure 1.—Per cent of substrate remaining after various times of exposure in the photochemical reactor (see text). Reaction solutions were *ca.* 0.07 *M* in substrate and *ca.* 0.45 *M* in acetone enolate ion (prepared by K metal method), in ammonia at reflux under N_2 atmosphere: ⊘, PhBr + acetone enolate in dark; ⊗, PhBr with illumination but no enolate ion; ⊖, PhI + acetone enolate ion in dark; ⊕, PhI with illumination but no enolate ion.

Even 0.68 mol % of this nitroxide appreciably retarded the reaction. Oxygen is also an inhibitor, as shown by the sluggishness of reaction under air. These experiments testify to a radical chain mechanism.

Reaction Mechanism.—Of three types of mechanism which come to mind, two are easily rejected, while the third gives a good account of the facts.

The possibility that these are photo-SNAr reactions, such as occur between nitrophenyl ethers and diverse nucleophiles,[6] is rejected because those reactions do not display radical characteristics, because bromobenzene, etc., do not show appreciable absorption at wavelengths above 290 nm, and in view of the very short irradiation times which sufficed in most of our experiments. The possibility that phenyl radicals are generated by photolytic homolysis of bonds between carbon and halogen or other nucleofugic groups is rejected because even homolysis of iodobenzene requires long illumination (*ca.* 20 hr) with 253.7-nm light,[7] and photolysis of other halobenzenes is even slower.[8]

The mechanism of Scheme I is compatible with our observations.

This is a photostimulated SRN1 mechanism.[9] Steps 3, 4, and 5 constitute a cycle with radical intermediates,

(6) E. Havinga, R. O. de Jongh, and M. E. Kronenberg, *Helv. Chim. Acta*, **50**, 2550 (1967); R. L. Letsinger, O. B. Ramsay, and J. H. McCain, *J. Amer. Chem. Soc.*, **87**, 2945 (1965); F. Pietra, *Quart. Rev., Chem. Soc.*, **23**, 519 (1969).

(7) W. Wolf and N. Kharasch, *J. Org. Chem.*, **30**, 2493 (1965).

(8) N. Kharasch, R. K. Sharma, and H. B. Lewis, *Chem. Commun.*, 418 (1966).

(9) J. K. Kim and J. F. Bunnett, *J. Amer. Chem. Soc.*, **92**, 7463, 7464 (1970).

SCHEME I

$$\text{Electron source} + \text{PhX} \xrightarrow{h\nu} [\text{PhX}]\cdot^- + \text{residue} \quad (2)$$

$$[\text{PhX}]\cdot^- \longrightarrow \text{Ph}\cdot + \text{X}^- \quad (3)$$

$$\text{Ph}\cdot + \text{CH}_3\text{COCH}_2^- \longrightarrow [\text{PhCH}_2\text{COCH}_3]\cdot^- \quad (4)$$

$$[\text{PhCH}_2\text{COCH}_3]\cdot^- + \text{PhX} \longrightarrow [\text{PhX}]\cdot^- + \text{PhCH}_2\text{COCH}_3 \quad (5)$$

$$\text{Termination steps} \quad (6)$$

and thus accommodate the inhibition experiments (Figure 2), which indicate a radical chain mechanism.

Oxygen and di-*tert*-butyl nitroxide may interfere with propagation of the reaction chain by trapping phenyl radicals and/or by taking electrons from $[\text{PhCH}_2\text{COCH}_3]\cdot^-$ radical anions, in the latter case being reduced to $O_2\cdot^-$ and di-*tert*-butylhydroxylamine anion, respectively.[10]

The mechanism of Scheme I is very similar to that previously proposed[4] for condensation of halobenzenes and other substrates with acetone enolate ion stimulated by K metal in liquid ammonia, reactions which have many characteristics in common with these light-stimulated reactions. Photostimulation of *aliphatic* SRN1 reactions has been reported.[11] Irradiation of solutions of halobenzenes with dimethylaniline in methanol gives rise to phenyl radical intermediates, and reaction steps similar to our steps 2 and 3 have been proposed.[12]

The identity of the electron source in step 2 is not clear. Possibilities are the enolate ion itself, or an enolate ion derived from an aldol condensation product of acetone. Further investigation of this question is planned.

Synthetic Utility.—Run 17, Table I, was carried out on a preparative scale and afforded 21 g of pure phenylacetone. The only by-product was 1,1-diphenyl-2-propanone. It demonstrates the potentiality of these reactions for synthesis. In contrast to similar reactions provoked by alkali metals,[4] the phenylacetone obtained in the present study is virtually free of 1-phenyl-2-propanol. In utilization of the present method for the purpose of synthesis, care must be taken to exclude air; see the run under air in Figure 2.

Experimental Section

Reactions Reported in Figure 1.—In a typical run, a solution of potassium acetone enolate was prepared by reaction of 5.4 g (0.138 mol) of potassium metal with 10.4 ml (0.142 mol) of acetone in 320 ml of ammonia under nitrogen in a flask provided with a cold finger condenser cooled by solid CO_2 in 2-propanol. Chlorobenzene (2.0 ml, 0.02 mol) was added, the solution was stirred and kept for 15 min in the dark, and a sample was taken. The reaction flask was then placed in the photochemical reactor equipped with 350-nm lamps, and *ca.* 1-ml samples were taken, by means of a piece of 8-mm glass tubing J-shaped at the lower end, after measured periods of irradiation. Each sample was added to 1 ml of water; the mixture was extracted with 1 ml of diethyl ether and a portion of the ether layer was examined by glpc on a column of 20% Carbowax 20M on Chromosorb P, with thermal conductivity detector. The peaks for chlorobenzene and phenylacetone were suitably corrected for molar response; the per cent of chlorobenzene unreacted plotted in Figure 1 represents (moles chlorobenzene)/(moles chlorobenzene plus moles phenylacetone) and, in view of the substantial amount of benzene formed (see below), is something of an overstatement. When, after 190 min irradiation, chlorobenzene could no longer be detected, the reaction mixture was treated with excess NH_4Cl, 200 ml of diethyl ether was added together with measured amounts of toluene and *p*-dichlorobenzene to act as internal standards, the ammonia was allowed to evaporate, and water was added. The ether layer was washed with water, dried over anhydrous Na_2SO_4, and examined by glpc, suitable molar response corrections being made. Obtained were benzene (31%), phenylacetone (61%), 1,1-diphenyl-2-propanone (5%), and about 1% of material with the same retention time as that of 1-phenyl-2-propanol.

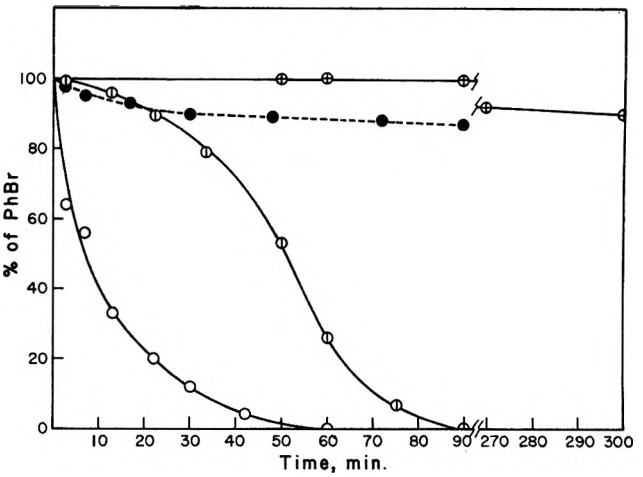

Figure 2.—Per cent of bromobenzene remaining after various times of exposure to external 150-W tungsten lamp, as affected by radical scavengers: ○, without scavengers; ①, with 0.68 mol % di-*tert*-butyl nitroxide; ⊕, with 4.3 mol % di-*tert*-butyl nitroxide; ●, under air. In all experiments, PhBr was *ca.* 0.09 *M*, and acetone enolate ion (prepared by K metal method) was *ca.* 0.45 *M*, in ammonia at reflux.

Reactions Reported in Figure 2.—Essentially the same technique was employed, except that irradiation was provided by a 150-W tungsten lamp placed about 10 cm from the wall of the reaction flask and somewhat above it; the flask and lamp were crudely surrounded by aluminum foil to reduce glare into the laboratory.

Reaction of Acetone with Potassium Metal in Ammonia.—To a stirred solution of 6.9 g (0.177 mol) of potassium metal in 360 ml of anhydrous liquid ammonia at reflux was added acetone, drop by drop, until the blue color was discharged; a total of 13.8 ml (0.188 mol) of acetone was required. Excess NH_4Cl was added, followed by diethyl ether (200 ml) and toluene (10 ml), and the ammonia was evaporated through a condenser at −30 to −20°. The toluene was to act as an internal standard for glpc purposes. Glpc analysis of a sample of the remaining ether solution indicated a 32% yield of 2-propanol and 38% recovery of acetone; there were also some small peaks for less volatile substances. Water was added to the evaporation residue, and glpc analysis of a sample of the ether layer indicated 25% of 2-propanol and 38% of acetone. The infrared spectrum of a sample of the 2-propanol formed, isolated by glpc, was identical with that of an authentic sample. The balanced equation, $2CH_3COCH_3 + 2K \rightarrow CH_3COCH_2K + (CH_3)_2CHOK$, would accord with the observed consumption of nearly equimolar amounts of potassium and acetone and would call for equimolar amounts of acetone and 2-propanol to appear as products of the experiment described. It is not clear why less 2-propanol than acetone was found, or why these substances account for only 70% of the acetone originally introduced.

Preparative Scale Reaction (Run 17).—Into a 2-l., three-neck, round-bottom flask equipped with magnetic stirrer, dropping funnel, and cold finger condenser cooled by solid CO_2 in 2-propanol, dried and flushed with nitrogen, were placed 100 g (0.89 mol) of potassium *tert*-butoxide and 700 ml of anhydrous ammonia. Not all the potassium *tert*-butoxide dissolved. Acetone (55 ml, 0.75 mol) was added dropwise with good stirring over a

(10) We thank a referee for pointing out the electron-theft possibility.

(11) N. Kornblum, R. E. Michel, and R. C. Kerber, *J. Amer. Chem. Soc.*, **88**, 5662 (1966); G. A. Russell and W. C. Danen, *ibid.*, **88**, 5663 (1966); **90**, 347 (1968); N. Kornblum and F. W. Stuchal, *ibid.*, **92**, 1804 (1970).

(12) C. Pac, T. Tosa, and H. Sakurai, *Bull. Chem. Soc. Jap.*, **45**, 1169 (1972).

period of 40 min. After a further 15 min, 25 ml (0.24 mol) of bromobenzene was added *via* the same dropping funnel, the reaction flask was placed in the photochemical reactor equipped with 350-nm lamps, and irradiation was started, the solution being constantly stirred and gently swept with nitrogen. Samples (*ca.* 1 ml) were taken by the procedure described above and analyzed by glpc; after 110 min, the bromobenzene had all reacted. To the reaction mixture, solid NH_4Cl was added until the orange-yellow solution became pale yellow, 350 ml of ether was added, and the ammonia was evaporated. Sufficient water was added to dissolve the inorganic salts and the ether layer was separated. The water layer was extracted with a further 150 ml of ether. The combined ether extracts were washed thrice with 100-ml portions of water saturated with NaCl and dried over anhydrous Na_2SO_4. One-tenth of the ether solution was separated from the rest; measured amounts of toluene and *p*-dichlorobenzene were added to it; glpc analysis of the resulting mixture indicated 86% of phenylacetone and 14% of 1,1-diphenyl-2-propanone to have been formed, but no significant amount of benzene. The remaining nine-tenths of the ether solution was concentrated and distilled under vacuum; 21.0 g (73%) of phenylacetone, bp 103–106° (19 Torr), of purity >98% as judged by glpc and nmr, was isolated.

Registry No.—Acetone enolate ion, 24262-31-5.

Acknowledgments.—We thank Dr. William J. Boyle, Jr., for a sample of di-*tert*-butyl nitroxide, and Professor Frederick D. Greene for suggesting its use.

Mechanisms of SNi Reactions. The Effect of Aralkyl Group Structure on Ion-Pair Return in the Decomposition of Aralkyl Thiocarbonates[1]

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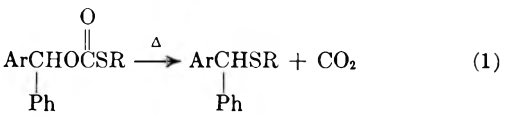
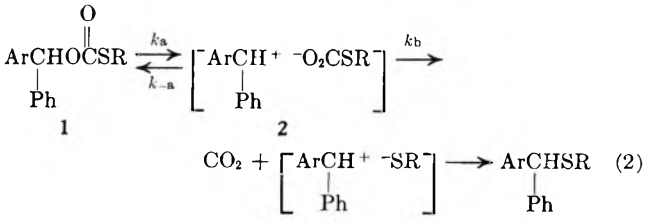
The effect of a change in the nature of Ar in $ArPhCH^+$ on the extent and stereochemistry of ion-pair return accompanying the decomposition of aralkyl *S*-methyl thiocarbonates (eq 2) has been examined by investigating the behavior of *p*-methylbenzhydryl and α-naphthylphenylcarbinyl *S*-methyl thiocarbonates (**1b** and **1c**) and comparison of the results with those obtained earlier with *p*-chlorobenzyhydryl *S*-methyl thiocarbonate. The change from Ar = *p*-ClC_6H_4 to *p*-$CH_3C_6H_4$ leads to a decrease in the percentage of ion pairs **2** undergoing return and to an increase in the fraction doing so with racemization, in accord with the effect expected of a structural change that leads to an increase in the stability of the carbonium ion portion of the ion pair, and, where appropriate, with the results of Goering and Hopf on a related system. In contrast the change from Ar = *p*-ClC_6H_4 to α-$C_{10}H_7$, while also leading to a carbonium ion of increased stability, leads to only very small changes in the extent and stereochemistry of ion pair return. The implications of this result are discussed.

Previous work[2] has shown that the thermal decomposition of aralkyl thiocarbonates (eq 1), which occurs



(1)

when these compounds are heated in a polar aprotic solvent at 130–170°, takes place *via* the two-step mechanism outlined in eq 2 and that extensive ion-pair



(2)

return from **2** to thiocarbonate (step k_{-a}) accompanies the decomposition.

In this earlier study[2] the variation in both the extent and stereochemistry of ion-pair return was investigated for a trio of *p*-chlorobenzhydryl (Ar = *p*-ClC_6H_4) thiocarbonates as a function of (1) changes in the structure of the thioalkyl (RS–) group and (2) a change from a relatively polar (benzonitrile) to a less polar solvent (bromobenzene). In the present investigation we have explored the effect of changes in the structure of Ar in the carbonium ion portion of **2** on ion-pair return by studying the decomposition of a pair of aralkyl *S*-methyl thiocarbonates in benzonitrile and comparing the results with those obtained earlier[2] for the decomposition of *p*-chlorobenzhydryl *S*-methyl thiocarbonate (**1a**, Ar = *p*-ClC_6H_4; R = CH_3) in this solvent. The two thiocarbonates chosen for study were *p*-methylbenzhydryl (**1b**, Ar = *p*-$CH_3C_6H_4$; R = CH_3) and the α-naphthylphenylcarbinyl (**1c**, Ar = α-$C_{10}H_7$; R = CH_3) *S*-methyl thiocarbonate.

The reasons for choosing these two particular thiocarbonates were as follows. As judged by the rates of solvolysis of the corresponding aralkyl chlorides in aqueous acetone,[3,4] both *p*-$CH_3C_6H_4CHPh^+$ and α-$C_{10}H_7CHPh^+$ are more stable carbonium ions than *p*-$ClC_6H_4CHPh^+$. However, while with Ar = *p*-$CH_3C_6H_4$ this increase in carbonium ion stability is achieved with no change in the steric requirements of the Ar group, this is not the case with Ar = α-$C_{10}H_7$, since α-naphthyl represents a significantly bulkier group than *p*-chlorophenyl. Our interest was first to compare the effect of the change from Ar = *p*-ClC_6H_4 to *p*-$CH_3C_6H_4$ on the extent and stereochemistry of ion-pair return in the thiocarbonate decomposition with the results of Goering and Hopf[5] on the effect of the same change on ion-pair return in the solvolysis of para-substituted benzhydryl *p*-nitrobenzoates. Second, we were interested in the extent to which the change in steric bulk of Ar on going to Ar = α-$C_{10}H_7$ would have any significant effect on ion-pair return.

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) J. L. Kice, R. L. Scriven, E. Koubek, and M. Barnes, *J. Amer. Chem. Soc.*, **92**, 5608 (1970).

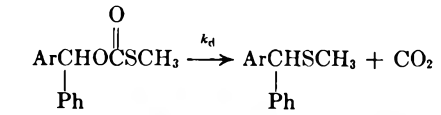
(3) L. Verbit and E. Berlinger, *ibid.*, **86**, 3307 (1964).

(4) J. R. Fox and G. Kohnstam, *Proc. Chem. Soc.*, 115 (1964).

(5) H. L. Goering and H. Hopf, *J. Amer. Chem. Soc.*, **93**, 1224 (1971).

Results

Using optically active and ^{18}O-labeled thiocarbonates one can measure the rates associated with the following processes.



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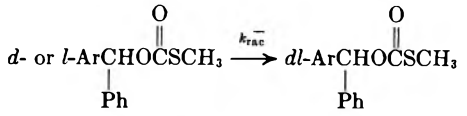

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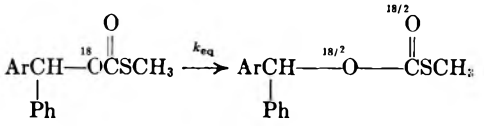


(5)

One can also determine the stereochemistry of the aralkyl methyl sulfide, ArPhCHSCH$_3$, produced by the decomposition of optically active thiocarbonate. It turns out, as was also true in earlier work,[2] that the sulfide is in each instance racemic. Because of this one can determine k_{rac} by measuring k_α, the first-order rate constant for the rate of loss of optical activity by the solution during the decomposition of optically active thiocarbonate, and then taking advantage of the fact that, since the sulfide product is racemic, $k_\alpha = k_{rac} + k_d$.

Rates of decomposition of the thiocarbonates, k_d, were determined, as before,[2] by following the disappearance of the absorption band due to the carbonyl group of the thiocarbonate in the infrared.

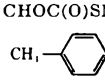
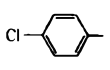
The rate constant for equilibration of the oxygen-18 label in the thiocarbonate, k_{eq}, was measured by partially decomposing samples of labeled thiocarbonate, recovering the undecomposed thiocarbonate, reducing it with lithium aluminum hydride, and then determining the ^{18}O content of the alcohol ArPhCHOH isolated from this reduction. Earlier work[2] has shown that the rate of equilibration of the label can be determined reliably by this procedure.

The necessary optically active and ^{18}O-labeled thiocarbonates were synthesized by reaction of the optically active or ^{18}O-labeled alcohol, as appropriate, with methyl chlorothiolformate, CH$_3$SCOCl.

Table I gives the values of k_{eq}, k_α, and k_d for **1b** and **1c** in benzonitrile at 135° as determined in the present work together with the previously measured[2] values of these rate constants for **1a** in this same solvent at 145°.

TABLE I

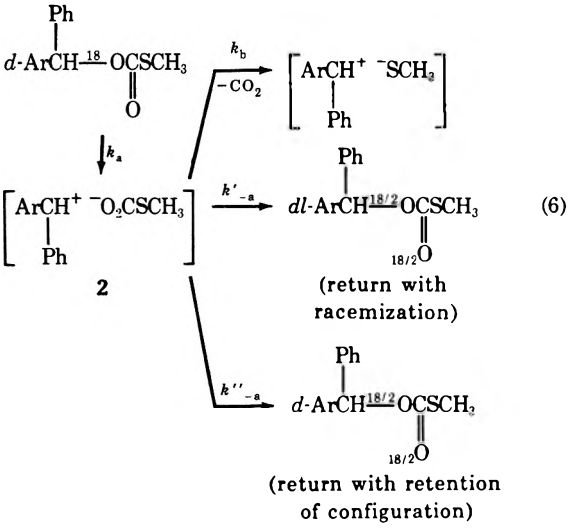
KINETICS OF THE DECOMPOSITION OF ARALKYL *S*-METHYL THIOCARBONATES IN BENZONITRILE

Ar in ArPhCHOC(O)SMe	Temp, °C	$k_{eq} \times 10^5$, sec^{-1}	$k_\alpha \times 10^5$, sec^{-1}	$k_d \times 10^5$, sec^{-1}
	135	44 ± 4	28.1 ± 0.2	9.1 ± 0.6
	135	38 ± 3	18.4 ± 0.8	4.9 ± 0.4
	145[a]	5.1 ± 0.4	2.6 ± 0.1	0.65 ± 0.01
	166[b]			6.0

[a] Data from ref 2. [b] Data from J. L. Kice, R. A. Bartsch, M. A. Dankleff, and S. L. Schwartz, *J. Amer. Chem. Soc.*, **87**, 1734 (1965).

Discussion

The ion pair **2** (eq 2) formed by dissociation of the aralkyl–oxygen bond in the thiocarbonate can either undergo loss of CO_2 (step k_b) or return to thiocarbonate (step k_{-a}). Goering and Linsay[6] have provided evidence that, for carbonium–carboxylate ion pairs involving strongly resonance-stabilized carbonium ions, such as ArPhCH$^+$ $^-$O$_2$CSR, ion-pair return results in essentially complete equilibration of the oxygen-18 label between the ether and carbonyl oxygens, so that k_{eq} is a reliable indicator of total ion-pair return in such systems. As outlined in eq 6, return can take



(6)

place with either loss (step k'_{-a}) or retention (step k''_{-a}) of configuration.

The various rate constants in eq 6 can be related to k_{eq}, k_α, and k_d in the following manner.

$$(k_b/k'_{-a}) = \frac{k_d}{k_\alpha - k_d} \quad (7a)$$

$$(k_b/k''_{-a}) = \frac{k_d}{k_{eq} + k_d - k_\alpha} \quad (7b)$$

$$\left(\frac{k'_{-a}}{k'_{-a} + k''_{-a}}\right) = \frac{k'_{-a}}{k_{-a}} = \frac{k_\alpha - k_d}{k_{eq}} \quad (7c)$$

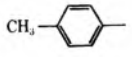
$$\left(\frac{k_b}{k'_{-a} + k''_{-a}}\right) = \frac{k_b}{k_{-a}} = \frac{k_d}{k_{eq}} \quad (7d)$$

It is also possible to analyze the data in Table I on the basis of a mechanism (eq 8) where one assumes that there are two types of ion-pair intermediates, one of which has lost its stereochemical memory and the other of which has not, and where one assigns rate constants, k_2 and k_4, to the rates at which "optically active" ion pairs *d*-**2** and *d*-**3** undergo loss of configuration. (A mechanism of this variety involving two ion pairs with different stereochemical behavior was felt by Goering and Levy[7] to be needed in order to explain certain aspects of their data on ion-pair return phenomena accompanying the solvolysis of *p*-chlorobenzhydryl *p*-nitrobenzoate in aqueous acetone.) Since the aralkyl sulfide formed is optically inactive, if we

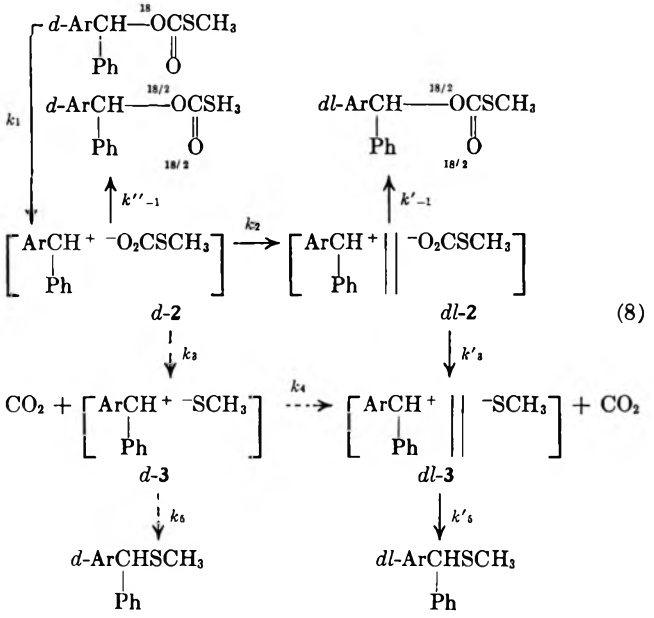
(6) H. L. Goering and E. C. Linsay, *J. Amer. Chem. Soc.*, **91**, 7435 (1969).
(7) H. L. Goering and J. F. Levy, *ibid.*, **86**, 120 (1964).

TABLE II

BEHAVIOR OF ION PAIRS IN THE DECOMPOSITION OR ARALKYL S-METHYL THIOCARBONATES IN BENZONITRILE

Ar in ArPhCHOC(O)SMe	Temp, °C	$\left(\frac{k_b}{k'_{-a}}\right)$	$\left(\frac{k_b}{k''_{-a}}\right)$	$\left(\frac{k'_{-a}}{k'_{-a}+k''_{-a}}\right)$	$\left(\frac{k_b}{k'_{-a}+k''_{-a}}\right)$	% Return to thiocarbonate—total	% Return to thiocarbonate—With retention	% Return to thiocarbonate—With racemization	% Ion pairs losing CO_2
	135	0.48 ± 0.04	0.36 ± 0.06	0.43 ± 0.04	0.21 ± 0.02	83	47	37	17
	135	0.36 = 0.03	0.20 ± 0.03	0.35 ± 0.03	0.13 ± 0.01	88	57	31	12
	145	0.33 = 0.02	0.21 ± 0.03	0.38 ± 0.05	0.13 ± 0.01	89	55	34	11

are to assume a mechanism for the thiocarbonate decompositions as shown in eq 8, we must also assume



(8)

that reactions k_3 and k_5 play no role under our reaction conditions.[8] For this reason reactions k_3, k_4, and k_5 are shown with dashed arrows in eq 8.

The relationship of the experimentally measurable rate constants k_{eq}, k_α, and k_d to those in eq 8 is as follows.

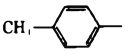
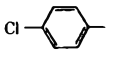
$$(k'_3/k'_{-1}) = \frac{k_d}{k_\alpha - k_d} \quad (9a)$$

$$(k_2/k''_{-1}) = \frac{k_\alpha}{k_{eq} + k_d - k_\alpha} \quad (9b)$$

Tables II and III give the values for the various rate-constant ratios (eq 7a-d and 9a-b) for the different thiocarbonates for the mechanisms shown in eq 6 and 8 as calculated from the data on k_{eq}, k_α, and k_d in Table I. One should recognize that because of the estimated experimental uncertainties in k_{eq}, k_α, and k_d (see Table I) the various rate-constant ratios in Tables II and III are only accurate to ±10% on the average. This should be kept in mind in the ensuing discussion.

TABLE III

VALUES OF (k'_3/k'_{-1}) AND (k_2/k''_{-1}) FOR DECOMPOSITION OF ARALKYL S-METHYL THIOCARBONATES IN BENZONITRILE

Ar in ArPhCHOC(O)SMe	Temp, °C	(k_3'/k'_{-1})	(k_2/k''_{-1})
	135	0.48 ± 0.04	1.12 ± 0.18
	135	0.36 ± 0.03	0.74 ± 0.10
	145	0.33 ± 0.02	0.85 ± 0.11

The data for the *p*-tolyl and α-naphthyl derivatives were obtained at 135° while the earlier data[2] for the slower reacting *p*-chlorobenzhydryl compound were for 145°. Since $k_b < k'_{-a}$ or k''_{-a}, it seems likely that $\Delta H^\ddagger$ for loss of CO_2 from $CH_3SCO_2^-$ is somewhat greater than $\Delta H^\ddagger$ for return. Therefore, in all probability the percentage of *p*-$ClC_6H_4PhCH^+{}^-O_2CSCH_3$ ion pairs undergoing return at 135° would be slightly larger than the 89% found at 145° and k_b/k'_{-a}, k_b/k''_{-a}, and $k_b/(k'_{-a} + k''_{-a})$ would all be somewhat smaller for this thiocarbonate at 135° than they are at 145°. The same will be true for k_3'/k'_{-1}. For various para-substituted benzhydryl *p*-nitrobenzoates Goering and Hopf[5] have shown that the $\Delta H^\ddagger$ associated with ion-pair return occurring with racemization is several kilocalories/mole larger than $\Delta H^\ddagger$ for return with retention. From this we would also expect that both $k'_{-a}/(k'_{-a} + k''_{-a})$ and k_2/k''_{-1} for the *p*-chlorobenzhydryl thiocarbonate would be somewhat lower at 135° than the values given in Tables II and III for 145°.

With this effect of temperature in mind we can now examine the data for the *p*-methylbenzhydryl and *p*-chlorobenzhydryl compounds and see whether it is in accord with our *a priori* expectations of the effect which a change in carbonium ion stability from *p*-$ClC_6H_4CHPh^+$ to *p*-$CH_3C_6H_4CHPh^+$ should have. From its rate of decomposition at higher temperatures (Table I) k_d for **1a** at 135° is calculated to be 0.21×10^{-5} sec^{-1}; this is about 45 times smaller than k_d for the *p*-methylbenzhydryl thiocarbonate at this temperature, and not particularly different from either the 90-fold difference in solvolysis rates of *p*-chlorobenzhydryl and *p*-methylbenzhydryl chlorides in aque-

(8) Since the decomposition of aralkyl chlorocarbonates gives aralkyl chlorides with a high degree of retention of configuration,[9] we believe that the failure to obtain optically active sulfide in the present systems would have to be due, within the framework of eq 8, *not* to k_4 being much faster than k_5, but rather to k_3 being much slower relative to k_2 for $CH_3SCO_2^-$ than is the case for $ClCO_2^-$ in the chlorocarbonate decomposition. The fact[10] that there is no equilibration of oxygen-18 in the undecomposed chlorocarbonate recovered from the partial decomposition of $PhCH_3CH^{18}OC(O)Cl$, while for the thiocarbonates in Table I $k_{eq} > k_d$, is in accord with such a postulate.

(9) K. B. Wiberg and T. M. Shryne, *J. Amer. Chem. Soc.*, **77**, 2774 (1955).

(10) J. L. Kice and G. C. Hanson, *Tetrahedron Lett.*, 2927 (1970).

ous acetone observed by Fox and Kohnstam[4] or the 22-fold difference in solvolysis rates of the *p*-nitrobenzoates observed by Goering and Hopf.[5] These facts clearly indicate that *p*-$CH_3C_6H_4CHPh^+$ is a somewhat more stable carbonium ion than *p*-$ClC_6H_4CHPh^+$. Since step k_b in eq 6 simply involves the loss of CO_2 from $CH_3SCO_2^-$, its rate should presumably be independent of the nature of the carbonium ion $ArCHPh^+$. On the other hand, one would expect that the rate of ion-pair return to thiocarbonate, steps k'_{-a} and k''_{-a}, in eq 6, should be faster the less stable the $ArPhCH^+$ carbonium ion. Thus one would expect that $k_b/(k'_{-a} + k''_{-a})$ should be larger for the *p*-methylbenzhydryl compound than for the *p*-chlorobenzhydryl, and this is indeed what is observed. As already noted, the actual value of $k_b/(k'_{-a} + k''_{-a})$ for **1a** at 135° is almost certainly smaller than the value of 0.13 found at 145°, and so the actual change in this ratio is undoubtedly slightly larger than from 0.13 to 0.21.

Goering and Hopf[5] have studied the stereochemistry of ion-pair return accompanying the solvolysis of *p*-methylbenzhydryl and *p*-chlorobenzhydryl *p*-nitrobenzoates. At a given temperature more of the return from the *p*-methylbenzhydryl ion pair occurs with racemization than with the *p*-chlorobenzhydryl ion pair. The same thing is true in the thiocarbonate decomposition, $k'_{-a}/(k'_{-a} + k''_{-a})$ being smaller for **1a** than for **1b** (particularly when one remembers that at 135° the value for the *p*-chlorobenzhydryl compound will be somewhat less than the value of 0.38 found at 145°). However, the effect is not as large in the present case as in the one studied by Goering and Hopf.[5] They report values of 0.60 and 0.35 for the *p*-methylbenzhydryl and *p*-chlorobenzhydryl *p*-nitrobenzoates, respectively, at 99.6°, a considerably larger change with substituent than the one from 0.43 to something somewhat less than 0.38 found in the thiocarbonate decomposition.

Nonetheless, the data for the change in both the extent and stereochemistry of ion-pair return in the thiocarbonate decomposition (eq 1) on going from Ar = *p*-ClC_6H_4 to Ar = *p*-$CH_3C_6H_4$ are generally in accord with one's expectations of what would be observed, based on (1) intuitive considerations of how the change in carbonium ion stability should influence $(k'_{-a} + k''_{-a})$ and k_b and (2) the results of Goering and Hopf[5] on the stereochemistry of ion-pair return involving the same pair of benzhydryl cations in another reaction. Satisfying though this situation may be, we should realize that this agreement of experiment with expectations occurs in a system in which the change in the stability of the carbonium ion partner in the ion pair is achieved without any significant change in the shape and steric requirements of the carbonium ion. We have only to turn from this case to the one involving the α-naphthylphenylcarbonium ion to see that when the steric requirements of the cation are significantly altered the picture is apparently no longer such a simple one.

Both the relative rates of decomposition of **1b** and **1c** (Table I) and the relative rates of solvolysis of *p*-methylbenzhydryl and α-naphthylcarbinyl chlorides[3] suggest that α-$C_{10}H_7CHPh^+$ and *p*-$CH_3C_6H_4CHPh^+$ do not differ much in stability as carbonium ions, both being more stable than *p*-$ClC_6H_4CHPh^+$. On that basis one might therefore have thought *a priori* that both $k_b/(k'_{-a} + k''_{-a})$ and $k'_{-a}/(k'_{-a} + k''_{-a})$ for **1c** would turn out to be very similar to those for the *p*-methylbenzhydryl thiocarbonate. In actual fact they turn out to be much closer to the values for the *p*-chlorobenzhydryl compound than to those for **1b**.

What is the explanation for this? Frankly, we don't know. Since we doubt that k_b should be sensitive in any way to the nature of the carbonium ion, we assume that it must be due to the fact that k'_{-a} and, to a greater extent, k''_{-a} are somewhat larger for **1c** than for **1b**. However, we do not have any really satisfying explanation for why this might be the case. Verbit and Berliner[3] have suggested that in the α-$C_{10}H_7CHPh^+$ ion there is about a 15° greater angle of twist between the two aryl groups than in the more coplanar Ph_2CH^+ or *p*-$CH_3C_6H_4CHPh^+$. While this could conceivably lead to return with retention being more strongly favored than in the case with a *p*-methylbenzhydryl cation and could therefore explain the smaller value of $k'_{-a}/(k'_{-a} + k''_{-a})$ for **1c** as compared to **1b**, it does not explain why $k_b/(k'_{-a} + k''_{-a})$ is less for the α-naphthyl compound; for, while one can see how the difference in geometry of the two carbonium ions could alter the stereochemistry associated with ion-pair return, there is no readily apparent reason why it should increase the total rate of return relative to the rate of loss of CO_2 from $CH_3SCO_2^-$ in the ion pair.

However, at the same time it is important to stress that the magnitude of the change in $k_b/(k'_{-a} + k''_{-a})$ from **1b** to **1c** is only a factor of 1.6, so that, if we assume that k_b remains the same, $\Delta F^{\ddagger}$ for k_{-a} would need only to decrease by 0.4 kcal/mol to account for the change. Ion-pair return to thiocarbonate is in each instance undoubtedly a highly exothermic reaction of relatively low $\Delta F^{\ddagger}$. From Hammond's principle[11] it would therefore be expected that the transition state for return would be *much closer* in structure to the ion pair than to the thiocarbonate. That being the case, it is certainly possible that it might be harder to predict accurately just what effect changes in carbonium ion structure would have on k'_{-a} and k''_{-a} than if the transition state for return were closer to the thiocarbonate in structure.

Our principal conclusion, therefore, is that, while the changes in ion-pair return with carbonium ion stability apparently follow predictable patterns when the change in carbonium ion stability is achieved without a significant change in the geometry of the carbonium ion, this is no longer necessarily true when the change in stability also involves a change in the geometry or steric requirements of the cation. In such cases the behavior of ion-pair return phenomena need not follow any readily predictable course. This suggests that one must exercise great caution in interpreting any variations in return behavior when comparing systems of this type.

Experimental Section

p-**Methylbenzhydrol-^{18}O.**—*p*-Methylbenzophenone (69 g, 0.35 mol) was dissolved in a mixture of 350 ml of dioxane, 35 ml (1.7 mol) of oxygen-18 enriched water (1.59 atom % ^{18}O), and 0.1 ml of concentrated sulfuric acid, and the solution was heated to re-

(11) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 34 (1955).

flux for 24 hr. The majority of the solvent was then distilled off and the residue was taken up in 100 ml of ether and dried over magnesium sulfate. The dried ether solution was added dropwise with stirring to a flask containing 7.5 g (0.2 mol) of lithium aluminum hydride and 100 ml of anhydrous ether. The mixture was stirred overnight at room temperature and then hydrolyzed by the addition of saturated ammonium chloride solution. The organic layer was separated and washed twice with water and then once with saturated sodium chloride; it was then dried over magnesium sulfate. The solvent was removed under reduced pressure and the *p*-methylbenzhydrol-^{18}O was recrystallized from hexane, yielding 6.5 g (94%) of ^{18}O-labeled alcohol, mp 51–53° (lit.[12] mp 51–53°), 1.42 atom % ^{18}O.

Unlabeled *p*-methylbenzhydrol was prepared from unlabeled *p*-methylbenzophenone by an analogous reduction with lithium aluminum hydride.

α-Naphthylphenylcarbinol.—This was prepared in 45% yield by reaction of phenylmagnesium bromide with α-naphthylaldehyde. After recrystallization from benzene–hexane it melted at 86° (lit.[12] mp 86.5°).

α-Naphthylphenylcarbinol-^{18}O.—α-Naphthylphenylcarbinol was oxidized to α-naphthyl phenyl ketone with Jones reagent using the procedure of Meinwald, Crandall, and Hymans.[14] The ketone was purified by chromatography on Florisil using benzene as eluent, followed by recrystallization from benzene–hexane, mp 74–75° (lit.[13] mp 75–76°), yield 75%.

The ketone was converted to α-naphthyl phenyl ketone-^{18}O using the same type of procedure as employed to label *p*-methylbenzophenone. The labeled ketone was then reduced to α-naphthylphenylcarbinol-^{18}O with lithium aluminum hydride. The labeled alcohol (1.56 atom % ^{18}O) was obtained in 80% yield, mp 85°.

Resolution of *p*-Methylbenzhydrol.—Racemic *p*-methylbenzhydrol acid phthalate (20 g) was resolved by the procedure outlined by Goering and Hopf.[5] However, instead of using the (−) enantiomer we employed partially resolved (+) enantioner, which was obtained by taking the mother liquor from the first crop of crystals of the quinidine salt of the half-phthalate and proceeding as follows. About 30 ml of solvent was evaporated from the 400 ml of mother liquor and the solution was set aside to allow material to crystallize. The crystals which formed were filtered off and discarded and the procedure was repeated until the volume of the solution had been reduced to only 150 ml. At this point the solvent was completely evaporated and the residual quinidine salt was decomposed in the manner described by Goering Hopf[5] to give 6.95 g of the partially resolved (+) acid phthalate, $[\alpha]^{25}_{589}$ +4.3° (chloroform). The acid phthalate was then converted to partially resolved (+)-*p*-methylbenzhydrol, $[\alpha]^{25}_{589}$ +2.5° (chloroform).

Resolution of α-Naphthylphenylcarbinol.—This was resolved using the procedure outlined by Smetana[13] involving successive recrystallizations of the brucine salt of the acid succinate of α-naphthylphenylcarbinol. The resolved alcohol was crystallized from carbon tetrachloride, yielding (−)-α-naphthylphenylcarbinol, mp 73–74°, $[\alpha]^{25}_{579}$ −38.2° (95% ethanol) [lit.[13] mp 74–75°, $[\alpha]_D$ −35.8° (95% ethanol)].

***p*-Methylbenzhydryl *S*-Methyl Thiocarbonate.**—*p*-Methylbenzhydrol, 2.00 g (0.01 mol), and 1.5 ml of dry pyridine were dissolved in 10 ml of benzene. Methyl chlorothioformate,[15] 2 ml in 10 ml of benzene, was then added dropwise to this solution at room temperature with stirring. After the addition was complete the reaction was stirred for 4 hr more. Then 20 ml of ether was added; the solution was washed with three portions of water and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column using benzene as eluent. Recrystallization from hexane afforded 1.9 g (72%) of *p*-methylbenzhydryl *S*-methyl thiocarbonate, mp 36–38°. *Anal.* Calcd for $C_{16}H_{16}O_2S$: C, 70.59; H, 5.93. Found: C, 70.66; H, 5.84.

α-Naphthylphenylcarbinyl *S*-Methyl Thiocarbonate.—This was synthesized using the same general procedure as for the *p*-methylbenzhydryl thiocarbonate. From 2.5 g (0.01 mol) of α-naphthylphenylcarbinol there was obtained, after recrystallization from benzene–hexane, 1.2 g (40%) of α-naphthylphenylcarbinyl *S*-methyl thiocarbonate, mp 91–92°. *Anal.* Calcd for $C_{19}H_{16}O_2S$: C, 73.99; H, 5.23. Found: C, 74.28; H, 5.01.

Preparation of Optically Active and ^{18}O Thiocarbonates.—These were prepared from the appropriate optically active or ^{18}O-labeled alcohols using the same synthetic procedures used for the normal thiocarbonates.

In the case of the ^{18}O-labeled thiocarbonates a sample of the thiocarbonate was then reduced with lithium aluminum hydride back to the alcohol, using a previously described procedure,[2] and the oxygen-18 content of the alcohol was determined in the same manner as in the kinetic studies of ^{18}O equilibration (*vide infra*). For both ^{18}O-labeled thiocarbonates the ^{18}O content of the alcohol isolated from the reduction agreed within experimental error with that of the labeled alcohol used for the synthesis, showing that no equilibration of oxygen-18 between the alkyl and acyl oxygens occurs during the synthesis and purification of the thiocarbonate.

(+)-*p*-Methylbenzhydryl *S*-methyl thiocarbonate prepared from (+)-*p*-methylbenzhydrol of $[\alpha]_{589}$ +2.5° had $[\alpha]^{25}_{579}$ +8.2° and $[\alpha]^{25}_{334}$ +44.5° (benzonitrile). When optically active α-naphthylphenylcarbinyl *S*-methyl thiocarbonate obtained from (−)-α-naphthylphenylcarbinol was allowed to crystallize slowly from benzene–hexane the first material which crystallized out was optically inactive. After this was removed, the solvent was removed from the filtrate and the residue was allowed to stand for 4 days in the refrigerator until crystals formed. This crystalline material, mp 75–79°, was optically active and had an infrared spectrum identical in all respects with the spectrum of a sample of racemic thiocarbonate of mp 91–92°. A difference between the melting point of the racemic and partially resolved thiocarbonate was also observed earlier[2] in the case of *p*-chlorobenzhydryl *S*-methyl thiocarbonate. The specific rotation of the 75–79°-melting thiocarbonate in benzonitrile at various wavelengths was as follows: $[\alpha]^{25}_{579}$ +17.3, $[\alpha]^{25}_{404}$ +28.6°, $[\alpha]^{25}_{366}$ +20.0°, $[\alpha]^{25}_{334}$ −24.4°.

Kinetic Studies of the Thermal Decomposition of Thiocarbonates.—The rates of decomposition of **1b** and **1c** were measured using the infrared method described in an earlier publication.[15]

Kinetic Studies of the Rate of Loss of Optical Activity.—A solution of optically active **1b** or **1c** in benzonitrile was placed in the same type apparatus used for the kinetic studies of the rate of decomposition, and the apparatus was heated in a constant-temperature bath. At appropriate time intervals aliquots were removed and their rotation measured at 25° in a water-jacketed polarimeter cell in a Perkin-Elmer Model 141 spectropolarimeter. The loss of optical activity was followed at 404 mμ for the α-naphthylphenylcarbinyl thiocarbonate and at 334 mμ for the *p*-methylbenzhydryl compound. The final rotation of the solution in each case was zero.

The rate of loss of optical activity, k_α, was determined from the slope of a plot of log α *vs.* time. Rates were reproducible within 5%.

Kinetic Studies of the Equilibrium of Alkyl and Acyl Oxygens.—Except for the method used to determine the oxygen-18 content of the alcohol obtained on reduction of samples of thiocarbonate recovered after partial decomposition, the procedure was the same as that used earlier[2] to study oxygen-18 equilibration accompanying the decomposition of *p*-chlorobenzhydryl thiocarbonates. Rather than the procedure of Doering and Dorfman,[16] which was used in the earlier work to detremine the ^{18}O content of the alcohol, the following alternate procedure was employed. Mass spectra were taken of purified samples of alcohol on a Hitachi RMU-6 mass spectrometer. Each sample was scanned several times at different intensities. The ratio (M + 2)/(M + 1), where M is the main molecular peak, was determined by measuring peak heights accurately.

From this, *P*, the atom per cent oxygen-18 in the alcohol, was calculated using eq 10a for the *p*-methylbenzhydrol and eq 10b for the α-naphthylcarbinol data. These equations are obtained by taking the normal values of (M + 1)/(M + 2) for $C_{14}H_{14}O$

$$P = 15.392\left(\frac{M+2}{M+1}\right) - 1.099 \quad \text{for } C_{14}H_{14}{}^{18}O \quad (10a)$$

$$P = 18.633\left(\frac{M+2}{M+1}\right) - 1.633 \quad \text{for } C_{17}H_{14}{}^{18}O \quad (10b)$$

(12) A. G. Davis, J. Kenyon, B. J. Lyons, and T. A. Rohan, *J. Chem. Soc.*, 3474 (1954).

(13) R. D. Smetana, Ph.D. Thesis, Pennsylvania State University, 1964.

(14) J. Meinwald, J. Crandall, and W. E. Hymans, *Org. Syn.*, **45**, 77 (1965).

(15) J. L. Kice, R. A. Bartsch, M. A. Dankleff, and S. L. Schwartz, *J. Amer. Chem. Soc.*, **87**, 1734 (1965).

(16) W. von E. Doering and E. Dorfman, *ibid.*, **75**, 5595 (1953).

and $C_{17}H_{14}O$, respectively, tabulated by Benyon[17] and then making provision for the fact that the oxygen-18 content is going to be variable in this case, rather than having the normal isotopic abundance used in calculating the tables in Benyon's book. The reliability of this method of determining P for the alcohol samples was verified by comparing the value of P for a sample of *p*-methylbenzhydrol determined in this way with the value determined by the method of Doering and Dorfman.[16] Within experimental error the results were the same.

The rate of ^{18}O equilibration between alkyl and acyl oxygens in the thiocarbonate was determined by plotting log $(P - P_\infty)/(P_0 - P_\infty)$ *vs.* time, where P_0 is the atom per cent oxygen-18 for a sample at $t = 0$, and $P_\infty = (P_0 + 0.204)/2$.

(17) J. H. Benyon, "Mass Spectrometry and Its Applications to Organic Chemistry," Elsevier, Amsterdam, 1960, pp 521, 537.

Registry No.—**1a**, 3326-54-3; (±)-**1b**, 38379-31-6; (+)-**1b**, 38379-32-7; **1b**-^{18}O, 38379-33-8; (±)-**1c**, 38379-34-9; (+)-**1c**, 38379-35-0; **1c**-^{18}O, 38379-36-1; *p*-methylbenzhydrol-^{18}O, 38379-37-2; *p*-methylbenzophenone, 134-84-9; α-naphthylphenylcarbinol-^{18}O, 38379-39-4; α-naphthyl phenyl ketone, 642-29-5; α-naphthyl phenyl ketone-^{18}O, 38379-41-8; (+)-*p*-methylbenzhydrol acid phthalate, 38379-42-9; (+)-*p*-methylbenzhydrol, 75832-67-4; (−)-α-naphthylphenylcarbinol, 1517-61-9; (±)-*p*-methylbenzhydrol, 38379-45-2; (±)-α-naphthylphenylcarbinol, 38379-46-3.

Protonation of Fumaric and Maleic Acids and Their Diethyl Derivatives

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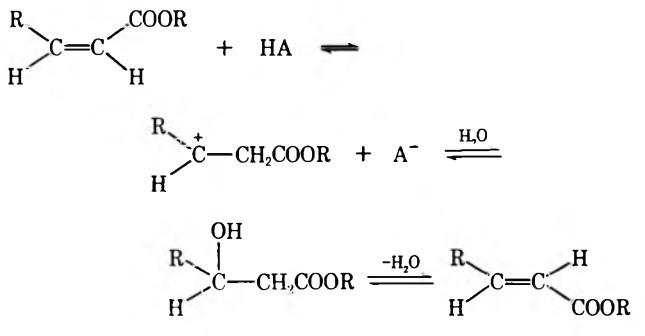
Strong acid media were employed to protonate maleic and fumaric acid and their diethyl ester derivatives. Nuclear magnetic resonance (nmr) showed that preferential oxygen protonation was occurring. In none of the compounds studied could protonation of the carbon–carbon double bond be observed.

As part of our continuing studies[1] of carbocations in strongly acidic solvents, we have investigated the thermodynamics of diprotonation of a series of diacids, diesters, and diketones. In light of the long-standing controversy regarding the site of protonation of the isomeric maleic and fumaric acids,[2] it was necessary to verify the structure of the protonated species in strong acid systems. That structure is the subject of this paper.

Many cis–trans isomerizations of α,β-unsaturated carboxylic acids are acid catalyzed. The mechanism of these reactions has been thoroughly studied. From their results Noyce and coworkers[3] detailed the mechanism as an addition–elimination in which the first step was protonation of the ethylenic linkage followed by the hydration of the resulting carbocation (Scheme I).

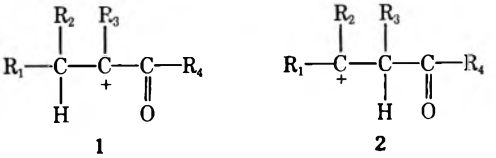
Richards, *et al.*,[2] recently concluded from secondary

SCHEME I



kinetic isotope effects and isotopic exchange experiments on the fumarase-catalyzed isomerization of *l*-malate to fumarate that the same type of carbocation intermediate is involved. This mechanism is quite different from that proposed by Fahey and Schneider[4] for the addition of HCl to diethyl maleate and fumarate in acetic acid. In compounds like XCH=CHY where X has positive character and is itself a base (*e.g.* O=COEt), protonation on carbon may not be the most favorable process. Fahey and Schneider have proposed that the interconversion of malate to fumarate might proceed *via* a modification of the 1,4-addition mechanism originally proposed by Ogg and Nozaki.[5] As they point out, formation of a carbocation adjacent to a carbonyl group is surprising. However, the data of Hansen, *et al.*,[2] seem to require this intermediate in the enzyme-catalyzed reaction.

Observation of the carbocation from malate or fumarate in strong acid, in conjunction with deuterium incorporation, would present strong evidence in favor of protonation of the –C=C– bond. α,β-Unsaturated carboxylic acids and carbonyl compounds have previously been shown to protonate on oxygen in superacid media.[6] However, no studies of maleic and fumaric acids or their derivatives appear to have been published. Previous attempts to prepare cations of the type **1** and **2**



1 **2**

by treating α- or β-halo ketones or aldehydes in strong acid have proven unsuccessful.[7] However, Kuta and

(1) J. W. Larsen, *J. Amer. Chem. Soc.*, **93**, 5107 (1971); J. W. Larsen, P. A. Bouis, M. W. Grant, and C. A. Lane, *ibid.*, **93**, 2067 (1971); J. W. Larsen, *ibid.*, **92**, 5136 (1970); J. W. Larsen, S. Ewing, and M. Wynn, *Tetrahedron Lett.*, 539 (1970).

(2) R. A. Alberty, W. G. Miller, and H. F. Fisher, *J. Amer. Chem. Soc.*, **79**, 3973 (1957); D. E. Schmidt, Jr., W. G. Nigh, C. Tanzer, and J. H. Richards, *ibid.*, **91**, 5849 (1969); R. C. Fahey and H. Schneider, *ibid.*, **92**, 6885 (1970); J. N. Hansen, E. L. Dinova, and P. D. Boyer, *J. Biol. Chem.*, **244**, 6270 (1969).

(3) D. S. Noyce, H. S. Avarbock, and W. L. Reed, *J. Amer. Chem. Soc.*, **84**, 1647 (1962); D. S. Noyce, P. A. King, F. B. Kirby, and W. L. Reed, *ibid.*, **84**, 1632 (1962).

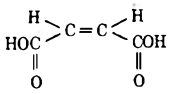
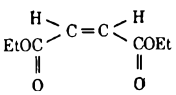
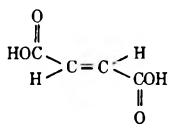
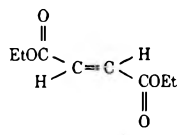
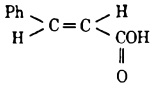
(4) R. C. Fahey and H. Schneider, *ibid.*, **92**, 6885 (1970).

(5) K. Nozaki and R. Ogg, Jr., *ibid.*, **63**, 2583 (1941).

(6) For a general review see G. A. Olah, A. M. White, and D. H. O'Brien, *Chem. Rev.*, **70**, 561 (1970).

(7) G. A. Olah, Y. Halpern, Y. K. Mo, and G. Liang, *J. Amer. Chem. Soc.*, **94**, 3554 (1972).

TABLE I[h]

Registry no.	Compd	Temp, °C	OH	α-CH_2	β-CH_3	H_β of $X(H)C=C(H_\alpha)Y$	H_α of $H_\beta(X)C=C(H_\alpha)Y$	Solvent
110-16-7		37	12.9			6.27		$DMSO-d_6$
		37				7.05		D_2SO_4
		−80				7.13[g]		FSO_3H, FSO_3H–SbF_5[f]
141-05-9		37		4.11[a]	1.21[b]	6.10		CCl_4
		37		4.76	1.72	6.94		D_2SO_4
		−80		4.80	1.72	7.09		FSO_3H
		0		5.31	1.80	7.34		FSO_3H–SbF_5[f]
		−60	13.86	5.31	1.80	7.34		FSO_3H–SbF_5[f]
110-17-8		37	12.28				6.68	$DMSO-d_6$
		37					7.12	D_2SO_4
		−80					7.53	FSO_3H, FSO_3H–SbF_5[f]
623-91-6		37		4.16[a]	1.25[b]		6.70	CCl_4
		37		4.81	1.74		7.26	D_2SO_4
		−80		5.20	1.81		7.65	FSO_3H
		0, −60		5.32	1.84		7.69	FSO_3H–SbF_5[f]
		−60	13.77	5.32	1.84		7.69	FSO_3H–SbF_6[f]
140-10-3		37	13.21				6.46_α 7.83_β	$DMSO-d_6$[c]
		37					6.65_α 8.35_β	D_2SO_4[d]
		−80					6.78_α 8.60_β	FSO_3H[e]

[a] Quartet, J = 7.5 Hz. [b] Triplet, J = 7.5 Hz. [c] Ph multiplet 7.45. [d] Ph multiplet 7.58. [e] Ph multiplet 7.63. [f] 11.5 mol % SbF_5 in FSO_3H. [g] Protonated anhydride form. [h] Chemical shifts are in δ values.

Pospisil[8] examined the protonation of fumaric acid and reported that in D_2SO_4 the ratios of hydroxylic protons to protons bound to carbon is 2:3. This evidence led them to propose that fumaric acid is protonated on carbon in sulfuric acid. Chemical shifts for their spectra were not reported.

Results and Discussion

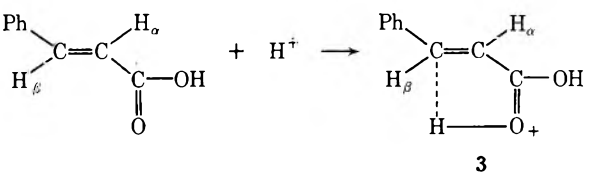
In order to substantiate the claim of preferential –C=C– protonation,[8] maleic and fumaric acid and their diethyl derivatives were dissolved in strong acids, and their proton nmr (pmr) spectra were investigated. Table I gives a summary of the chemical shifts. There is no evidence in the nmr spectra for carbon protonation. If a small amount of reversible carbon protonation were occurring in D_2SO_4, the signal due to the vinyl protons should diminish with time. Noyce, *et al.*,[3] have reported that incorporation of deuterium occurs with *trans*-cinnamic acid. This did not occur with maleic or fumaric acid and their diethyl derivatives. The spectra were unchanged after 48 hr in D_2SO_4 at 25°.

Brower[9] has shown that the carbocations formed upon monoprotonation of malonic acid and its methyl ester have the same structure (H)MeO(C=O)CH_2C(=O)-OHMe(H)$^+$. Assuming similar behavior, fumaric and maleic acids and their diethyl derivatives would provide an intramolecular internal standard, since the ethyl groups are not subject to exchange with the solvent. The result of this investigation shows a proton ratio of 2:4:6 between the ethylene, methylene, and methyl groups, also indicating no protonation of the ethylene group in diethyl maleate and fumarate.

In strong acid media it has been demonstrated that the proton on the carbonyl group can be observed at low temperature.[6] However, even at −80°, no –OH$^+$ signal could be observed in FSO_3H or FSO_3H–SbF_5 for the acids listed in Table I. Brower reported the same behavior for malonic acid derivatives. Evidently, under the acidic conditions used, the solute ions rapidly exchange protons with the solvent and are thus not observed.

The diesters show markedly different behavior. The chemical shift data (Table I) indicate that in FSO_3H diethyl maleate is monoprotonated while the fumarate is diprotonated. In FSO_3H–SbF_5 both are diprotonated. Under conditions of diprotonation the –OH$^+$ signal of diethyl fumarate appears as a slightly broadened singlet at −13.77 ppm. Presumably this could be the result of unresolved coupling. The spectrum of diethyl maleate appears as a much broader singlet. The detection of the hydroxylic protons in the diesters can be attributed to the added stability provided by the presence of the ethyl group. Apparently the ethyl group stabilizes the protonated ester sufficiently to slow down the rapid exchange of the acidic proton with the solvent.

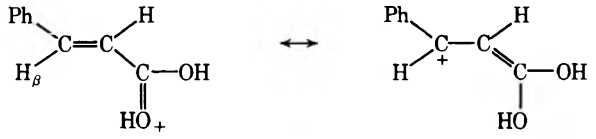
The pmr spectrum of protonated *trans*-cinnamic acid was also investigated, since Brand and Fleet[10] proposed structure **3** as a result of their polarographic studies. However, from the pmr data it can be seen that the β hydrogen in protonated cinnamic acid is appreciably deshielded in comparison to the α



3

(8) L. Pospisil and J. Kuta, *Collect. Czech. Chem. Commun.*, **34**, 742 (1969).
(9) D. M. Brouwer, *Recl. Trav. Chim. Pays-Bas*, **87**, 225 (1968).
(10) M. J. Brand and B. Fleet, *J. Electroanal. Chem.*, **16**, 341 (1968).

hydrogen, suggesting a significant amount of positive charge on the β carbon. Further studies into the



hindered rotation about the C–O partial double bond are being pursued in this laboratory.

Thus there is no evidence for protonation of the –C=C– of maleic and fumaric acids in strong acids. The relationship of this observation to the path of enzymatic catalyzed cis–trans isomerization is not clear. It does seem that, if the enzyme-catalyzed reaction is indeed proceeding *via* carbon protonation, then there must be in the enzyme a highly specific arrangement of the active site, forcing the proton onto carbon rather than onto the more basic carboxyl group.

Experimental Section

Materials.—All compounds were commercially available and were distilled or recrystallized before use. All compounds were dried thoroughly, liquids over 4 Å molecular sieves and solids over P_2O_5 under vacuum.

Spectra.—Room-temperature nmr spectra were recorded on a Varian A-60 spectrometer. All chemical shifts (δ) are reported in parts per million relative to internal tetramethylamonium bromide taken as δ 3.2.

Low-temperature spectra were recorded on a Varian HA-100 spectrometer equipped with a variable-temperature probe.

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Notes

Reaction of Nitroxyl Radicals with Metal Carbonyls

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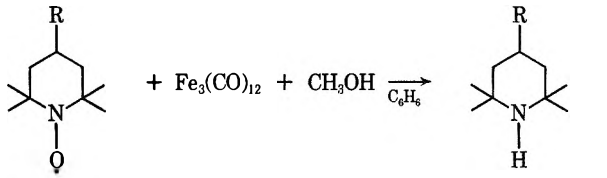
Received September 6, 1972

Deoxygenation reactions have been observed from treatment of sulfoxides,[1] amine oxides,[2] azoxy compounds,[2,3] nitrones,[2] and *C*-nitroso compounds[2,3] with iron pentacarbonyl [$Fe(CO)_5$]; nitro compounds with $Fe(CO)_5$,[2,4] diiron enneacarbonyl [$Fe_2(CO)_9$],[4] or triiron dodecacarbonyl [$Fe_3(CO)_{12}$–methanolic benzene];[5] *N*-nitroso compounds with $Fe(CO)_5$[2] or group VI metal carbonyls;[6] and *N*-phenyl-2-oxa-3-azabicyclo-[2.2.2]octene-5 with $Fe_2(CO)_9$.[7] There have been no reports, to the author's knowledge, of the reaction of metal carbonyls with nitroxyl radicals, an important group of compounds[8,9] potentially capable of undergoing deoxygenation to amino radicals. This note describes the reaction of iron carbonyls and group VI metal carbonyls with nitroxyl radicals.

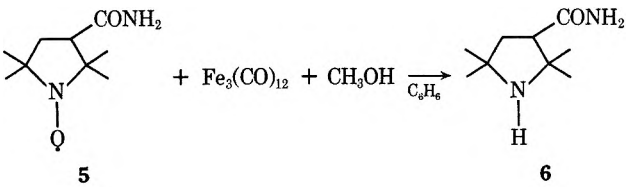
Reaction of 2,2,6,6-tetramethylpiperidine-1-oxyl (**1**) with either $Fe(CO)_5$ in hot benzene or $Fe_2(CO)_9$ in benzene at room temperature gave a very unstable non-



1, R = H
3, R = $NHCOCH_3$

2, R = H
4, R = $NHCOCH_3$

carbonyl containing organometallic compound. No amine was isolated from these reactions. However, treatment of **1** with $Fe_3(CO)_{12}$ in benzene containing a small amount of methanol (conditions under which the hydridoundecacarbonyltriferrate anion is generated)[5] did result in the formation of the deoxygenated product **2** in 42% yield. Similarly, 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxyl (**3**) gave the amine **4** in 55% yield and **6** was obtained from **5** in 41% yield. There-



5 **6**

fore, $Fe_3(CO)_{12}$ is a useful reagent for reducing nitroxyl radicals to amines.[10] No bipiperidyl or bipyrrolidyl derivatives were produced in these reactions,[11] although small amounts of *N*-formyl amines[4,6,12] were apparently formed.

(1) H. Alper and E. C. H. Keung, *Tetrahedron Lett.*, 53 (1970).
(2) H. Alper and J. T. Edward, *Can. J. Chem.*, **48**, 1543 (1970).
(3) A. S. Filatov and M. A. Englin, *Zh. Obshch. Khim.*, **39**, 783 (1969); *J. Gen. Chem. USSR*, **39**, 743 (1969).
(4) H. Alper, *Inorg. Chem.*, **11**, 976 (1972).
(5) J. M. Landsberg, L. Katz, and C. Olsen, *J. Org. Chem.*, **37**, 930 (1972).
(6) H. Alper, *Organometal. Chem. Syn.*, **1**, 69 (1970).
(7) Y. Becker, A. Eisenstadt, and Y. Shvo, *Tetrahedron Lett.*, 3183 (1972).
(8) E. G. Rozantsev, "Free Nitroxyl Radicals," Plenum Press, New York, N. Y., 1970.
(9) O. H. Griffith and A. S. Waggoner, *Accounts Chem. Res.*, **2**, 17 (1969).
(10) For other reductive methods, see N. Kornblum and H. W. Pinnick, *J. Org. Chem.*, **37**, 2050 (1972), and references cited therein.
(11) D. Mackay and W. A. Waters, *J. Chem. Soc. C*, 813 (1966), unsuccessfully attempted to prepare bi(2,2,6,6-tetramethyl)piperidyl from *N*-nitroso-2,2,6,6-tetramethylpiperidine.
(12) W. F. Edgell, M. T. Yang, B. J. Bulkin, R. Bayer, and N. Koizumi, *J. Amer. Chem. Soc.*, **87**, 3080 (1965).

Treatment of **1** with molybdenum hexacarbonyl in refluxing *n*-hexane gave an off-white diamagnetic substance whose elemental analysis and vapor pressure osmometric molecular weight determination indicated the composition $(C_9H_{18}NO)_2Mo_3$. The infrared (ir) spectrum of the product (KBr) showed *no* terminal metal carbonyl stretching bands (2100–1800 cm^{-1}) but did exhibit intense absorption at 960, 926, and 808 cm^{-1} due, at least in part, to N–O stretching with oxygen coordination to the metal. The mass spectrum was similar to that reported by Morrison and Davies[13] for **1**. Although the structure of the product is not known, it is clear that deoxygenation does not occur here, in contrast to the results with $Fe_3(CO)_{12}$. Tungsten hexacarbonyl reacted with **1** to give a solid analogous to that obtained using $Mo(CO)_6$. Chromium hexacarbonyl failed to react with **1** under the described conditions.

Experimental Section

Melting points were determined on a Fisher-Johns or Gallenkamp apparatus and are uncorrected. Boiling points are also uncorrected. Elemental analyses were carried out by A. Bernhardt, West Germany, and Meade Microanalytical Laboratory, Amherst, Mass. Infrared spectra were obtained on a Perkin-Elmer 457 spectrophotometer; the wavelength readings were calibrated with polystyrene film. Nmr spectra were obtained on a Varian A-60 spectrometer, employing tetramethylsilane as the internal standard.

The three iron carbonyls and chromium hexacarbonyl were purchased from Pressure Chemical Co. and were used as received. Climax Molybdenum Co. provided $Mo(CO)_6$ and $W(CO)_6$. Mr. William Moore prepared **1** following Rozantsev's procedure.[14] Radicals **3** and **5** were commercial products. All reactions were run under a nitrogen atmosphere.

Deoxygenation of Nitroxyl Radicals by $Fe_3(CO)_{12}$.—A mixture of $Fe_3(CO)_{12}$ (4.50 g, ~9 mmol), absolute methanol (2.0 ml), and dry benzene (50 ml) was refluxed with stirring for 6 hr. The nitroxyl radical (10 mmol), solid or in benzene (10–17 ml), was added to the iron hydride solution and the mixture was then refluxed for 9–18 hr. The solution was cooled and filtered, and work-up was effected in the following manner for the various reactions.

A. 2,2,6,6-Tetramethylpiperidine-1-oxyl.—The ir spectrum (neat) of the red oil, obtained on flash evaporation of the filtrate, showed it to consist largely of **2**, but a weak carbonyl stretching absorption at 1665 cm^{-1} indicated the possible presence of a small amount of *N*-formyl-2,2,6,6-tetramethylpiperidine. This by-product was also formed in reactions of **3** and **5**, but in all instances analytically pure samples could not be obtained owing to contamination by a metal carbonyl complex. The oil was repeatedly triturated with pentane. Flash evaporation of the dried pentane extract and subsequent distillation of the residue gave 0.59 g (42%) of 2,2,6,6-tetramethylpiperidine, bp 153–155° (lit.[15] bp 151–152°), identified by comparison with an authentic sample.

B. 4-Acetamido-2,2,6,6-tetramethylpiperidine-1-oxyl.—The filtered material was washed well with dry ether, and the washings were added to the filtrate. Flash evaporation of the filtrate gave an oil, which was dissolved in ether. Pentane was then added until precipitation of **4** was complete. Filtration gave 1.10 g (55%) of 4-acetamido-2,2,6,6-tetramethylpiperidine, mp 118–120° (lit.[16] mp 120°).

C. 3-Carbamoyl-2,2,5,5-tetramethylpyrrolidine-1-oxyl.—The filtered material was washed well with chloroform. Work-up as described in B gave **6** in 41% yield, mp 126.5–128.0° (lit.[17] mp 129–130°).

Reaction of 2,2,6,6-Tetramethylpiperidine-1-oxyl (1) with Group VI Metal Carbonyls.—A mixture of **1** (0.60 g, 3.85 mmol), $Mo(CO)_6$ (1.21 g, 4.63 mmol), and dry hexane (35 ml) was refluxed for 1 day. The solution was filtered hot, the filtrate depositing more solid on cooling. After refiltration, the solid was vacuum sublimed at 50° to remove any unreacted $Mo(CO)_6$. The off-white solid decomposed without melting at >210°: ir (KBr) 960 (s), 926 (s), 808 (s–vs), 613 (s), and 573 cm^{-1} (m); nmr (DMSO-d_6) δ 1.08 (s), 1.36 (s), 1.48 (s), 1.56 (m).

Anal. Calcd for $C_{18}H_{36}Mo_3N_2O_2$: C, 36.04; H, 6.04; N, 4.66; Mo, 47.91; mol wt, 600. Found: C, 36.79; H, 6.00; N, 4.25; Mo, 47.50; mol wt, 618 (osmometry, $CHCl_3$).

Tungsten hexacarbonyl reacted with **1** to give a white solid having no melting point below 300°, ir (KBr) 979 (s), 958 (s, sh), 890 (w–m), 814 (vs), 448 cm^{-1} (m).

Anal. Calcd for $C_{18}H_{36}N_2O_2W_3$: C, 25.09; H, 4.20; N, 3.24; W, 63.83. Found: C, 25.76; H, 4.85; N, 3.21; W, 62.99.

2,2,6,6-Tetramethylpiperidine-1-oxyl was inert to $Cr(CO)_6$ under the reaction conditions used for $Mo(CO)_6$.

Registry No.—**1**, 2564-83-2; $Mo(CO)_6$, 13939-06-5; $C_{18}H_{36}Mo_3N_2O_2$, 37213-92-6; $W(CO)_6$, 14040-11-0; $C_{18}H_{36}N_2O_2W_3$, 37213-93-7.

Acknowledgments.—This research was supported by the Research Foundation of the State of New York. The author is grateful to the Climax Molybdenum Co. for supplying generous quantities of molybdenum and tungsten hexacarbonyls.

(13) A. Morrison and A. P. Davies, *Org. Mass Spectrom.*, **3**, 353 (1970).

(14) Reference 8, p 217.

(15) N. Leonard and E. Nommensen, *J. Amer. Chem. Soc.*, **71**, 2808 (1949).

(16) E. G. Rozantsev and Y. V. Kokhanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1477 (1966); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **15**, 1422 (1966).

(17) H. Pauly, *Justus Liebigs Ann. Chem.*, **322**, 113 (1902).

A Mild, Nonacidic Method for Converting Secondary Nitro Compounds into Ketones

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Received January 3, 1973

The utility in synthesis of the mainfold transformations of nitroparaffins and nitro olefins[1] would be considerably enhanced if facile methods for converting nitro groups into carbonyl groups were at hand, and, indeed, there has recently been renewed interest in such transformations, especially as they relate to the synthesis of 1,4 diketones.[2,3] The purpose of this note is to describe a simple and effective method for converting secondary nitro compounds into ketones and diketones which does not use acids[4] or oxidizing[5] or reducing agents.[2] Its usefulness may be gauged from the data presented in Table I, especially if it is borne in mind that the yields of ketones and 1,4 diketones refer to pure, isolated products.

Our procedure derives from an observation reported in 1956 which appears to have been little, if at all, noticed, namely that 2-nitrooctane, while unaffected by

(1) (a) Houben-Weyl, "Methoden der Organischen Chemie," 4th ed, E. Müller, Ed., Vol. X, part 1, Georg Thieme Verlag, Stuttgart, 1971. (b) "The Chemistry of the Nitro and Nitroso Groups," H. Feuer, Ed., part 2, Interscience-Wiley, New York, N. Y., 1970, Chapter 3. (c) E. D. Bergmann, D. Ginsberg, and R. Pappo, *Org. React.*, **10**, 179 (1959).

(2) J. E. McMurry and J. Melton, *J. Amer. Chem. Soc.*, **93**, 5309 (1971).

(3) D. St. C. Black, *Tetrahedron Lett.*, 1331 (1972).

(4) The Nef reaction [W. E. Noland, *Chem. Rev.*, **55**, 137 (1955)] involves the action of base to form the nitroparaffin salt which is then treated with a mineral acid. In the most recent paper[3] on the subject, 3 *N* hydrochloric acid is employed. The reductive procedure of McMurry and Melton[2] also involves acidic solutions.

(5) H. Shechter and F. T. Williams [*J. Org. Chem.*, **27**, 3699 (1962)] have described the permanganate oxidation of nitroparaffin salts to aldehydes and ketones.

TABLE I
THE CONVERSION OF SECONDARY NITRO COMPOUNDS INTO KETONES

Nitro compd[a]	Ketone[b]	Yield, %
2-Nitropropane	Acetone	70
2-Nitrooctane	2-Octanone	83
Nitrocyclohexane	Cyclohexanone	67
Nitrocycloheptane	Cycloheptanone	88
α-Phenylnitroethane	Acetophenone	79
5-Nitro-2-hexanone	2,5-Hexanedione	76
5-Nitro-2-octanone	2,5-Octanedione	71

[a] Registry numbers are, respectively, 79-46-9, 4609-91-0, 1122-60-7, 2562-40-5, 7214-61-1, 35223-72-4, and 7404-84-4. [b] Registry numbers are, respectively, 67-64-1, 111-13-7, 108-94-1, 502-42-1, 98-86-2, 110-13-4, and 3214-41-3.

nitrite esters and by sodium nitrite, is converted by their joint action into 2-octanone.[6] The overall reaction appears to be that of eq 1 and, consistent with this

$$\begin{matrix} R_2CH \\ | \\ NO_2 \end{matrix} + CH_3CH_2CH_2ONO + NaNO_2 \longrightarrow R_2C{=}O + CH_3CH_2CH_2OH + NaNO_3 + N_2O \quad (1)$$

view, nitrous oxide has been isolated and identified as one of the products. It should be emphasized that primary nitroparaffins on treatment with a nitrite ester and sodium nitrite give carboxylic acids and not aldehydes.[6]

As regards the mechanism of the reaction of eq 1, the sequence shown is suggested. Evidence for the first

$$\begin{matrix} R_2CH \\ | \\ NO_2 \end{matrix} + NO_2^- \rightleftharpoons \begin{matrix} R_2C^- \\ | \\ NO_2 \end{matrix} + HNO_2 \quad (2)$$

$$\begin{matrix} R_2C^- \\ | \\ NO_2 \end{matrix} + CH_3CH_2CH_2ONO \longrightarrow \begin{matrix} R_2CNO \\ | \\ NO_2 \end{matrix} + CH_3CH_2CH_2O^- \quad (3)$$

$$CH_3CH_2CH_2O^- + HONO \longrightarrow CH_3CH_2CH_2OH + NO_2^- \quad (4)$$

$$\begin{matrix} R_2CNO \\ | \\ NO_2 \end{matrix} + NO_2^- \longrightarrow R_2C{=}\ddot{N}O^- + N_2O_4 \quad (5)$$

$$R_2C{=}\ddot{N}O^- + O{=}NONO_2 \longrightarrow \left[R_2C{=}\overset{+}{N}O^- \begin{matrix} | \\ N{=}O \end{matrix} \leftrightarrow R_2\overset{+}{C}\ddot{N}O^- \begin{matrix} | \\ N{=}O \end{matrix} \right] + NO_3^- \quad (6)$$

I

$$I \longrightarrow \begin{matrix} & O & \\ & \diagup\diagdown & \\ R_2C & & N \\ & & | \\ & & N{=}O \end{matrix} \quad (7)$$

$$\begin{matrix} & O & \\ & \diagup\diagdown & \\ R_2C & & N \\ & & | \\ & & N{=}O \end{matrix} \longrightarrow R_2C{=}O + N_2O \quad (8)$$

two steps of this sequence has already been presented.[6] The next step (eq 4) presents no difficulties. The reaction of eq 5 is a nucleophilic displacement on the nitro group of an α-nitroso nitro compound, a process which was recognized some years ago,[6,7] and in eq 6 nitrogen tetroxide is employed as a nitrosating agent, a role in keeping with the fact that one of the structures assigned to it is $O{=}NONO_2$.[8] The reaction of eq 6 is also consonant with the well-known transformation of oximes to aldehydes and ketones by the action of nitrous acid.[9] The last three steps (eq 6, 7, and 8) parallel those proposed by Wieland and Grim as a consequence of their study of the nitrous acid–ketoxime reaction using ^{18}O-enriched nitrous acid.[10] Finally, the fact that 2-nitroso-2-nitropropane is smoothly converted to acetone on treatment with sodium nitrite at room temperature accords with the proposed reaction scheme.[6]

(6) N. Kornblum, R. K. Blackwood, and D. D. Mooberry, *J. Amer. Chem. Soc.*, **78**, 1501 (1956).
(7) N. Kornblum and J. H. Eicher, *J. Amer. Chem. Soc.*, **78**, 1495 (1956).

Experimental Section

n-Propyl nitrite (bp 49–50°, n^{20}D 1.3592) and *n*-octyl nitrite (bp 50–52° at 4 mm, n^{20}D 1.4127) were prepared from the alcohols.[11,12] Nitroethane, 1-nitrobutane, and 2-nitropropane (Commercial Solvents) and nitrocyclohexane (Du Pont) were distilled prior to use. Nitrocycloheptane (bp 40–42° at 0.5 mm, n^{20}D 1.4723) was prepared from the bromide.[13]

α-Phenylnitroethane.[14]—Dry sodium nitrite (69 g, 1.0 mol) is dissolved in 800 ml of DMSO. The stirred solution is cooled to 19° and 92.4 g (0.50 mol) of α-phenylethyl bromide is added all at once. Stirring is continued and the internal temperature is maintained at 19–25° (minimal exposure to light). After 20 min the solution is poured into water layered with benzene; the benzene phase is washed with water, dried, and concentrated under reduced pressure. The resulting oil is dissolved in hexane and vigorously stirred with three 150-ml portions of 85% phosphoric acid, each treatment lasting 75 min (minimal light exposure). The hexane solution is then washed with water, dried over anhydrous magnesium sulfate, concentrated, and then twice distilled. This gives 38 g (50% yield) of vpc-pure α-phenylnitroethane, bp 61–63° at 0.45 mm, n^{20}D 1.5221.

5-Nitro-2-octanone.—A solution of freshly distilled methyl vinyl ketone (43.1 g, 0.617 mol), 1-nitrobutane (63.6 g, 0.617 mol), and diisopropylamine (31.2 g, 0.308 mol) in 300 ml of chloroform is refluxed for 15 hr and then concentrated under reduced pressure. Two distillations of the residual oil give 74.6 g (70% yield) of vpc-pure, colorless 5-nitro-2-octanone, bp 72° at 0.45 mm, n^{20}D 1.4428 (lit.[15] n^{20}D 1.4414–1.4428).

5-Nitro-2-hexanone.—Methyl vinyl ketone and nitroethane were condensed exactly as above to give a 44% yield of 5-nitro-2-hexanone, bp 72–73° at 0.95 mm, n^{20}D 1.4401 (lit.[16] $n^{19.6}$D 1.4396).

Conversion of Nitro Compounds into Ketones. α-Phenylnitroethane into Acetophenone.—Under nitrogen 34.5 g (0.50 mol) of dry sodium nitrite is added to 200 ml of DMSO and this is followed by 15.12 g (0.10 mol) of α-phenylnitroethane and 17.82 g (0.20 mol) of *n*-propyl nitrite. The resulting mixture is stirred for 2 hr, in subdued light, at 23–28° (occasional cooling), after which it is poured into water layered with methylene chloride. The methylene chloride phase is separated, washed with water, and dried over anhydrous magnesium sulfate, and then the methylene chloride is removed. Distillation of the residual oil at 6 mm gives 9.45 g (79% yield) of pure acetophenone, bp 66–67°, n^{20}D 1.5341.

Nitrocycloheptane into Cycloheptanone.—Nitrocycloheptane (21.48 g, 0.15 mol), sodium nitrite (51.75 g, 0.75 mol), *n*-propyl nitrite (26.73 g, 0.30 mol), and 300 ml of DMSO are employed as above (reaction time 5 hr). This gives 14.78 g (88% yield of vpc-pure cycloheptanone, bp 50–52° at 6 mm, n^{20}D 1.4615.

Nitrocyclohexane into Cyclohexanone.—Nitrocyclohexane (18.91 g, 0.15 mol) is treated with sodium nitrite and *n*-propyl

(8) W. L. Jolly, "The Inorganic Chemistry of Nitrogen," W. A. Benjamin, New York, N. Y., 1964, p 81.
(9) J. M. Kliegman and R. K. Barnes, *J. Org. Chem.*, **37**, 4223 (1972).
(10) T. Wieland and D. Grim, *Chem. Ber.*, **96**, 275 (1963).
(11) W. A. Noyes, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 108.
(12) A. Chrétien and Y. Longi, *C. R. Acad. Sci.*, **220**, 746 (1945).
(13) N. Kornblum, *Org. React.*, **12**, 101 (1962). We are indebted to Mr. Thomas Cole for this preparation.
(14) This procedure represents a significant improvement on that in the literature [N. Kornblum, W. D. Gurowitz, H. O. Larson, and D. E. Hardies, *J. Amer. Chem. Soc.*, **82**, 3100 (1960)].
(15) H. Feuer and R. Harmetz, *J. Org. Chem.*, **26**, 1061 (1961).
(16) H. Shechter, D. L. Ley, and L. Zeldin, *J. Amer. Chem. Soc.*, **74**, 3664 (1952).

nitrite as above for 50 hr. Vpc-pure cyclohexanone is obtained in 67% yield (9.75 g), bp 154–155°, $n^{20}D$ 1.4505.

5-Nitro-2-hexanone into 2,5-hexanedione.—The nitro ketone (21.78 g, 0.15 mol), sodium nitrite (51.75 g, 0.75 mol), *n*-propyl nitrite (26.73 g, 0.30 mol), and 300 ml of DMSO are employed as above (reaction time 20 hr). Since the dione is water soluble, relatively large amounts of methylene chloride and relatively small amounts of water are used in the work-up. Also, the crude dione is chromatographed on silica gel prior to distillation. There is obtained 13.25 g (76% yield) of vpc-pure 2,5-hexanedione, bp 58–60° at 5 mm, $n^{20}D$ 1.4253. The nmr spectrum consists of a singlet at δ 2.1 (6 H) and a singlet at 2.6 (4 H).

5-Nitro-2-octanone into 2,5-Octanedione.—Using 25.97 g (0.15 mol) of this nitro ketone the reaction is carried out as in the preceding experiment (reaction time 52 hr). The vpc-pure dione (bp 44–45° at 0.47 mm) is obtained in 71% yield (15.13 g), $n^{20}D$ 1.4313 (lit.[17] $n^{23}D$ 1.4317).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.49; H, 10.14.

2-Nitropropane into Acetone.—To facilitate isolation of the product hexamethylphosphoramide (HMPA) was employed as the solvent and *n*-octyl nitrite as the nitrosating agent. Under nitrogen, a mixture of 55.20 g (0.80 mol) of dry sodium nitrite, 35.99 g (0.40 mol) of 2-nitropropane, and 79.61 g (0.50 mol) of *n*-octyl nitrite in 800 ml of HMPA is stirred at 25–28° (subdued light) for 4.5 hr. The acetone is removed directly from the reaction mixture at room temperature *in vacuo* and collected at −80°. Distillation from Drierite gives 16.10 g (70% yield) of pure acetone, bp 56–58°, $n^{20}D$ 1.3588.

Identification of Nitrous Oxide.—A colorless gas is evolved in all of these transformations. A sample of the gas produced in the conversion of 2-nitropropane to acetone (*vide supra*) was collected after passing through a −80° trap. Mass spectroscopy reveals, in addition to N_2 and O_2 peaks at *m/e* 28 and 32, peaks at *m/e* 44 (100%) for N_2O and *m/e* 30 (40%) presumed to be NO^+ derived from N_2O. A high resolution peak to peak comparison of the *m/e* 44 peak with the *m/e* 44 peak of CO_2 confirms the presence of nitrous oxide.[18] Calcd for N_2O: *m/e* 44.0011. Found: *m/e* 44.0003.

Registry No.—Sodium nitrite, 7632-00-00; α-phenylethyl bromide, 585-71-7.

Acknowledgment.—We thank the National Science Foundation and Eli Lilly and Co. for generous support.

(17) R. L. Huang, *J. Chem. Soc.*, 1749 (1956).

(18) We are indebted to Mr. W. Perry of the Purdue Mass Spectrometry Center for determining these spectra.

Datiscacin, a Novel Cytotoxic Cucurbitacin 20-Acetate from *Datisca glomerata*[1a,b]

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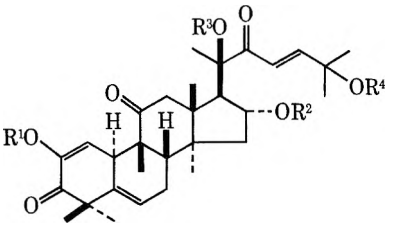
In the course of a continuing search for tumor inhibitors of plant origin, a chloroform extract of *Datisca glomerata* Baill. (Cucurbitaceae) was found to show significant activity against human carcinoma of the nasopharynx (KB) carried in cell culture.[2] A number of tumor-inhibitory principles have been isolated from this plant and the structure elucidation of one of these, datiscoside, has already been reported.[3] We report herein the structure elucidation of another cytotoxic principle, datiscacin (**1**), the first recognized cucurbitacin 20-acetate ester derivative.

The chloroform extract of the dried roots was subjected to successive solvent partitions and chromatographic separations, guided by the KB assay. Datiscacin[4] (**1**), $C_{32}H_{44}O_8$, mp 208–212°, $[\alpha]^{23}D$ −18°, was crystallized from a cytotoxic fraction.

Elemental analysis and spectral data for datiscacin supported its formulation as a cucurbitacin monoacetate ester. Acetylation of datiscacin under mild conditions with acetic anhydride–pyridine yielded a triacetate (**2**), indicative of the location of the original acetate group on the C-17 side chain. That datiscacin contains a diosphenol in ring A was indicated by its positive ferric chloride test, absorption at 6.13 μ in the infrared and 268 nm in the ultraviolet, a one-proton doublet at τ 4.29 in the nmr spectrum,[5] and a peak at *m/e* 164 in the mass spectrum.[6] The known cucurbitacin E (**3**) contains a ring A diosphenol and a C-25 acetate ester, but its markedly different optical rotation ($[\alpha]^{26}D$ −58°)[7] indicated that it differed from datiscacin. These considerations and the fact that there are but two hydroxyl groups in the cucurbitacin side chain led us to entertain the hypothesis that datiscacin is the C-20 acetate ester **1**.



1, $R^1 = R^2 = R^4 = H$; $R^3 = Ac$
2, $R^1 = R^2 = R^3 = Ac$; $R^4 = H$
3, $R^1 = R^2 = R^3 = H$; $R^4 = Ac$
4, $R^1 = R^2 = R^3 = R^4 = H$
5, $R^1 = R^2 = Ac$; $R^3 = R^4 = H$

Confirmation for the position of the acetate ester in **1** was derived from the results of periodate oxidation studies. Thus, datiscacin diacetate (**2**) was found to be unaffected by treatment with an excess of periodic acid, and the compound was recovered unchanged. In contrast, treatment of cucurbitacin I diacetate (**5**)[8] with periodic acid under the same conditions led to consumption of 1 molar equiv of the reagent, in accord with the expected sensitivity of the 20,22-ketol system.

Interrelation with a known cucurbitacin was deemed desirable to confirm the postulated structure and configuration of datiscacin. Hydrolysis of the tertiary C-20 acetate ester group to yield cucurbitacin I (**4**) was envisaged, but strong alkaline treatment was precluded by the known sensitivity of ring A diosphenols

(1) (a) Tumor Inhibitors. LXXXIII. Part LXXXII: S. M. Kupchan, R. W. Britton, M. F. Ziegler, and C. W. Sigel, *J. Org. Chem.* **38**, 178 (1973). (b) This investigation was supported by grants from the National Cancer Institute (CA-11718) and the American Cancer Society (IC-57H), and a contract with the National Cancer Institute (NIH-NCI-C-71-2099). (c) National Institutes of Health Postdoctoral Fellow, 1972–present.

(2) Cytotoxicity was assayed, under the auspices of the National Cancer Institute, by the procedure described in *Cancer Chemother. Rep.*, **25**, 1 (1962).

(3) S. M. Kupchan, C. W. Sigel, L. J. Guttman, R. J. Restivo, and R. F. Bryan, *J. Amer. Chem. Soc.*, **94**, 1353 (1972).

(4) Datiscacin showed significant cytotoxicity ($ED_{50} = 2.9 \times 10^{-2}$ μg/ml) against cells derived from the human carcinoma of the nasopharynx (KB).

(5) C. R. Noller, A. Melera, M. Gut, J. Shoolery, and L. F. Johnson, *Tetrahedron Lett.*, 15 (1960).

(6) H. Audier and B. Das, *ibid.*, 2205 (1966).

(7) S. M. Kupchan, A. H. Gray, and M. D. Grove, *J. Med. Chem.*, **10**, 337 (1967).

(8) D. Lavie and Y. Shvo, *J. Amer. Chem. Soc.*, **82**, 966 (1960).

to benzilic acid rearrangement and of the 23,24 bond of similar compounds to retro aldol cleavage.[9] In a parallel study, we recently found the alkaline solvolysis of the ester in a ketol acetate to be facilitated by the adjacent carbonyl group or its hemiketal adduct.[10] Accordingly, treatment of datiscacin (1) with sodium carbonate in aqueous methanol for 12 hr at room temperature effected a smooth solvolysis of the 20-acetate ester group, to yield cucurbitacin I (4). The interrelation completed the proof of the structure of datiscacin (1), the first recognized cucurbitacin 20-acetate ester derivative.

Experimental Section

Melting points were determined on a Mettler FP2 melting point apparatus. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. Ultraviolet spectra were recorded on a Coleman Hitachi EPS-3T recording spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian HA-100 spectrometer using TMS as an internal reference. Mass spectra were recorded on either Hitachi Perkin-Elmer RMU-63 or AEI MS-902 spectrometers, equipped with direct insertion probes. High-pressure liquid chromatography was carried out on a Waters ALC-202/401 liquid chromatographic system. Analytical and preparative tlc were carried out on Brinkmann Silplates. Petroleum ether refers to the fraction of bp 60–68°. Evaporations were carried out at reduced pressure below 40°. Analyses were carried out by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Extraction and Fractionation.—The dried ground roots of *Datisca glomerata* Baill. (10 kg)[11] were continuously extracted with chloroform for 20 hr. Evaporation gave crude extract A (270 g), which was partitioned between water (500 ml) and chloroform (two 1-l. portions). The chloroform solution was evaporated to give a viscous brown residue (C, 260 g). The aqueous solution was freeze-dried to yield fraction B (3 g). Fraction C was partitioned between aqueous methanol (1:9, 1 l.) and petroleum ether (three 1-l. portions). Evaporation of the aqueous methanol solution gave fraction D (230 g) and the combined petroleum ether extracts yielded residue E (25 g). Fraction D was partitioned between aqueous methanol (2:8, 1 l.) and carbon tetrachloride (two 1-l. portions). The aqueous methanol layer gave fraction F (154 g) and the carbon tetrachloride layer gave fraction G (70 g).

Isolation of Datiscacin.—Fraction G (70 g) was further fractionated by column chromatography on silica gel (1.2 kg, 70–325 mesh). Elution with chloroform followed by 5% methanol–chloroform yielded a fraction (H, 1.35 g) enriched in datiscacin. Fraction H was separated by repeated preparative tlc with diethyl ether and the main band was eluted with methanol to give a light-yellow gum. The gum was crystallized from ethanol to give datiscacin (1, 25 mg), $C_{32}H_{44}O_8$: mp 208–212°; $[\alpha]^{23}D$ −18° (*c* 0.87, $CHCl_3$); uv $\lambda_{max}^{CHCl_3}$ 231 nm (ε 9600), 268 (5400); ir (KBr) 2.79–2.88, 3.35, 3.41, 5.81, 5.95, 6.13, 7.14, 7.30, 7.89, 8.81, 8.89, 9.02, 10.1, and 12.6 μ; nmr ($CDCl_3$) τ 3.17 (1 H, d, *J* = 16 Hz), 3.75 (1 H, d, *J* = 16 Hz), 4.19 (1 H, s), 4.29 (1 H, d, *J* = 2.5 Hz), 4.47 (1 H, m), 5.90 (2 H, m), 8.19 (3 H, s), 8.62 (3 H, s), 8.63 (3 H, s), 8.74 (3 H, s), 8.76 (3 H, s), 8.82 (3 H, s), 8.92 (3 H, s), 9.12 (3 H, s), and 9.17 (3 H, s); mass spectrum *m/e* 496, 478, 401, 385, 383, 369, 367, 219, 164, 113, 96, and 43.

Anal. Calcd for $C_{32}H_{44}O_8 \cdot {}^1/_2H_2O$: C, 67.94; H, 8.02. Found: C, 67.81; H, 8.18.

Acetylation of Datiscacin (1) to Triacetate 2.—A solution of datiscacin (1, 10 mg) in anhydrous pyridine (0.5 ml) and acetic anhydride (0.5 ml) was stirred overnight at room temperature under nitrogen. The solution was evaporated *in vacuo* and the residue was dissolved in ethanol and reevaporated. The oily residue (10 mg) was separated by preparative tlc with diethyl ether. The product (8 mg) was crystallized from diethyl ether–hexane to give 2 (5 mg): mp 119–120°; $[\alpha]^{23}D$ −43° (*c* 1.40, $CHCl_3$); ir (KBr) 2.80, 3.35–3.52, 5.75, 5.92, 6.15, 6.90, 7.30, 8.00, 8.30, 9.65, and 13.4 μ; nmr ($CDCl_3$) τ 2.82 (1 H, d, *J* = 16 Hz), 3.58 (1 H, d, *J* = 16 Hz), 4.16 (1 H, m), 4.78 (1 H, m), 5.06 (1 H, s), 7.76 (3 H, s), 7.92 (3 H, s), 8.08 (3 H, s), 8.36 (6 H, s), 8.48 (6 H, s), 8.60 (6 H, s), and 8.88 (6 H, s); mass spectrum *m/e* 580, 538, 487, 485, 411, 409, 367, 351, 309, 111, 96, 79, 60, 45, and 43.

Anal. Calcd for $C_{36}H_{48}O_{10}$: C, 67.48; H, 7.55. Found: C, 67.10; H, 7.72.

Periodic Acid Titrations.—The titrations were performed essentially according to the procedure of Jackson.[12] A solution of substrate (13 mg) in 95% ethanol (3.00 ml) was treated with 0.043 *M* periodic acid (2.00 ml) in an erlenmeyer flask (25 ml). The flask was kept in the dark under nitrogen for 7 days. The solution was then treated with 0.056 *M* iodine solution (7.02 ml) and titrated with sodium arsenite (0.10 *M*, 3.06 ml) to the blue starch end point. Datiscacin diacetate (2) consumed no periodic acid and was recovered unchanged. Cucurbitacin I diacetate (5) consumed 1.1 molar equiv of periodic acid.[8]

Solvolysis of Datiscacin (1) to Cucurbitacin I (4).—A solution of datiscacin (1, 10 mg) in methanol (2 ml) was treated with aqueous sodium carbonate (0.1 *M*, 0.5 ml) and allowed to stand overnight at room temperature. The mixture was neutralized with acetic acid and extracted with ethyl acetate. Evaporation of the ethyl acetate solution gave a residue (8 mg) which was separated by preparative tlc with 7% methanol–chloroform. Elution of the major band followed by evaporation gave a crude product (4.5 mg) which was further separated by high-pressure liquid chromatography [column, Corasil II,[13] 3 ft × 0.375 in.; solvent, hexane–ether (3:7)]. The crystalline product (0.9 mg, from ether–petroleum ether) was characterized as cucurbitacin I (4) by mixture melting point, mass spectrum, tlc, and high pressure lc comparisons with an authentic sample.

Registry No.—1, 38308-89-3; 2, 38308-90-6; 4, 2222-07-3.

(9) *Cf.* D. Lavie, Y. Shvo, O. R. Gottlieb, and E. Glotter, *J. Org. Chem.*, **27**, 4546 (1962).

(10) S. M. Kupchan and G. Tsou, *ibid.*, **38**, 1055 (1973).

(11) The roots were collected in California in July 1962. The authors acknowledge with thanks receipt of the dried plant material from Dr. R. E. Perdue, Jr., U. S. Department of Agriculture, in accordance with the program developed by the National Cancer Institute.

(12) E. L. Jackson, *Org. React.*, **2**, 341 (1944).

(13) From Waters Associates Inc., Framingham, Mass.

A Synthesis of Homoserine Phosphate and a Blocked Derivative Suitable for Peptide Synthesis

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In the course of our studies of oligopeptide transport in *E. coli* it became of interest to synthesize peptides containing the amino acid homoserine phosphate. A search of the literature revealed no suitable chemical synthesis for either homoserine phosphate or a blocked derivative thereof. Homoserine phosphate has been prepared enzymically with crude yeast homoserine kinase;[1] we found the method cumbersome and not appropriate for the production of the relatively large quantities of blocked derivatives required for peptide synthesis. We wish to report a simple synthesis leading to *O*-diphenylphosphorohomoserine benzyl ester tosylate in an overall yield of 17% starting with homoserine. The compound can either be introduced at the carboxyl end of a suitably blocked peptide or subjected to hydrogenolysis to yield homoserine phosphate in roughly 100% yield. The synthesis has been carried out starting with DL-homoserine and L-homoserine;

(1) Y. Watanabe and K. Shimura, *J. Biochem.*, **43**, 283 (1956).

during the process of converting L-homoserine to homoserine phosphate, 19% racemization was found to occur.

Both homoserine and homoserine phosphate are intermediates in the biosynthesis of threonine. Watanabe, Konishi, and Shimura[2,3] have characterized two enzymic reactions in yeast; the first converts homoserine to homoserine phosphate, and the second converts this intermediate to threonine. The same pathway has been shown to exist in *N. crassa*[4,5] and in *E. coli*.[6] Neither compound has been found to be a constituent of proteins. The tendency of a carboxyl activated homoserine derivative (such as homoseryl tRNA) to lactonize may well be the reason nature has not made use of homoserine as a protein constituent.

The obstacle to a successful synthesis of homoserine phosphate has been the tendency of homoserine[7] or any of its N-blocked derivatives to undergo lactonization in acidic medium.[2] Moreover, *N*-benzyloxycarbonylhomoserine methyl ester is extremely base sensitive; merely washing an ethereal solution of the ester with saturated sodium bicarbonate leads to quantitative conversion of the material to the corresponding lactone. Thus, neither acidic nor basic conditions can be employed to synthesize an ester suitable for phosphorylation. It is not possible to phosphorylate a derivative blocked only at the amino function owing to rapid, initial formation of a mixed acyl phosphate anhydride followed by lactonization. Other active esters would also be expected to lactonize; in fact, we found that *N*-benzyloxycarbonylhomoserine azide lactonizes as rapidly as it is formed. It is worthy of note that several syntheses exist for *O*-phosphate esters of threonine and serine;[8] the well-known resistance of these compounds to β-lactone formation explains the ready accessibility of these two β-*O*-phosphate esters.

The obvious choice for an esterification under neutral conditions is a carbenoid-type reaction utilizing either diphenyldiazomethane or diazomethane. Although we were not able to make a benzhydryl ester following the procedure of Hardegger, *et al.*,[9] we did successfully synthesize *N*-benzyloxycarbonylhomoserine methyl ester. The ester can be phosphorylated with diphenyl phosphochloridate; however, the *N*-benzyloxycarbonyl-*O*-diphenylphosphorohomoserine methyl ester obtained from this reaction is completely refractile to hydrazinolysis, presumably owing to steric hindrance. Steric hindrance has been proposed as the explanation for the marked resistance of *N*-trityl amino acid esters to hydrazinolysis and base-catalyzed hydrolysis.[10] Although one presumably could hydrolyze the ester with methanolic potassium hydroxide, the likelihood of racemization in such a procedure led us to search for a different synthesis.

Given these problems, we turned to the synthesis of an N-blocked homoserine benzyl ester using an esterification procedure which, to our knowledge, has not previously been used in peptide chemistry. The key step in our sequence is the esterification of *tert*-butoxycarbonylhomoserine with 1-benzyl-3-*p*-tolyltriazene in ether.[11] A disadvantage of the reaction is that it produces *p*-toluidine as a by-product; as this base accumulates during the course of the reaction, the ethereal solution of *tert*-butoxycarbonylhomoserine benzyl ester becomes sufficiently basic such that the benzyl ester which has formed is subject to base-catalyzed lactonization. We could find no solution to this dilemma and this reaction is responsible for the greatest loss in yield. The ester is phosphorylated with diphenyl phosphorochloridate[12] and the *tert*-butoxycarbonyl function is removed with boron trifluoride etherate in ether[13] to give *O*-diphenylphosphorohomoserine benzyl ester, which is crystallized as its tosic acid salt. This compound has been successfully used in several peptide syntheses which will be reported separately. It has also been deblocked to give pure homoserine phosphate, which is chromatographically and biologically identical with material prepared enzymically by the procedure of Watanabe and Shimura.[1]

Using a biological assay, we find that the homoserine phosphate produced by deblocking *O*-diphenylphosphoro-L-homoserine benzyl ester is 19% racemic. The particular difficulties in synthesizing a carboxyl-blocked derivative of homoserine have forced us to make use of an esterification procedure which, to our knowledge, has not been used to esterify optically active compounds. Since only in the esterification step is a homoserine ester derivative subjected to basic conditions, we ascribe this racemization to the action of the *p*-toluidine produced in that reaction as a by-product.

Experimental Section[14]

N-tert-**Butoxycarbonyl-DL-homoserine.**—For the synthesis of this compound the DMSO method[15] proved to be the easiest. A heterogeneous solution of 2.0 g of DL-homoserine, 4.8 ml of triethylamine, and 2.6 ml of *tert*-butoxycarbonyl azide was stirred for 20 hr, after which time the solution was homogeneous. A noncrystallizable oil (4 g) was isolated which has a slight odor of DMSO. By the criterion of tlc, the material was homogeneous.

N-tert-**Butoxycarbonyl-DL-homoserine Benzyl Ester.**—The acid (8.5 g) was dissolved in 200 ml of anhydrous ether. 1-Benzyl-3-*p*-tolytriazene (11.3 g) (previously recrystallized from hexane) in 50 ml of anhydrous ether was added over a period of 15 min to the stirred solution of *tert*-butoxycarbonylhomoserine. The reaction was allowed to proceed for 1.5 hr at room temperature; although the reaction was not complete by this time, it was terminated since lactonization began to occur (tlc). Remaining *tert*-butoxycarbonylhomoserine can be removed from the ether by aqueous extraction whereas the lactone cannot. The benzyl ester (8 g) (as an oil) was isolated which was free of lactone and free acid (tlc).

O-**Diphenylphosphoro-DL-homoserine Benzyl Ester Tosylate.**—The benzyl ester (2.8 g) was phosphorylated with diphenyl

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(7) M. D. Armstrong, *J. Amer. Chem. Soc.*, **71**, 3399 (1949).
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(14) Tlc was performed on silica gel plates (Mann Research Laboratories) with 100% ethyl acetate as the developing solvent. Melting points are uncorrected.
(15) J. M. Stewart and J. D. Young, "Solid State Peptide Synthesis," W. H. Freeman, San Francisco, Calif., 1969, p 28.

phosphorochloridate (2.5 ml) in CCl_4 and anhydrous pyridine; 3.8 g of an orange oil was isolated. The free amine, obtained by removal of the *tert*-butoxycarbonyl function with boron trifluoride, was precipitated from ether with an ethereal solution of tosic acid. The crude tosic acid salt (2 g) was filtered from the ether after standing overnight in the cold. The yield for each step was difficult to calculate owing to the fact that none of the intermediates could be crystallized. However, starting with 3.5 g (29 mmol) of DL-homoserine, 4.5 g (7.3 mmol) of the crude tosic acid salt was isolated which represents an overall yield of 25%. The crude tosic acid salt can be twice crystallized from alcohol and ether with a 70% recovery to give crystals with a melting point of 110–112°.

Anal. Calcd for $C_{30}O_9NSPH_{32}$: C, 58.7; N, 2.29; H, 5.23. Found: C, 59.20; N, 2.39; H, 5.33.

Conversion of L-homoserine to the corresponding tosic acid salt (mp 109–110°) was effected in a similar yield.

L-Homoserine Phosphate.—*O*-Diphenylphosphoro-L-homoserine benzyl ester tosylate (122 mg) was converted to the free amine and dissolved in 2 ml of distilled acetic acid; 100 mg of PtO_2/C was added and the reaction mixture was subjected to hydrogenolysis at room temperature and pressure. The progress of the reaction was monitored by assaying the phosphate content of an aliquot of the reaction mixture[16] treated with alkaline phosphatase; it was found that the reaction required 4 days to go to completion. Homoserine phosphate was isolated in quantitative yield; the material cochromatographs with homoserine phosphate prepared enzymically, is ninhydrin and phosphate positive,[17] and, after alkaline phosphatase treatment, cochromatographs with homoserine. In both cases one-dimensional chromatography was performed with Whatman Chromatography Paper No. 1 with phenol–water (80:20) as the developing solvent.[1]

Racemization Assay.—In order to determine the degree of racemization accompanying our synthesis of L-homoserine phosphate we made use of the auxotroph, *E. coli* M-145.[18] This organism can utilize L-homoserine in the place of three of its required amino acids, methionine, threonine, and isoleucine. It cannot, however, utilize homoserine phosphate as such owing to the impermeability of this anion. Thus, in order to assay the material for its optical purity, it was dephosphorylated with alkaline phosphatase.[19] The enzymic reaction produced homoserine in virtually quantitative yield (paper chromatography); any remaining homoserine phosphate will not interfere with the biological assay, as it cannot be utilized by the bacterium. As shown in Table I, the homoserine from L-homoserine phosphate

TABLE I
GROWTH YIELD OF M-145 ON HOMOSERINE AND HOMOSERINE PHOSPHATE

Sample	Klett units per micromoles of material
L-Homoserine	530
DL-Homoserine	270
L-Homoserine phosphate[a]	430
DL-Homoserine phosphate[a]	270

[a] The number of micromoles of phosphate released by the alkaline phosphatase is taken to be the number of micromoles of homoserine available to the organism to support its growth. See Experimental Section for details.

is 81% as effective as an L-homoserine standard in supporting growth of the auxotroph, indicating that 19% of the synthetic material is D-homoserine phosphate.

Registry No.—*N*-*tert*-Butoxycarbonyl-DL-homoserine, 38308-92-8; DL-homoserine, 1927-25-9; triethylamine, 121-44-8; *tert*-butoxycarbonyl azide, 1070-19-5; *N*-*tert*-butoxycarbonyl-DL-homoserine benzyl ester, 38308-93-9; 1-benzyl-3-*p*-tolyltriazene, 17683-09-9; *O*-diphenylphosphoro-DL-homoserine benzyl ester tosylate, 38308-95-1; *O*-diphenylphosphoro-DL-homoserine benzyl ester, 38308-96-2; diphenylphosphorochloridate, 2524-64-3; L-homoserine phosphate, 4210-66-6; *O*-diphenylphosphoro-L-homoserine benzyl ester tosylate, 38308-98-4.

Acknowledgment.—This work was supported by Research Grant AM-10336 from the National Institutes of Health.

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Base-Catalyzed Condensation of Aldehydes with Ethyl Bis(diethylphosphonomethyl)phosphinate[1]

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As a possible synthesis of ethyl (diethylphosphonomethyl)vinylphosphinates **4** we have explored the base-catalyzed condensation of aldehydes with ethyl bis(diethylphosphonomethyl)phosphinate (**2**). Based on previously reported results[2] as well as our experience, the base-catalyzed condensation of tetraethyl methylenediphosphonate (**1**) with aldehydes is an excellent synthetic method for vinylphosphonates. We therefore expected that, during the course of the base-catalyzed reaction of **2** with aldehydes, diethyl phosphate ion would be eliminated with the formation of **4**. Instead, **5** was eliminated with the formation of **3**. The course of the reaction was the same when a number of solvents (benzene, ethanol, DMSO, ether, 1,2-dimethoxyethane) and a number of bases (sodium hydride, sodium ethoxide, potassium *tert*-butoxide) were used. The reaction is stereoselective with formation of predominantly the *trans*-vinylphosphonates. The stereochemistry was assigned on the basis of the nmr spectra and gas chromatograms.[3]

In order to change the electronic and steric properties of the central phosphorus atom, phenyl bis(diethylphosphonomethyl)phosphinate and isopropyl bis(diisopropylphosphonomethyl)phosphinate were prepared and reacted with isobutyraldehyde. The results were the same as with **2**. No attempt has been made to maximize these factors. From our very limited study we cannot indicate why the C–P bond of a phosphinate is cleaved in preference to a C–P bond of a phosphonate. Examination of models of possible transition states and intermediates has not lead us to an explanation.

One practical utilization of this reaction is the synthesis of compounds such as **5**. Such compounds are

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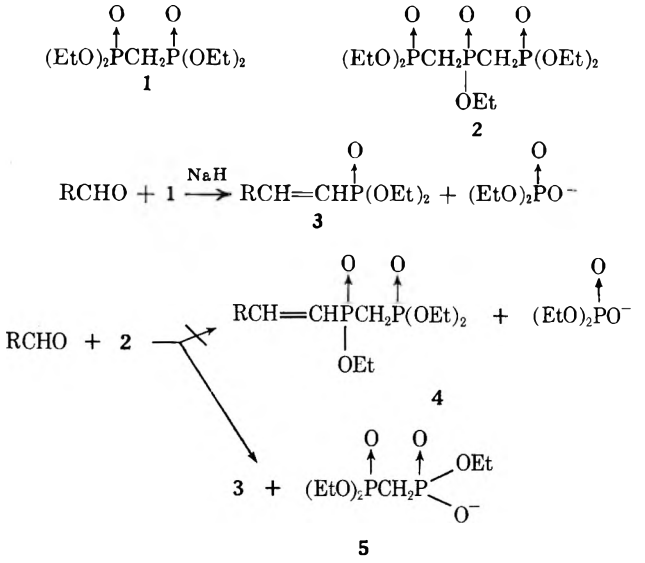
not easily prepared without the use of some unsymmetrical intermediate.



Experimental Section[4]

Diethyl β-Styrylphosphonate (3, R = Phenyl).—A solution of 15.8 g (0.04 mol) of **2**[5] in 25 ml of C_6H_6 was added dropwise to a stirred suspension of 1.7 g (0.04 mol) of sodium hydride (57% dispersion in mineral oil) in 50 ml of C_6H_6. When the solution had become clear, 4 g (0.038 mol) of benzaldehyde in 25 ml of C_6H_6 was added dropwise. Stirring was continued overnight. The C_6H_6 was washed with 100 ml of H_2O in five portions and was concentrated to an oil, which after distillation afforded 3.7 g (41%) of the phosphonate: bp 122–126° (0.025–0.05 mm) [lit. bp 137–138° (0.03 mm),[5a] 125–126° (0.3 mm),[6b] 134° (1.5 mm),[6c] 116–118° (0.35 mm),[2a] 138° (2 mm)[6d]]; $n^{20}D$ 1.5250 [lit. $n^{20}D$ 1.5665,[6a] 1.5298,[6c] 1.5325[6d]]; nmr[6b] (CCl_4) δ 7.35–8.06 (m, 6, C_6H_5CH=), 6.3 (t, 1, J = 18 Hz, C=CHP),[3b,7] 4.15 (m, 4, J = 9 Hz, $POCH_2$), and 1.35 (t, 6, J = 8 Hz, $POCH_2CH_3$); ir[6b] (neat) 690, 740 (phenyl), 1620 (CH=CH), 1160 (POC), and 1250 cm^{-1} (P=O).

The aqueous extract was evaporated to obtain a glassy solid, which was dried under reduced pressure. The resulting solid was pulverized to obtain 8.07 g (76%) of the sodium salt **5**, mp 104–109°. A 1-g sample of the salt was dissolved in 100 ml of water and passed through an Amberlite IR-120 H. C. P. column (2 × 32 cm). Evaporation of the eluate gave 0.93 g of triethyl hydrogen methylenediphosphonate (**5**) as a gum: nmr (CCl_4) δ 12.05 (s, 1, POH), 4.22 (m, 6, J = 8 Hz, $POCH_2$), 2.58 (t, 2, J = 22 Hz, PCH_2P) and 1.39 (t, 9, J = 8 Hz, $POCH_2CH_3$); ir (neat) 1240 (P=O) and 1170 cm^{-1} (POC).

Anal. Calcd for $C_7H_{18}O_6P_2$: C, 32.31; H, 6.97; P, 23.81. Found: C, 32.19; H, 6.77; P, 23.98.

Diethyl 3-Methyl-1-butenylphosphonate [3, R = $(CH_3)_2CH$].—The procedure was the same as that described above. Evaporation of the C_6H_6 layer gave a yellow liquid, which was distilled under reduced pressure to obtain 4.7 g (57%) of diethyl 3-methyl-1-butenylphosphonate: bp 45° (0.025 mm); $n^{25}D$ 1.4372; ir (neat) 1640 (CH=CH), 1375, 1395 (Me_2CH), 1250 (P=O), and 1165, 1025 cm^{-1} (POC); nmr[3c] (CCl_4) δ 6.84 (m, 1, J_{HH} = 7, J_{HH} = 18, J_{HP} = 23 Hz, CH=CP), 5.65 (t, 1, J_{HH} = J_{HP} = 18 Hz, C=CHP), 4.13 (m, 4, J = 7 Hz, $POCH_2$), 2.5 (m, 1, Me_2CH), 1.3 (t, 6, J = 7 Hz, $POCH_2CH_3$), and 1.1 (d, 6, J = 7 Hz, CH_3CHCH_3).

The nmr spectrum is consistent with that reported[3c] for the trans isomer.

Gc analysis indicates less than 1% of a compound with smaller retention volume than the major component. This minor component is believed to be the cis isomer.

Registry No.—**2**, 18033-91-5; *trans*-**3** (R = *i*-Pr), 33536-50-4; *cis*-**3** (R = *i*-Pr), 18689-34-4; **5**, 38379-50-9; **5** sodium salt, 38379-51-0.

Acknowledgment.—We wish to thank Dr. John K. Baker for helpful discussions of the nmr spectra.

(4) Melting points were taken on a Mel-Temp melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Nmr spectra were taken on a Jeolco Model C-60-HL spectrometer using tetramethylsilane as an internal standard. Gas chromatograms were obtained with a 5 ft × 0.25 in. column packed with 10% 20M Carbowax on 80–100 mesh Chromosorb W. The column was maintained at 200° in a Perkin-Elmer Model 900 chromatograph equipped with a flame ionization detector. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

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Claisen Condensation. A Method for the Synthesis of Long Chain Dicarboxylic Acids

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Earlier syntheses of α,ω-dicarboxylic acids utilized the oxidation of α,ω-glycols, the hydrolysis of dinitriles, the malonic ester synthesis with α,ω-dibromides, and the Crum-Brown–Walker[2] application of the Kolbe[3] synthesis. Combinations of these procedures have provided pathways for the syntheses of α,ω-dioic acids in the range of 11 to 34 carbon atoms.[4–8] Newer methods have been developed by Lettré,[9] Hünig,[10–13] Buchta,[14,15] and others.[16–23] It was our purpose to utilize a compound which could give even- and odd-numbered dicarboxylic acids. Methyl *N*,*N*-dimethylsebacamate (**4**) might be condensed by Claisen and acyloin procedures to yield dicarboxylic acids of 19 and 20 carbon atoms, respectively. Only the former was successful.

(1) Abstracted from the M.S. thesis of R. W. Shubart, Roosevelt University, June, 1970.

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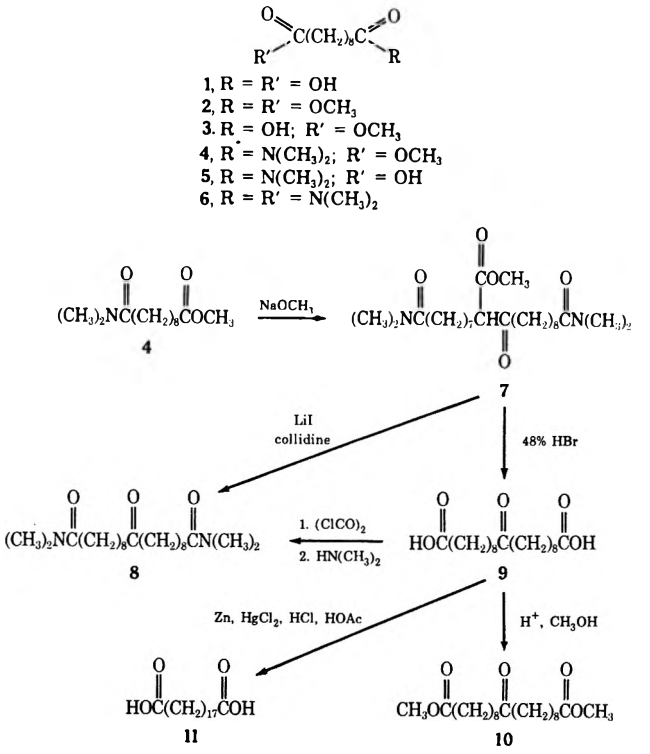

Sebacic acid (**1**) was readily converted into its dimethyl ester **2** by the method of Clinton and Laskowski.[24] Methyl hydrogen sebacate (**3**) was prepared through the formation of its barium salt[22] and subsequent acid treatment. The procedure of Dietzel[25] was also tried but gave no disproportionation. Thionyl chloride was used to convert **3** into its acid chloride, which was treated immediately with aqueous dimethylamine to give methyl *N*,*N*-dimethylsebacamate (**4**). The assigned structure was consistent with the observed spectral data and elemental analysis. In addition, compounds **5** (mp 54–56°) and **6** (mp 87–88°), prepared by the usual methods, completed the series.

The Claisen condensation of **4** was accomplished under anhydrous conditions without a solvent.[26] In order to confirm the structure of **7**, it was transformed into the diamide **8** by the procedure of Eschenmoser.[27] Hydrolysis of **7** with 48% hydrobromic acid yielded 10-oxononadecanedioic acid (**9**), which was readily converted into **8**. The dimethyl ester **10** had a melting range of 57–58° (lit. mp 50–52°[28] and 63.4°,[29,30] but spectral data was in agreement with the compound noted. The reduction of the 10-oxo group of **9** using the Huang-Minlon modification of the classical Wolff–Kishner procedure[11,31] was unsuccessful. A Clemmensen reduction following the procedure of Günthard[21] did give nonadecanedioic acid (**11**).

The acyloin condensation was run according to a known successful method[32] but it ran into difficulty from the start. The reaction evolved copious amounts of dimethylamine, indicating probable reaction with both functional groups of **4**. Several materials were isolated by chromatography but none was identified.

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Experimental Section

All chemicals were reagent grade unless otherwise indicated. Melting points were taken on a Fisher-Johns apparatus and are uncorrected. The elemental analyses were performed by Dr. F. B. Strauss of Oxford, England.

Methyl *N*,*N*-dimethylsebacamate (4).—A solution of **3** (75.7 g, 0.351 mol) in thionyl chloride (52.1 g, 0.438 mol) was heated on a hot-water bath for 1.5 hr. After removal of excess thionyl chloride under vacuum and flushing with benzene, the red acid chloride was added dropwise over 15 min to a precooled solution of 25% aqueous dimethylamine (648 ml) maintained at 5–10°. The solid was extracted immediately with benzene, the extracts were washed with water and dried with sodium sulfate, and the benzene was evaporated to give 71.4 g (0.295 mol, 83.7%) of a very low melting white crystalline solid. It was recrystallized by dissolution in hexane (500 ml) at room temperature and filtered from a small amount of insoluble white solid which was identified as **6**, and the clear solution was cooled. After several days in the refrigerator, the solid was collected and quickly washed with cold hexane. It was placed back in the refrigerator as 36.7 g (0.1516 mol, 43.2%) of white solid, mp 24°. Continued concentrations of the mother liquor gave more crops with successively lower melting points. Repeated recrystallizations from hexane gave clear colorless needles, mp 27–28°.[33]

Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 63.83; H, 10.07; N, 5.69.

***N*,*N*,*N*′,*N*′-Tetramethyl-9-carbomethoxy-10-oxononadecane Diamide (7).**—Fresh sodium methoxide was prepared by dissolving sodium metal (1.15 g, 0.05 mol) in methanol (30 ml). Careful evaporation of the excess methanol *in vacuo* left the sodium methoxide as a white powder in the bottom of the flask. Compound **4** (24.3 g, 0.10 mol) was added, and the mixture was placed in a hot-water bath. Vacuum from a water aspirator was applied as the mixture bubbled quite vigorously for 1 hr and then subsided. Total heating under vacuum was continued for 24 hr. After cooling, the "glassy" solid was treated while cooling with a mixture of 25% aqueous acetic acid (30 ml) and benzene (25 ml). After separation of the benzene layer, the aqueous layer was diluted with saline solution (30 ml) and extracted twice more with benzene. The combined benzene extracts were washed with a 50% saturated sodium chloride solution, dried over sodium sulfate, and evaporated to give 24.1 g (0.053 mol, 106%, crude) of a clear orange oil. Tlc showed the presence of a small amount of starting material (possibly 5%). The product could be purified by continuous extraction of the orange oil with hot hexane for 4 days (73% recovery) or for 7 days (90% recovery) to give a clear yellow oil which was then chromatographed on silica gel (80–200 mesh, 1.0 g of oil/14 g of silica). After removal of the starting material by elution with ethyl acetate, a mixture of ethyl acetate–acetone (1:1) eluted the product as an almost colorless clear oil. Yields ranged from 70 to 75%.

Anal. Calcd for $C_{25}H_{46}N_2O_5$: C, 66.05; H, 10.20. Found: C, 65.82; H, 10.30.

10-Oxononadecanedioic Acid (9).—A mixture of **7** (5.0 g, 0.011 mol) and 48% HBr (21 ml) was refluxed for 24 hr, cooled, and then diluted with an equal volume of water. The precipitated solid was collected and washed with water. Two recrystallizations from acetonitrile (75 ml) gave 2.94 g (0.0086 mol, 78%) of a white powder, mp 122–124° (lit. mp 123.5[34] and 124°[35]).

***N*,*N*,*N*′,*N*′-Tetramethyl-10-oxononadecanediamide (8).**—A. —A mixture of **7** (4.75 g, 0.0105 mol), anhydrous lithium iodide (10.6 g, 0.079 mol), prepared by heating the trihydrate under vacuum, and freshly distilled collidine (100 ml, bp 170°) was refluxed for 14 hr under nitrogen. After cooling to room temperature, the reaction mixture was acidified by the addition of concentrated HCl (87 ml) in water (250 ml). The acidified solution was extracted with benzene. The benzene layer was washed with water, dried over sodium sulfate, and evaporated to give 2.63 g

(33) It is also possible to distil **4** at 151–153° (0.03–0.04 mm), but it is very tedious and there is decomposition.
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(0.0065 mol, 63.3%) of an orange oil which solidified on cooling, mp 57–60°. Three recrystallizations from hexane gave 0.62 g of a white powder, mp 72–73°.

Anal. Calcd for $C_{23}H_{44}N_2O_3$: C, 69.65; H, 11.18; N, 7.06. Found: C, 69.74; H, 11.38; N, 6.69.

B.—Oxalyl chloride (4.5 g, 0.355 mol) was added dropwise over 45 min to 9 (1.0 g, 0.0029 mol) in benzene (5 ml). The mixture was stirred for 1 hr as gases evolved and then warmed in a hot-water bath for 15 min in order to effect complete solution and an end to the evolution of gases. The excess oxalyl chloride was evaporated under vacuum, and the tan-orange crude acid chloride was added along with a small amount of benzene to a precooled solution of 25% aqueous dimethylamine (15 ml) maintaining a temperature of 5–10°. The solid was extracted with benzene. The combined extracts were washed with water, dried over potassium carbonate, and evaporated to leave an oil which quickly solidified on cooling. Recrystallization from hexane (200 ml) gave 0.84 g (0.00212 mol, 72%) of a white powder, mp 72–73°. This material was spectrally identical with the solid made in part A and a mixture melting point was determined at 71–73°.

Dimethyl 10-Oxononadecanedioate (10).—A mixture of crude 9 (0.4 g), methanol (25 ml), and concentrated sulfuric acid (1 drop) was refluxed for 48 hr. The cooled reaction mixture was diluted with aqueous sodium carbonate, and the precipitated beige solid was extracted with ether. The ether solution was dried with sodium sulfate and the ether was evaporated, leaving a gummy white solid. Four recrystallizations, two from hexane (30 ml) plus DARCO and two from 30–60° ligroin (10 ml), gave 70 mg of a white powder, mp 57–58° (lit. mp 50–52°[28] and 63–64°[29,30]).

Nonadecanedioic Acid (11).—A mixture of mossy zinc metal (10 g, 0.153 g-atom), mercuric chloride (1.0 g, 0.00369 mol), water (20 ml), and concentrated HCl (1 ml) was prepared in a 250-ml flask. Compound 9 (1.0 g, 0.0029 mol) was added followed by a mixture of glacial acetic acid (10 ml) and concentrated HCl (10 ml). The mixture was heated to reflux with good stirring, and an additional amount of concentrated HCl (30 ml) was added portionwise over the next 24 hr. After another 24 hr of reflux, the cooled reaction mixture was diluted with water. The precipitated white solid was collected and washed with water. Recrystallization from acetonitrile (75 ml) gave 0.55 g (0.00166 mol, 58%) of white crystals, mp 115–117° (lit. mp 118–119°[34,36]).

Registry No.—**3**, 818-88-2; **4**, 38312-53-7; **7**, 38312-54-8; **8**, 38312-55-9; **9**, 18197-46-1; **10**, 29263-75-0; **11**, 6250-70-0.

Acknowledgment.—The authors are grateful to the Witco Chemical Corporation for a research grant and to the Pennwalt Corporation for a very generous supply of sebacic acid.

(36) A. Blomquist, *J. Amer. Chem. Soc.*, **74**, 4203 (1952).

Determination of C-22 Epimers in Steroids Using Nuclear Magnetic Resonance Spectroscopy[1]

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In a recent publication the stereospecific syntheses of (20*S*,22*R*)- and (20*S*,22*S*)-17α,20,22-trihydroxycholesterol were described.[2] The determination of configuration at C-22 was secured from an examination of the ORD/CD spectra of the 22-benzoate esters of derivatives of these compounds.

The present communication reports a method based on nmr analyses of the hydroxy compounds which achieves the same result. Table I presents the 60-MHz nmr chemical shift data for cholesterol and a number of related compounds, obtained from $CDCl_3$ solutions. The pertinent signals are those for the C-21 methyl and the C-22 proton(s), although the signals for the C-18 and C-19 methyls are also listed for reference.

The C-21 methyl signal of cholesterol (I) occurs as a doublet, centered at *ca.* 55.2 Hz ($J \cong 5.0$ Hz), partially obscured by the doublet from the C-26,27 methyls. In (20*S*)-hydroxycholesterol (II) the C-21 methyl signal is shifted 21.8 Hz downfield. In neither spectrum is a unique signal for the C-22 protons discernable.

In the spectra of both (22*R*)- and (22*S*)-hydroxycholesterol (III and IV, respectively) the signals for the C-22 proton is shifted downfield to *ca.* 215 Hz, and hence are not useful for isomer identification. As seen from Table I, the signals for the C-18, C-19, and C-21 methyls likewise do not differentiate the isomers. A similar situation is observed for the spectra of the two isomeric (22*R*)- and (22*S*)-3α,5-cyclo-5α-cholestane-6β,22-diol 6-methyl ethers (V and VI, respectively).

When the spectra of the two epimeric (20*S*,22*R*)- and (20*S*,22*S*)-3α,5-cyclo-5α-cholestane-6β,20,22-triol 6-methyl ethers (VII and VIII, respectively) are compared, two pronounced differences are discerned. After assigning the signals for the C-18, C-19, C-26, and C-27 methyls, a singlet is observed at 72 Hz for the 22*R* isomer and at 77 Hz for the 22*S* isomer, which can only be assigned to the C-21 methyl protons. In addition, for the 22*R* isomer a triplet corresponding to one proton ($J = 7$ Hz) is observed at 222 Hz, while for the 22*S* isomer a broadened signal, also corresponding to one proton, is observed at *ca.* 195 Hz. These signals must be assigned to the C-22 protons of the isomers.

From the data cited for the two isomeric (22*R*)- and (22*S*)-hydroxycholesterols, it is to be noted that the conformation of the C-22 hydroxyl group, by itself, has no appreciable effect on the chemical shift of the C-21 methyl protons. Yet the above data show that when hydroxyl functions are present at *both* C-20 and C-22 a 5-Hz difference is observed between the chemical shifts of the C-21 methyl protons of the two isomers. The simplest explanation consistent with these observations is that factors influencing the chemical shift of the C-21 methyl protons differ in the two isomers. Through-bond contributions to these factors should be essentially identical for both isomers. Hence a steric or through-space explanation appears reasonable. In order for this explanation to be valid, when the C-20 hydroxyl group is present some functional group which contributes to the chemical shift of the C-21 methyl protons must adopt a different steric relationship to the C-21 methyl group in the (22*R*)-hydroxy isomer than it does in the (22*S*)-hydroxy isomer.

Molecular models show that the (20*S*)- and 22-hydroxyl groups are well situated for intramolecular hydrogen bonding. That this is indeed occurring in these compounds is confirmed by the chemical shifts of the hydroxyl protons, which are observed at *ca.* 120 Hz for both compounds. Both spectra were obtained from

(1) This work was supported by funds from the U. S. Public Health Service, RR05528, and institutional funding from the Worcester Foundation for Experimental Biology.

(2) R. C. Nickolson and M. Gut, *J. Org. Chem.*, **37**, 2119 (1972).

TABLE I

CHEMICAL SHIFTS OF SELECTED RESONANCES OF CHOLESTEROL AND SOME OF ITS DERIVATIVES[a]

No.	Compd	18 CH_3	19 CH_3	21 CH_3	22 H
I	Cholesterol	41.0	60·5	55.2	?
II	(20*S*)-Hydroxycholesterol	52.0	61.0	77.0	?
III	(22*R*)-Hydroxycholesterol	42.0	60.5	*ca.* 53.5	*ca.* 215
IV	(22*S*)-Hydroxycholesterol	41.5	60.0	*ca.* 53.5	*ca.* 215
V	(22*R*)-3α,5-Cyclo-5α-cholestane-6β,22-diol 6-methyl ether	44.5	61.5	*ca.* 54.5	*ca.* 215
VI	(22*S*)-3α,5-Cyclo-5α-cholestane-6β,22-diol 6-methyl ether	44.0	61.5	*ca.* 54.5	*ca.* 215
VII	(20*S*,22*R*)-3α,5-Cyclo-5α-cholestane-6β,20,22-triol 6-methyl ether	56.0	60.5	72.0	222
VIII	(20*S*,22*S*)-3α,5-Cyclo-5α-cholestane-6β,20,22-triol 6-methyl ether	58.0	60.5	77.0	*ca.* 195
IX	(20*S*,22*R*)-3α,5-Cyclo-22,23-epoxy-24-nor-5α-cholane-6β,20-diol 6-methyl ether	54.0	61.0	75.0	177.5
X	(20*S*,22*S*)-3α,5-Cyclo-22,23-epoxy-24-nor-5α-cholane-6β,20-diol 6-methyl ether	54.5	62.0	83.0	*ca.* 172
XI	(20*S*,22*R*)-3α,5-Cyclo-24-nor-5α-cholane-6β,20,22,23-tetrol 6-methyl ether	54.0	61.0	73.0	217
XII	(20*S*,22*S*)-3α,5-Cyclo-24-nor-5α-cholane-6β,20,22,23-tetrol 6-methyl ether	54.0	61.0	78.0	210

[a] In hertz, downfield from internal TMS. All spectra were recorded on a Varian Associates DA-60 IL spectrometer, from $CDCl_3$ solutions.

ca. 0.2–0.3 *M* solutions (in $CDCl_3$). At such concentrations of steroids, when only *intermolecular* hydrogen bonding occurs, the hydroxyl signals are observed at higher field. For example, the hydroxyl signal for a solution of comparable concentration of (22*R*)-3α,5-cyclo-5α-cholestane-6β,22-diol 6-methyl ether occurs at 91 Hz. It has previously been shown that even at infinite dilution the signal of an intramolecularly hydrogen bonded hydroxyl will occur at lower field than that for a hydroxyl which does not undergo intramolecular hydrogen bonding.[3]

From molecular models, it is observed that when intramolecular hydrogen bonding occurs between the (20*S*)- and (22*R*)-hydroxyls the C-22 proton is situated cis to the C-21 methyl. For the similar situation between the (20*S*)- and (22*S*)-hydroxyls the C-22 proton is *trans* to the C-21 methyl. Conversely, the remainder of the side chain (carbons 23 through 27) is situated trans to the C-21 methyl in the 22*R* isomer and cis in the 22*S* isomer. This is illustrated in Figure 1.

From the spectra of testosterone and epitestosterone it is observed that the C-17 proton cis to the C-18 methyl (in epitestosterone) gives a signal some 5 Hz further downfield than does the C-17 proton trans to the C-18 methyl (in testosterone). With the formation of an intramolecular hydrogen bond, as shown in Figure 1, a similar situation might be expected to be observed for the signals of the C-22 protons of the two isomers under discussion.

As mentioned earlier, this is indeed observed for the C-22 proton, the difference being *ca.* 7 Hz.

It thus follows that a likely explanation for the observed difference in chemical shifts for the C-21 methyl protons of the two isomers arises from the different steric orientation of carbons 23–27 with respect to the C-21 methyl group in the two isomers (*cf.* Figure 1). The hydroxyl groups of the two isomers are situated in sterically equivalent positions with respect to the C-21 methyls, and are not *per se* responsible for the difference in chemical shifts.

(3) T. A. Wittstruck and J. F. Cronan, *J. Phys. Chem.*, **72**, 4243 (1968).

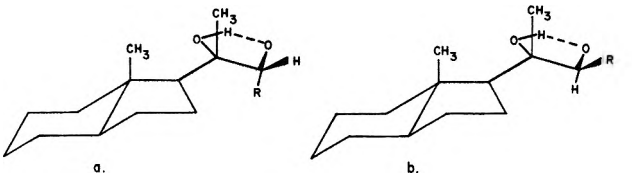

Figure 1.—Conformations adopted upon intramolecular hydrogen bonding between (a) (20*S*)-hydroxyl and (22*R*)-oxygen function, (b) (20*S*)-hydroxyl and (22*S*)-oxygen function in steroids. Only rings C and D of steroid are shown.

The fact that a sharp triplet is observed for the C-22 proton in the 22*R* compound but not in the 22*S* compound probably reflects freedom of rotation about the C-22–23 bond in the former but not in the latter.

The spectra of several other pairs of isomers containing the (20*S*)-hydroxyl function as well as an oxygen function of C-22 were examined in the light of the above interpretation. Thus, the lower melting isomer of (20*S*)-3α,5-cyclo-22,23-epoxy-24-nor-5α-cholane-6β,-20-diol 6-methyl ether (IX) gives its C-21 methyl signal at 75 Hz, whereas its higher melting isomer (X) gives the C-21 methyl signal at 83 Hz. The spectrum of the former shows a triplet ($J \cong 3$ Hz) at 177.5 Hz for the C-22 proton. For the latter isomer the C-22 signal occurs further upfield and in fact merges with the signals from the C-23 protons, giving an ABC pattern. (This multiplet has not been analyzed by exact analysis; hence the precise values of the chemical shifts for these protons are not available.) On the basis of the above interpretation the lower melting isomer must be assigned the 22*R* configuration, while the higher melting isomer is assigned the 22*S* configuration.

The two isomers of (20*S*)-3α,5-cyclo-24-nor-5α-cholane-6β,20,22,23-tetrol 6-methyl ether (XI and XII) give similar results. For the higher melting isomer (XI), the signals for the C-22 and C-23 protons all occur at approximately the same chemical shift so that only a slightly broadened (*ca.* 6 Hz) peak is observed centered at 217 Hz. The lower melting isomer (XII) gives a slight separation for the signals of these

protons. The C-22 proton gives a signal at 210 Hz while the C-23 protons give a broader signal centered at 220 Hz.

Based on the above examples, this method of assignment of conformation at C-22 appears to be sufficiently general to be considered whenever the C-20, C-22 diol system is present.

The author wishes to thank Dr. Marcel Gut for supplying most of the samples. Compound II,[4] and the epimeric pairs III and IV,[5] have previously been reported in the literature. The chemistry of the remaining compounds (V–XII), which were obtained from Dr. Gut, has not yet been published. Their nmr spectra agreed fully with the assigned structures.

Registry No.—I, 57-88-5; II, 516-72-3; III, 17954-98-2; IV, 22348-64-7; V, 38379-54-3; VI, 38379-55-4; VII, 38379-56-5; VIII, 38379-57-6; IX, 38379-58-7; X, 38379-59-8; XI, 38379-60-1; XII, 38379-61-2.

(4) V. Petrow and I. A. Stewart-Webb, *J. Chem. Soc.*, **46**, 75 (1956).
(5) N. K. Chaudhuri, R. Nickolson, H. Kimball, and M. Gut, *Steroids*, **15**, 525 (1970).

Sulfonation of Terpene Derivatives. Aluminum Hydride Desulfurization of Sultones

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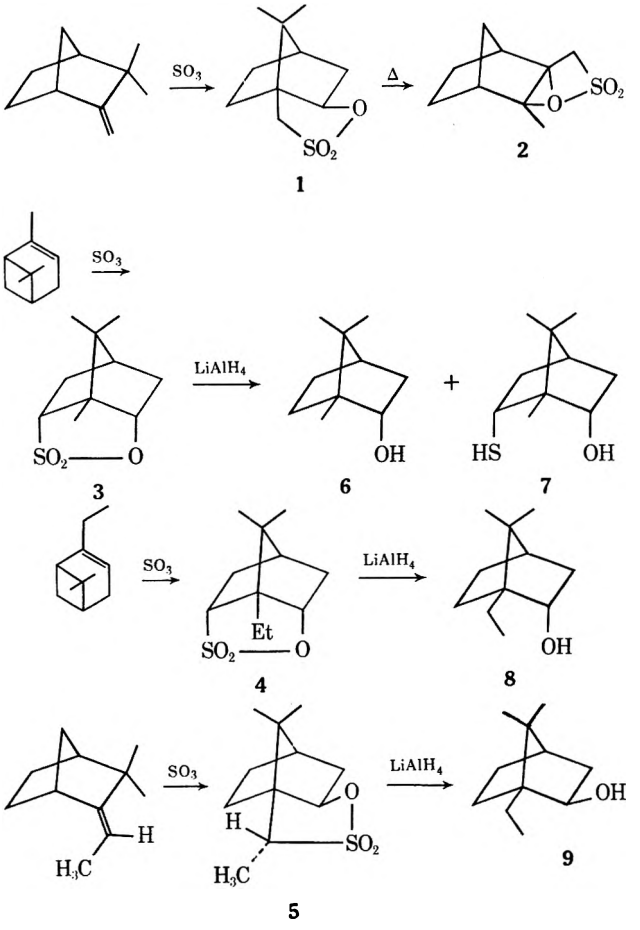
The reaction of camphene with sulfur trioxide–dioxane complex[1] in methylene chloride affords 10-isobornylsultone (**1**), which rearranges thermally at 150–170° to camphenesultone (**2**).[2] Herein we report that sulfonation of α-pinene, α-ethylapopinene, and 8-methylcamphene afford 6-bornylsultone (**3**), 10-methyl-6-bornylsultone (**4**), and 10-methyl-10-isobornylsultone (**5**), respectively, in poor to good yield.

6-Bornylsultone (**3**) exhibits normal sulfonate ester infrared absorption at 7.6 and 8.7 μ. The nmr spectrum, in addition to showing three methyl singlets, displays a broadened one-proton doublet centered at 4.60 ppm assigned to the C-2 proton and a broadened doublet of doublets centered at 3.15 ppm attributed to the C-6 proton.

The structure of **3** was confirmed by aluminum hydride[3] or lithium aluminum hydride reduction[2] to borneol (**6**). 6-*endo*-Mercaptoborneol (**7**) was also isolated from the lithium aluminum hydride reduction[4] and exhibited two eight-line nmr signals, after trifluoroacetic acid was added to remove the spin coupling of the –SH proton, consistent with the di-endo-configurational assignment.[5]

Sulfonation of 8-methylcamphene[6] yields a single isomer of 10-methyl-10-isobornylsultone (**5**), which is assigned an *endo*-10-methyl configuration on the assumption that sulfonation of the camphene double bond occurs from the more accessible exo face of the molecule.

10-Methyl-10-isobornylsultone (**5**) is transformed into 10-methyl-isoborneol (**9**) on reduction with aluminum hydride, while 10-methyl-6-bornylsultone affords 10-methylborneol (**8**) under the same conditions.



The sulfonation–desulfurization sequence described above provides a convenient method for the preparation of 10-substituted borneol and isoborneol derivatives. Although the sulfonation of pinene and camphene derivatives involve Wagner–Meerwein shifts, the reaction is free of Nametkin methyl migration, which plays an important role in the addition of acetic acid derivatives to 8-substituted camphene derivatives.[7] Desulfurization of sultones with lithium aluminum hydride proceeds slowly, and, at best, gives poor to fair yields of sulfur-free alcohol. Reduction with aluminum hydride, on the other hand, is relatively rapid and affords good yields of alcohols.

(1) For the sulfonation of olefins see F. Bordwell, R. D. Chapman, and C. E. Osbourne, *J. Amer. Chem. Soc.*, **81**, 2002 (1959); F. Pueshal and C. Kaiser, *Chem. Ber.*, **98**, 735 (1965), and references cited therein.
(2) J. Wolinsky, D. R. Dimmel, and T. W. Gibson, *J. Org. Chem.*, **32**, 2087 (1967).
(3) J. Wolinsky and R. Lau, *Syn. Commun.*, 2, 327 (1972).
(4) The lithium aluminum hydride reduction of terpene sultones will be described in a forthcoming publication.
(5) We attribute the absence of eight-line signals in sultone **3** to the presence of the sultone ring which distorts the bond angles of the bornane ring.
(6) 8-Methylcamphene consists of a mixture of *anti*-8-methyl and *syn*-8-methyl isomers in a ratio of 13:1, respectively.[7]
(7) J. Wolinsky and E. J. Eustace, to be published.

Experimental Section[8]

6-Bornylsultones (3).—To a freshly prepared solution of 266 g (1.52 mol) of sulfur trioxide–dioxane complex in 400 ml of methylene chloride at −78° was added (2 hr) a solution of 184 g (1.35 mol) of α-pinene (practical grade, 90% $[\alpha]_D$ +46°) in methylene chloride. The solution was allowed to warm to room temperature and stirred for 17 hr. Ether was added and the solution was washed with saturated salt solution, dried ($MgSO_4$), and concentrated to leave 165 g of a dark brown oil, which slowly deposited crystals. Recrystallization of the solid from methanol, sublimation *in vacuo*, and chromatography of the mother liquors on neutral alumina yielded a total of 21.0 g (7.3%) of 6-bornylsultone (**3**). The analytical sample of **3** was obtained by recrystallization from 2:1 hexane–THF and showed mp 198–199°; $[\alpha]_D$ −12.6° (*c* 6.28, $CHCl_3$); ir (CCl_4) 7.4 and 8.6 μ; nmr (CCl_4) 0.93 and 1.00 (s's, 6, CH_3CCH_3), 1.37 (s, 3, CH_3), 3.15 (d of d, 1, $-CHSO_2-$), and 4.60 ppm (broadened d, 1, –CHO–); mass spectrum (70 eV) *m/e* (rel intensity) no parent ion, 148 (9.0), 137 (5), 109 (23), 108 (100), 93 (29), 67 (19), and 41 (20).

Anal. Calcd for $C_{10}H_{16}O_3S$: C, 55.53; H, 7.46; S, 14.83. Found: C, 55.61; H, 7.42; S, 14.71.

Lithium Aluminum Hydride Reduction of 6-Bornylsultone (3). A. 6-*endo*-Mercaptoborneol (7).—To a stirred slurry of 0.53 g (14 mmol) of $LiAlH_4$ in 20 ml of freshly distilled THF was added 1.0 g (4.6 mmol) of sultone **3**. The solution was heated at reflux for 50 hr and then the excess hydride was destroyed with water. The solids were dissolved in 5% HCl and extracted with ether. The ethereal solution was dried ($MgSO_4$) and evaporated to yield 0.62 g of an oil, which on glpc analysis proved to be a mixture of borneol (**6**), 6-mercaptoborneol (**7**), and 6-bornylsulfinate ester[3] in the ratio of 5:55:40. Preparative glpc yielded 6-*endo*-mercaptoborneol (**7**): mp 149–151° (sublimes, sealed tube); ir (CCl_4) 2.80, 3.90, 8.9 and 9.4 μ; nmr (CCl_4) 0.88 and 0.95 (s's, 9, 3 CH_3), 1.71 (t, 1, J = 4.7 Hz, C_1H), 1.97 (d, 1, J = 6.5 Hz, CHSH), 3.17 (s, 1, OH), 3.25 (m, 1, –CHSH), and 4.12 ppm (A portion of AMNX, 1, $J_{2\text{-exo},3\text{-endo}}$ = 10 Hz, $J_{2\text{exo-},3\text{-exo}}$ = 4.5 Hz, $J_{2\text{-exo},6\text{-exo}}$ = 2.1 Hz, –CHOH). Addition of F_3CCO_2H causes the signal at 3.25 to shift to 3.47 ppm ($J_{5\text{-endo},6\text{-exo}}$ = 10.5 Hz, $J_{5\text{-exo},6\text{-exo}}$ = 5.7 Hz, $J_{2\text{-exo},6\text{-exo}}$ = 2.5 Hz) and the signal at 4.12 to shift to 4.37 ppm ($J_{2\text{-exo},3\text{-endo}}$ = 10.0, $J_{2\text{-exo},3\text{-exo}}$ = 5.0 Hz, and $J_{2\text{-exo},6\text{-exo}}$ = 2.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 186 (5.4), 153 (3.8), 152 (7.8), 135 (8.6), 134 (7.4), 108 (100), 93 (28).

Anal. Calcd for $C_{10}H_{18}OS$: C, 64.46; H, 9.74. Found: C, 64.21; H, 9.55.

B. Borneol (6).—A solution of 700 mg (3.2 mmol) of sultone **3** in 5 ml of dry THF was added to a slurry of 700 mg (17.9 mmol) of $LiAlH_4$ in 10 ml of dry THF. The mixture was refluxed for 60 hr, cooled, and worked up in the normal fashion to yield an oil which by glpc analysis contained 39% borneol (**6**), 45% **7**, and 16% 6-bornylsulfinate ester.[3] The isolated product and authentic borneol had identical retention times on two glpc columns (SE-30, 160°, and Carbowax 20M, 200°). In addition, the reduction product has ir, mass, and nmr spectra identical with those of the authentic borneol.

Aluminum Hydride Reduction of 6-Bornylsultone (3).—A mixture of 1.38 g (36.6 mmol) of lithium aluminum hydride, 1.46 g (11.00 mmol) of aluminum chloride, and 790 mg (3.66 mol) of **3** was refluxed for 40 hr. The usual work-up gave 0.34 g (35%) of borneol, $[\alpha]^{24}_D$ +31.1° (EtOH) {lit.[9] $[\alpha]_D$ +37.4° (EtOH)}.

10-Methyl-10-isobornylsultone (5).—To a solution of 10.7 g (0.064 mol) of sulfur trioxide–dioxane complex in 30 ml of methylene chloride at −78° was added slowly 8.55 g (0.057 mol) of (±)-8-methylcamphene[6] in 20 ml of methylene chloride. The solution was allowed to warm to room temperature and stirred for 18 hr. Ether was added and the solution was washed with 10% sodium bicarbonate solution and saturated salt solution and dried ($MgSO_4$); the solvent was removed to yield an oil. Crystallization from hexane–THF (10:1) and chromatography of the mother liquors on silica gel afforded a total of 5.89 g (44.9%) of (±)-10-methyl-10-isobornylsultone (**5**): mp 91–94°; ir (CCl_4) 7.57 and 8.56 μ; nmr ($CDCl_3$) 0.96 and 1.01 (s's, 6, CH_3CCH_3), 1.37 (d, 3, J = 7 Hz, CH_3CH–), 3.25 (q, 1, J = 7 Hz, CH_3CH–), and 4.24 ppm (d of d, –CHO–); mass spectrum (70 eV) *m/e* (rel intensity) no parent ion, 149 (34), 122 (90), 107 (80), 105 (49), 93 (42), 81 (44), 67 (40), 41 (100), and 39 (53).

Anal. Calcd for $C_{11}H_{18}O_3S$: C, 57.36; H, 7.68; S, 13.92. Found: C, 57.25; H, 7.60; S, 13.68.

Aluminum Hydride Reduction of 10-Methyl-10-isobornylsultone (5).—To a stirred slurry of 2.62 g (19.6 mmol) of aluminum chloride and 2.48 g (65.4 mmol) of lithium aluminum hydride in 100 ml of ether at 0° was added a solution of 1.5 g (6.54 mmol) of sultone **5** in 25 ml of ether. The solution was heated at reflux for 40 hr and cooled, and 25 ml of ethyl acetate, followed by 25 ml of water, was added. The salts were removed and washed with ether, and the combined ether solution was washed with water, dried ($MgSO_4$), and evaporated to leave a foul-smelling oil. Sublimation *in vacuo* gave 670 mg (61%) of 10-methylisoborneol (**9**): mp 52–54°, ir (CCl_4) 2.92 μ; nmr ($CDCl_3$) 0.99 (t, 3, CH_3), 0.80 and 1.08 (s's, 6, CH_3CCH_3), 2.30 (m, 1, OH), and 3.84 ppm (m, 1, –CHO–); mass spectrum (70 eV), *m/e* (rel intensity) 168 (3.5), 107 (29), 95 (100), 93 (23), 79 (26), 69 (25), 67 (32), 55 (37), 53 (28), 43 (46), and 41 (86).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.26; H, 12.10.

10-Methylcamphor (10).—To a solution of 200 mg of 10-methylisoborneol (**9**) in 10 ml of acetone at 0° was added 2 ml of Jones reagent over a 10-min period. The mixture was stirred for 1 hr, and 2 ml of isopropyl alcohol was added. The salts were removed by filtration and washed with ether. The combined filtrates were washed with water, dried ($MgSO_4$), concentrated, and evaporatively distilled *in vacuo* to yield 164 mg (83%) of 10-methylcamphor (**10**): ir (neat) 5.74 μ; nmr ($CDCl_3$) 0.86, 0.97 (s's, 6, CH_3CCH_3), and 0.97 ppm (t, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 166 (18), 122 (29), 109 (37), 95 (100), 83 (18), 69 (17), 67 (18), 55 (40), and 41 (31).

The oxime of 10-methylcamphor displayed mp 103–104° (lit.[10] mp 104°).

(+)-10-Methyl-6-bornylsultone (4).—To a stirred slurry of 21.8 g (0.14 mol) of sulfur trioxide–dioxane complex in 65 ml of methylene chloride at −78° was added (1 hr) a solution of 21.0 g (0.14 mol) of α-ethylapopinene,[11-13] $[\alpha]^{21}_D$ −49.8° ($CHCl_3$), in methylene chloride. The reaction mixture was stirred at −78° for 2 hr and at ambient temperature for 18 hr. The reaction was worked up in the usual manner affording a yellow oil which was chromatographed on silica gel. The early fractions yielded 5.8 g (28%) of *p*-ethylcumene: n^{25}_D 1.4898 (lit.[14] n^{25}_D 1.4900); nmr ($CDCl_3$) 1.19 (t, 3, J = 7.5 Hz, CH_3), 1.23 (d, 6, J = 7 Hz, $(CH_3)_2CH$), 2.58 (q, 2, J = 7.5 Hz, $-CH_2-$), 2.72 (septet, 1, J = 7.0 Hz, –CH–), and 7.08 ppm (m, 4, Ar H). The later fractions yielded 1.28 g (4%) of (+)-10-methyl-6-bornylsultone (**4**). The analytical sample of **4** was obtained by recrystallization from pentane and showed mp 178–179°; ir (CCl_4) 7.40 and 8.64 μ; $[\alpha]^{24}_D$ +15.3° (c 2.10, $CHCl_3$); nmr ($CDCl_3$) 0.99, 1.07 (s's, 6, CH_3CCH_3), 1.05 (t, 3, J = 7 Hz, CH_3), 3.48 (d of d, 1, $-CHSO_2$), and 4.81 ppm (broad d, 1, –CHO–); mass spectrum (70 eV) *m/e* (rel intensity) no parent ion, 123 (14), 122 (100), 107 (39), 95 (15), 55 (22), 43 (25), 41 (38), and 39 (14).

Anal. Calcd for $C_{11}H_{18}O_3S$: C, 57.36; H, 7.88; S, 13.92. Found: C, 57.27; H, 7.80; S, 13.70.

Desulfurization of 10-Methyl-6-bornylsultone (4).—To an ice-cold slurry of 635 mg (16.7 mmol) of lithium aluminum hydride and 665 mg (5.0 mmol) of aluminum chloride in 20 ml of ether was added 384 mg (1.67 mmol) of sultone **4**. The reaction mixture was heated at reflux for 40 hr and worked up in the usual fashion to give 134 mg of crude 10-methylborneol contaminated by three minor unidentified materials. A pure sample of 10-methylborneol was isolated by vpc using a 15% Carbowax column at 180° and showed mp 59–60° (lit.[10] mp 57.5°); ir (neat) 2.92 μ; nmr ($CDCl_3$) 0.88 (s, 3, CH_3), 0.97 (s and t, 6, CH_3, and CH_3CH_2-), 2.57 (m, 1, OH), and 4.19 ppm (A portion of AMNX, 1, $J_{2\text{-exo},6\text{-exo}}$ = 1.5 Hz, $J_{2\text{-exo},3\text{-exo}}$ = 3.5 Hz, $J_{2\text{-exo},3\text{-endo}}$ = 10 Hz, –CHO–); mass

(8) All melting and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord, Model 137-B. Nmr spectra were measured with a Varian Associates A-60 spectrometer. Optical rotations were measured with a Zeiss polarimeter. Mass spectra were determined by the Purdue University Spectral Service employing a Hitachi RMU-6A mass spectrometer. Gas–liquid chromatography was performed on an Aerograph 90-P instrument using a 5-ft 20% SE-30 on Chromosorb column at 160–180°. Microanalyses were performed by Dr. C. S. Yeh and associates.

(9) E. Beckmann, *Justus Liebigs Ann. Chem.*, **250**, 353 (1889).

(10) G. Ohloff, G. Schade, and H. Farnow, *Chem. Ber.*, **90**, 113 (1957).

(11) Obtained in 67% yield by lithium aluminum hydride reduction of nopol tosylate: mp 49–50°, $[\alpha]^{24}_D$ −27.4° (*c* 5.23, $CHCl_3$), lit.[12] mp 49–50°.

(12) R. T. Arnold and M. J. Danzig, *J. Amer. Chem. Soc.*, **79**, 892 (1957).

(13) G. Ohloff, H. Farnow, and G. Schade, *Chem. Ber.*, **89**, 1549 (1956).

(14) J. P. Bain, *J. Amer. Chem. Soc.*, **68**, 638 (1946).

spectrum (70 eV) m/e (rel intensity) 168 (7.6), 124 (18), 109 (23), 95 (100), 67 (11), 55 (20), 43 (14), 41 (34), and 39 (14).

Oxidation of 10-methylborneol using the Jones procedure gave (−)-10-methylcamphor, $[\alpha]^{24}D$ −23.4° (c 2.69, EtOH) (lit.[10] $[\alpha]^{20}D$ −25°), whose ir and nmr spectra were identical with those of (±)-10-methylcamphor obtained by oxidation of 10-methylisoborneol (9).

Registry No.—**3**, 38359-42-1; **4**, 38359-43-2; **5**, 38359-44-3; **7**, 38359-45-4; **9**, 38359-46-5; **10**, 38359-47-6; α-pinene, 80-56-8; (±)-8-methylcamphene, 38359-48-7; α-ethylapopinene, 38359-49-8.

A New Synthesis of 2,3,6,7-Tetramethylnaphthalene and Its Electrochemistry

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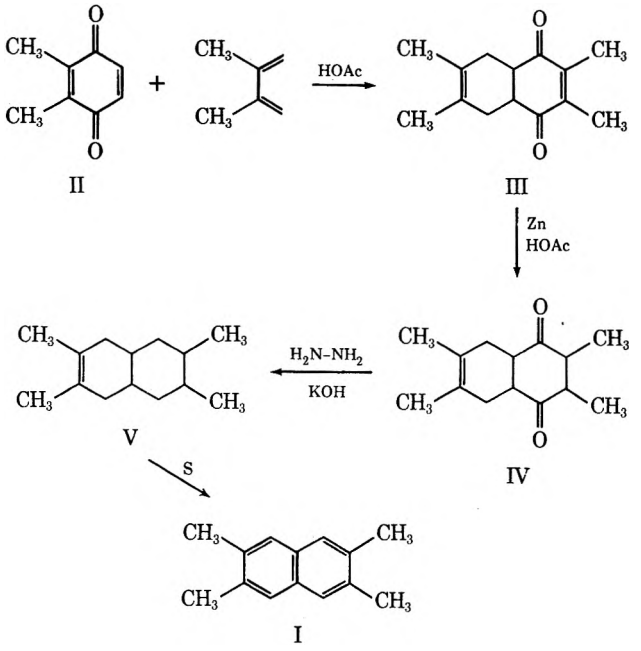
2,3,6,7-Tetramethylnaphthalene (I) was first prepared by Mosby[1b] from 2,3,6,7-tetramethylnaphthalene-1,4-dinitrile. The synthesis of this compound involved a rather long and tedious route. As we needed this compound in rather large quantities, a more convenient route was desired. The resultant synthesis is presented in this paper along with electrochemical data.

Results

Synthesis.—The synthesis of I is outlined in Scheme I. The unsaturated diketone III was synthesized by

SCHEME I



II III IV V I

Diels-Alder reactions of 2,3-dimethylbenzoquinone (II) with 2,3-dimethylbutadiene as reported by Fieser and Ardao.[2] Attempted reduction of the carbonyl groups of III using Wolff–Kishner, Clemmenson, sodium, or chlorobenzoxazole methods under various conditions gave negative results. The aromatized hydroquinone appeared to be the typical product. It was thought that saturation of the quinone-type double bond in III might reduce the molecule's tendency to aromatize. Thus, when III was treated with zinc dust in glacial acetic acid, the desired reduction to IV occurred. Furthermore, IV was then reduced by the Wolff–Kishner procedure to V in 67% yield. Heating hydrocarbon V with sulfur produced I.

Electrochemistry.—I was reduced in dimethylformamide (DMF) and oxidized in acetonitrile (AN), *n*-butyronitrile (BN), and propylene carbonate (PC). I apparently reduced cathodic to solvent breakdown in AN, BN, and PC, while oxidizing anodic to the breakdown of DMF. Table I gives the data obtained from the reduction on mercury. Polarographic determination of the half-wave reduction potential ($E_{1/2}$) was impossible owing to the fact that the wave came at the foot of solvent breakdown. Therefore, an approximate $E_{1/2}$ was calculated from the cyclic voltametry data.[3]

TABLE I
REDUCTION OF I IN DMF AT A HANGING MERCURY DROP ELECTRODE[a]

E_{peak}	−2.74 V
$E_{1/2}$[b]	−2.71 V
$E_{c\ peak} - E_{a\ peak}$	0.096 V
Sweep rate	200 mV/sec

[a] These values in volts *vs.* the saturated calomel electrode (sce). [b] Reference 3.

The results for the oxidation of I on platinum are shown in Table II. The oxidation waves from cyclic voltametry are chemically irreversible, showing no cathodic current in AN or BN up to 100 V/sec and only a barely noticeable cathodic current in PC at 20 V/sec. The peak potentials are also dependent on sweep rate.

TABLE II
OXIDATION OF I[a]

Solvent	E_{peak}	Sweep rate, mV/sec
AN	1.43	200
BN	1.53	200
PC	1.39	200

[a] Volts *vs.* sce.

Discussion

Synthesis.—The synthesis we have presented provides a more convenient alternative to the existing procedure. It utilized readily available starting materials and relatively simple reactions. In addition, it promises to provide a versatile route to other substituted naphthalenes. Thus, variations in the 2,3 substituents of the starting quinone would determine the substituents in the 2 and 3 position of the final naphthalene. Similarly, the 2 and 3 substituents on

(1) (a) Ethyl Fellow, 1971–1972. (b) W. L. Mosby, *J. Amer. Chem. Soc.*, **75**, 3600 (1953).

(2) L. Fieser and M. I. Ardao, *ibid.*, **78**, 774 (1956).

(3) R. S. Nicholson and I. Shain, *Anal. Chem.*, **30**, 706 (1964).

the butadiene moiety would determine the 6 and 7 substituents in the naphthalene product.

Electrochemistry.—Qualitatively the reduction and oxidation potentials of I correlate with the electron-donating effects of methyl groups (Table III). The

TABLE III

MOLECULAR ORBITAL ENERGIES OF NAPHTHALENIC COMPOUNDS WITH THEIR REDUCTION AND OXIDATION POTENTIALS[f,g]

	Naphthalene	Dimethyl-naphthalene	Tetramethyl-naphthalene
LUMO[a,c]	−0.6180	−0.6480	−0.6770
HFMO[b,c]	+0.6180	+0.5617	+0.5083
Reduction potential	−2.58	−2.68	−2.71
Oxidation potential	+1.72[e]	+1.56[d]	1.44[d]

[a] Lowest unoccupied molecular orbital. [b] Highest filled molecular orbital. [c] These values in units of β_0. [d] These values are cyclic voltametry peak potentials taken at 0.5 V/sec. [e] Estimated from $E_{1/2}$ of +1.70 at a rotated platinum disk as determined in R. D. Rieke, W. E. Rich, and T. H. Ridgway, *J. Amer. Chem. Soc.*, **93**, 1962 (1971). [f] Data for the LUMO of naphthalene and dimethylnaphthalene are from ref *e*. The energies for the remaining MO's were determined as in ref *e*. [g] Data in volts *vs.* sce.

peak potential (E_{peak}) for the oxidation of I exhibits a large amount of solvent dependence. The reference electrode used in these studies was an aqueous saturated calomel electrode (sce). Use of the sce introduces an unknown liquid–liquid junction potential between the sce and the electrolytic solution. Differences in the junction potential between the sce and the various solvent systems probably account for the major portion of solvent dependence of I.[4a]

Experimental Section

Cyclic voltametric (CV) experiments were performed with a solid state three-electrode instrument. The cell used has been described elsewhere.[4b] The platinum bead electrode used for the oxidation work was pretreated with aqua regia for 2 min, washed with distilled water, and dried before each experiment. Melting points were taken on an oil bath type instrument and are uncorrected. Nuclear magnetic resonance spectra were recorded for solutions in carbon tetrachloride with tetramethylsilane internal reference on a JEOL-C-60-HL instrument. Gas chromatography was done with a Hewlett-Packard 5750 on a 6.5 ft × 0.25 in. 20% SE-30 on Chromosorb W column. Infrared spectra were obtained with a Perkin-Elmer 257 spectrometer.

Chemicals.—Spectro Grade acetonitrile (Matheson Coleman and Bell) was dried by addition of Al_2O_3 which had been dried at 400° for 24 hr. *n*-Butyronitrile was stirred with $KMnO_4$ and anhydrous Na_2CO_3 and heated to 70°. Fast distillation at 15 mm gave BN with an impurity evident in the uv spectrum which could not be removed by fractionation. However, this BN was acceptable, giving limits of +1.7 to −1.6 on platinum. Propylene carbonate was prepared by the method of Nelson and Adams.[5] Spectro Grade dimethylformamide obtained from Matheson Coleman and Bell was refluxed over copper sulfate through a Soxhlet containing Linde 4A molecular sieves under vacuum, not allowing the pot temperature to rise above 50°. The DMF was then distilled under vacuum into a receiver cooled to −78°, where it was stored under N_2.

Tetraethylammonium perchlorate (TEAP) was purchased from Eastman and purified by a standard procedure.[6] Tetra-*n*-butylammonium perchlorate (TBAP) was made according to a published procedure.[7]

All AN solutions were 0.1 *M* in TEAP, PC solutions were 0.25 *M* in TEAP, and BN solutions were 0.1 *M* TBAP.

In all experiments I was 1 mmol and was purified by gc.

2,3,6,7-Tetramethyl-4a,5,8,8a-tetrahydro-1,4-naphthaquinone (III).—Quinone II was prepared as described by Fieser and Ardao[2] and allowed to react with 2,3-dimethylbutadiene as has been described,[2] yielding III (73–84%), mp 104.5–105° (lit.[2] mp 103–104°), ir 1671 cm^{-1} (CH_2Cl_2).

2,3,6,7-Tetramethyl-2,3,4a,5,8,8a-hexahydro-1,4-naphthoquinone (IV).—Compound III (35.9 g, 0.165 mol) was dissolved in HOAc (180 ml) and added to a vigorously stirred suspension of activated[8] zinc dust in H_2O (100 ml). After 8 min the suspension was filtered, cooled, and diluted with H_2O to give a crop of white needles (7.0 g). The solution was then neutralized with $NaHCO_3$ and saturated with NaCl. A solid appeared at the top of the solution, and was skimmed off and extracted with acetone; the acetone was stripped off and the product was dried *in vacuo*, yielding IV (total of 21.9 g, 79%, 0.1 mol): mp 129–130° (CCl_4); ir 1708 cm^{-1} (CH_2Cl_2); mass spectrum *m/e* 220.1462 (calcd for $C_{14}H_{20}O_2$, 220.1553).

2,3,6,7-Tetramethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene (V).—Diketone IV (28.9 g, 0.13 mol) was treated with hydrazine hydrate (115 ml, 99%) in diethylene glycol (500 ml) until all IV had dissolved. KOH (120 g) in diethylene glycol (480 ml) was added and the mixture was refluxed for 1 hr. The condenser was removed and the solution temperature was allowed to rise to 185°, at which point the condenser was replaced and the solution was refluxed for 5 hr, cooled, and extracted with petroleum ether (bp 30–60°) which was stripped off, leaving light yellow oil V (17.0 g, 67%, 0.089 mol). This product was chromatographed through a 2 × 15 cm column of Al_2O_3 with hexane, yielding a colorless liquid: nmr τ 8.175, 8.47, 8.68, 8.93, 9.05, 9.13, 9.25 (peaks overlap too much to allow valid integration); ir (neat) 2960 (w), 2904 (m), 1455 (w), 1378 (w) cm^{-1}; mass spectrum *m/e* 192.1884 (calcd for $C_{14}H_{24}$, 192.1878).

2,3,6,7-Tetramethylnaphthalene (I).—Octahydrodecalin V (3.54 g, 18 mmol) was mixed with sulfur (2.45 g, 76 mmol) and heated at 235° for 5 min. The reaction mixture was cooled and extracted with petroleum ether, which was evaporated and the residue was chromatographed on a 2 × 50 cm column of alumina (Merck) to yield I (1.51 g, 45%, 8.2 mmol). The product was light yellow, indicating an impurity: mp 188–190° (lit.[1] mp 191.0–191.5°); nmr τ 7.66 (12 H, methyl), 2.63 (4 H aromatic) (lit.[9] 7.64); mass spectrum *m/e* 184.1254 (calcd for $C_{14}H_{16}$, 184.1252).

Registry No.—I, 1134-40-3; III, 38312-84-4; IV, 38312-85-5; V, 38312-86-6.

Acknowledgment.—Partial support of this research by the National Science Foundation is gratefully acknowledged.

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(5) R. Nelson and R. Adams, *J. Electroanal. Chem.*, **13**, 184 (1967).

(6) C. K. Mann, "Electroanalytical Chemistry," Vol. 3, A. J. Bard, Ed., Marcel Dekker, New York, N. Y., 1969, p 133.

(7) Reference 6, p 132.

(8) K. Tsuda, E. Ohki, and S. Nozoe, *J. Org. Chem.*, **28**, 783 (1963).

(9) F. F.-H. Yew, R. J. Kiuland, and B. J. Mair, *Anal. Chem.*, **36**, 843 (1964).

The Reaction of Bromomethylenecyclopropane with Potassium *tert*-Butoxide

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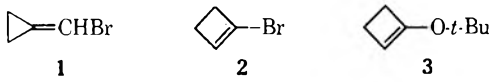
In continuation of our study of rearrangement reactions of terminal halo olefins,[1] we report here the reaction of bromomethylenecyclopropane (1) with potas-

(1) K. L. Erickson, *J. Org. Chem.*, **36**, 1031 (1971); K. L. Erickson, J. Markstein, and K. Kim, *ibid.*, **36**, 1024 (1971), and references cited therein.

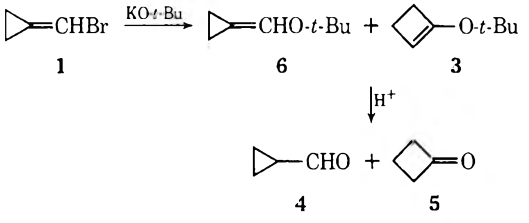
sium *tert*-butoxide. This compound completes the series of exocyclic vinyl halides.

Of particular interest was whether **1** would give rise to the ring-enlarged bromide, 1-bromocyclobutene (**2**), in analogy to the bromomethylenecyclobutane system,[2] or whether it would produce instead the ring-enlarged enol ether, 1-*tert*-butoxycyclobutene (**3**), the reaction course followed by the larger ring bromomethylenecycloalkanes.[3]



1 **2** **3**

Bromomethylenecyclopropane (**1**) was prepared by bromination–dehydrobromination of methylenecyclopropane.[4,5] When **1** was treated with neat potassium *tert*-butoxide at 100°, an immediate reaction occurred. The volatile products consisted of a 1.3:1.0 mixture of cyclopropanecarboxaldehyde (**4**) and cyclobutanone (**5**). No 1-bromocyclobutene (**2**) (independently synthesized) was detected. Since the volatile products were isolated by collection on an acid-washed vapor phase chromatography column, the carbonyl compounds, rather than the *tert*-butyl enol ethers, were obtained. Spectral data on the crude products verified the presence of enol ethers.



1 **6** **3**

4 **5**

1-*tert*-Butoxymethylenecyclopropane (**6**) most likely arises by either a displacement or an addition–elimination reaction. Several mechanisms are possible for the formation of the ring-expanded product, 1-*tert*-butoxycyclobutene (**3**). The carbenoid–cycloalkyne pathway established for the larger ring homologs[3] would involve cyclobutyne here, a somewhat unattractive intermediate. The cleavage–recombination mechanism proposed for the rearrangement of bromomethylenecyclobutane to 1-bromocyclopentene,[1] if operative here, would lead to 1-bromocyclobutene (**2**), which then needs to be converted to enol ether **3**. However, 1-bromocyclobutene appears to be stable to the reaction conditions. If **1** is not purified by vapor phase chromatography, it contains small amounts of 1-bromocyclobutene (and 1-bromo-2-methylpropene). This impure material, when treated with potassium *tert*-butoxide, gives product mixtures still containing **2**, while product mixtures from pure **1** show no detectable 1-bromocyclobutene. 1-*tert*-Butoxymethylenecyclopropane (**6**) by ring opening and reclosure could give rise to **3** directly, but it is difficult to understand why **6** would rearrange to **3** if **1** does not rearrange to **2**.

Bässler and Hanack[5] have reported the production of cyclobutanone from bromomethylenecyclopropane (**1**) under solvolytic conditions (60 or 80% aqueous ethanol at 130–150°) in the presence of triethylamine, and these authors postulate a vinyl cation intermediate. While such a cation is possible under their reaction conditions, it is highly unlikely in neat potassium *tert*-butoxide. In fact, these authors have not ruled out the possibility of the solvolysis reaction proceeding *via* a carbene–cycloalkyne or some alternate pathway. However, it does appear that a strong base is needed for ring enlargement to occur in our case. When potassium *tert*-butoxide is replaced by potassium hydroxide, the only volatile product found is cyclopropanecarboxaldehyde (**4**).

Failure to observe any 1-bromocyclobutene (**2**) in the potassium *tert*-butoxide reaction mixture indicates that the ring enlargement of halomethylenecycloalkanes to 1-halocycloalkenes is restricted to halomethylenecyclobutyl systems. The reason for this specificity is not yet known.

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. The nmr spectra were obtained with a Jeolco Model C-60H spectrometer using tetramethylsilane as an internal standard. Vapor phase chromatographic analyses were performed with a Varian Aerograph Model 90-P3 unit. The column used was a 10 ft × 0.25 in., 20% Carbowax 20M on 60/80 Chromosorb W A/W DMCS at 100° unless otherwise noted.

Reaction of Bromomethylenecyclopropane (1) with Potassium *tert*-Butoxide. General Procedure.—Sample sizes of vinyl bromide ranged from 0.15 to 1.50 g; a 20% excess of base was used.

Potassium *tert*-butoxide was placed in a nitrogen-flushed round-bottom flask with a side arm stoppered by a serum cap. A nitrogen inlet was attached, atop which were placed two condensers. In earlier runs, a Dry Ice cooled trap was connected to the system to collect escaping volatile products, but this was found to be unnecessary.

The reaction vessel was heated to 100°, and the vinyl bromide was injected beneath the surface of the hot butoxide. Heating was continued for an additional 10–20 min, and then the mixture (dark brown) was cooled. Water was added, and extraction of this aqueous mixture with pentane or ether followed. The solvent was removed by distillation through a Vigreux column, and the residue was flash distilled. Vpc examination showed one predominant peak which was identified as a 1.3:1.0 mixture of cyclopropanecarboxaldehyde (**4**) and cyclobutanone (**5**) (combined yield ~30%). Identification was made by comparison of ir and nmr spectra and vpc retention times with those of authentic samples. There were several minor products of insufficient quantity for further study; however, none of these appeared to be 1-bromocyclobutene, as evidenced by the absence of ir absorption at 11.75 μ where **2** displays a very intense band.

Inorganic bromide determinations on the aqueous phase of the reaction mixture gave consistent values of ~83%. Polymeric material (nonbromine containing) was produced.

Reaction of Bromomethylenecyclopropane (1) with Potassium Hydroxide.—The above procedure was followed employing powdered potassium hydroxide in place of potassium *tert*-butoxide. Work-up afforded cyclopropanecarboxaldehyde (**4**) as the only identifiable volatile product, 2,4-dinitrophenylhydrazone mp 181–183° (lit.[6] mp 185.5–186.5°). No cyclobutanone was produced.

1,2-Dibromocyclobutane. A. From *trans*-Cyclobutane-1,2-dicarboxylic Acid.—To a stirred slurry of 11.65 g (0.052 mol) of red mercuric oxide and 15 ml of CCl_4 in a 100-ml round-bottom flask equipped with a condenser and drying tube and protected from light was added a slurry of 20 ml of CCl_4, 5.0 g (0.035 mol) of *trans*-cyclobutane-1,2-dicarboxylic acid, and 5.54 g (0.035 mol) of bromine. The mixture was stirred at 25° for 2 hr, during which time the induction period expired, and a vigorous reaction ensued. The mixture was then heated at 45° for 3 hr. Bromine was added in 1-g lots as the color faded. The mixture was cooled and filtered, and the salts were washed with fresh CCl_4. The

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(3) K. L. Erickson and J. Wolinsky, *J. Amer. Chem. Soc.*, **87**, 1142 (1965).
(4) R. Köster, S. Arora, and P. Binger, *Synthesis*, 322 (1971).
(5) T. Bässler and M. Hanack, *Tetrahedron Lett.*, 2171 (1971).
(6) L. I. Smith and E. R. Rogier, *J. Amer. Chem. Soc.*, **73**, 4047 (1951).

CCl_4 filtrate was distilled through a Vigreux column to remove the solvent, and then the residue was flash distilled, giving poor yields of the dibromide.

B. From Cyclobutene.—Cyclobutene was prepared by dehydrochlorination of chlorocyclobutane. Two grams (0.022 mol) of chlorocyclobutane (Ash-Stevens, Inc.) was injected onto 2.85 g (0.025 mol) of sublimed potassium *tert*-butoxide it 100°. The apparatus used was that described for the reaction of 1 with potassium *tert*-butoxide. The product gas was led directly into a pentane solution of bromine and pyridine[7] cooled to −80°. The mixture was allowed to warm to room temperature. It was washed with water, 5% $NaHSO_3$, 10% HCl, and water and dried, and the pentane was removed. Distillation of the residue afforded 1.2 g, bp 60–79° (15 mm), of a four-component mixture from which the desired dibromide (major product) was isolated by vpc (10 ft × 0.125 in., 20% SE-30 on 60/80 Chromosorb W A/W DMCS at 130°).

1-Bromocyclobutene (2).—This material was prepared by the dehydrobromination of 1,2-dibromocyclobutane as described in the literature.[8,9] When passed through the gas chromatograph, 1-bromocyclobutene appeared to undergo some ring opening to 2-bromo-1,3-butadiene. The nmr of vpc-collected material showed additional vinyl hydrogen absorption, and the ir displayed additional bands at 8.30, 10.27, and 11.24 μ. Intense absorption at these positions is observed in the ir of 2-bromo-1,3-butadiene.[10] Similar electrocyclic ring openings of cyclobutenes to butadienes on the vpc have been observed in our laboratory.[11]

Registry No.—1, 33745-37-8; potassium *tert*-butoxide, 865-47-4.

Acknowledgments.—We are grateful to Professors P. Abell and P. Maitte for providing us with ir spectra of 1-bromocyclobutene and 1,2-dibromocyclobutane.

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Boric Acid Catalyzed Tishchenko Reactions

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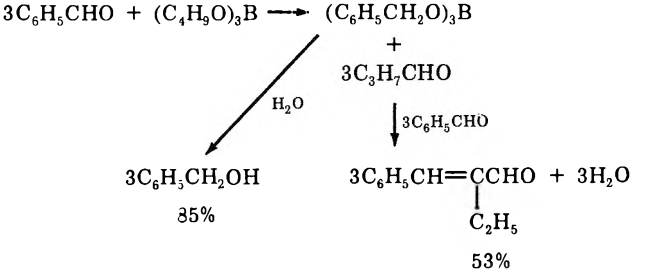
A recent article has described the use of boric acid catalysts for the aldol condensation of aldehydes and ketones.[1] It has now been found that boric acid is also an effective catalyst for the dismutation of certain aldehydes to the corresponding esters *via* a Tishchenko type reaction.[2] Aldehydes which may be used are those which are not readily susceptible to aldol condensation or to resinification.

When paraformaldehyde was heated with a catalytic quantity of boric acid in cyclohexane in an autoclave at 250° for 5 hr, essentially complete conversion of the formaldehyde was observed, and a 77% yield of methyl formate was isolated by distillation. Under similar conditions, isobutyraldehyde reacted more slowly. After 6 hr at 250°, a 74% aldehyde conversion was found and a 72% yield (based on reacted isobutyraldehyde) of isobutyl isobutyrate was obtained. Reaction temperatures of 200 and 225° gave comparable isobutyraldehyde conversions with somewhat reduced yields of ester. Table I summarizes results obtained with typical aldehydes.

When acrolein, furfural, or crotonaldehyde were treated under identical conditions only tars and resins were produced; this was somewhat surprising in view of the low acidity of boric acid. Lowering the reaction temperature to 150° in an attempt to prepare allyl acrylate from acrolein gave a low molecular weight solid polymer. The isolation of an appreciable amount of *n*-butyl butyrate from *n*-butyraldehyde is particularly noteworthy in view of the reported[1] production of only aldol condensation product from *n*-heptaldehyde under similar conditions.

In order to more fully define the scope of catalytic activity of boric acid, several additional experiments were conducted using benzaldehyde as the substrate. Addition of 25 ml of water to the boric acid catalyst completely destroyed the catalytic activity. Substitution of fused boric oxide for the boric acid resulted in a 17% benzaldehyde conversion after 6 hr at 250° with a 50% yield of benzyl benzoate. The use of tetrahydrofuran solvent also inhibited the reaction; under the same conditions only a 5% benzaldehyde conversion was realized. High temperatures are necessary for the disproportionation of the relatively unreactive benzaldehyde, since no reaction was observed after 18 hr reflux (180°) of neat benzaldehyde over boric acid. Activated alumina, in relatively large quantities, also functioned as a Tishchenko catalyst, albeit much more slowly. A 9% conversion was obtained after 8 hr at 250° and a 35% conversion and 78% yield of ester were obtained after 7 hr at 325°.

The use of *n*-butyl borate as a Tishchenko catalyst was also tested. The only products isolated were benzyl alcohol and α-ethylcinnamaldehyde. Reaction of benzaldehyde with *n*-butyl borate at atmospheric pressure is known[3] to give benzyl alcohol (after hydrolysis) and *n*-butyraldehyde; in this work using a closed system the butyraldehyde condensed with the excess benzaldehyde to form α-ethylcinnamaldehyde.



The Tishchenko reaction has been previously found to be catalyzed by strongly basic alkali metal alkoxides, the amphoteric aluminum alkoxides, and strong acids.[4] Although boric acid is an exceedingly weak acid, it appeared possible that, at the elevated temperatures used in this study, acid catalysis might indeed be occurring. However, neither acetic acid nor *p*-toluenesulfonic acid produced more than trace quantities of benzyl benzoate under similar conditions. An alternative explanation, which appears much more attractive, is based on the electrophilic nature of the

(1) R. D. Offenhauer and S. F. Nelsen, *J. Org. Chem.*, **33**, 775 (1968).
(2) (a) W. Tishchenko, *Zh. Fiz. Khim.*, **38**, 355 (1906); (b) R. M. Wagner and H. D. Zook, "Synthetic Organic Chemistry," Wiley, New York, N. Y., 1953, p 494.
(3) V. K. Kuskov and A. N. Neverov, *Zh. Obshch. Khim.*, **29**, 1127 (1959); *Chem. Abstr.*, **54**, 1393 (1960).
(4) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 269.

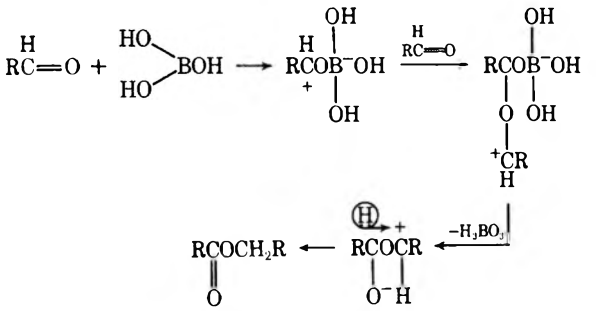
TABLE I[a]

$2RCHO \longrightarrow RCO_2CH_2R$

R	Registry no. (RCHO)	Mol	Conversion, %	Yield,[b] %	Bp, °C (mm)	Registry no. (RCO_2CH_2R)
H	50-00-0	5.83	100	77	32–33	107-31-3
$(CH_3)_2CH$-	78-84-2	3.13	74	72	144–145	97-85-8
$C_4H_9C(C_2H_5)H$-	123-05-7	1.95	52	90	113–115 (1.0)	7425-14-1
c-C_6H_9[d]	100-50-5	2.05	91	60	115–117 (0.5)	2611-00-9
C_6H_5	100-52-7	2.36	34	90	137–140 (0.2)	120-51-4
n-C_3H_7	123-72-8	3.54	82	12[c]	60–65 (12.0)	109-21-7

[a] Reactions were carried out for 6 hr at 250° using 20 g (0.32 mol) of boric acid in 200 ml of heptane or cyclohexane diluent. [b] Based on reacted aldehyde. [c] The total product contained 83% of 2-ethyl-2-hexenal and 17% of n-butyl n-butyrate. [d] 1-Cyclohex-3-enyl.

boron atom. Upon coordination with a carbonyl group and rehybridization from sp^2 to sp^3 the boron atom would become tetracovalent and assume a formal negative charge.[5]



Addition of a second mole of aldehyde to the charged intermediate, loss of boric acid, and intramolecular hydride transfer would occur as depicted. This scheme would account for the observation that fused boric oxide is an inferior catalyst, since formation of a charged tetracovalent intermediate would become much more difficult. The decrease in rate of reaction using the relatively basic tetrahydrofuran solvent and complete inhibition by added water would be expected, since both would compete with the carbonyl group for coordination with the boron atom.

Experimental Section[6]

Disproportionation of Aldehydes over Boric Acid.—A 1-l. stainless steel Magnedrive[7] autoclave was charged with 20 g (0.32 mol) of boric acid, 200 ml of solvent, and the quantity of aldehyde shown in Table I. The autoclave was sealed, flushed with nitrogen, and heated at 250°. After cooling, the product was removed, filtered, and fractionated through a 0.75 × 36 in. helices packed column. The product esters were identified by comparison of their infrared and nmr spectra with those of authentic samples.

Boric Acid Catalyzed Reaction of n-Butyraldehyde.—A mixture of 255 g (3.54 mol) of n-butyraldehyde and 20 g of boric acid in 200 ml of heptane was heated for 6 hr at 250°. After filtration and fractionation there was obtained 45.9 g of unreacted n-butyraldehyde and 164.3 g of material, bp 60–65° (12 mm), which by glpc analysis (10 ft × 0.25 in. Carbowax 20M on Chromosorb P, 150°) was found to consist of 83% 2-ethyl-2-hexenal and 17% n-butyl n-butyrate.

Reaction of Benzaldehyde with n-Butyl Borate.—A mixture of 250 g (2.36 mol) of benzaldehyde, 21 g (0.091 mol) of freshly distilled n-butyl borate,[8] and 200 ml of dry cyclohexane was heated for 6 hr at 200°. The resulting product was washed with water, then with Na_2CO_3 solution, dried ($MgSO_4$), and filtered, and the cyclohexane was removed. The residue, weighing 257.3 g, was analyzed by glpc on a 10 ft × 0.25 in SE-30 on Chromosorb P column at 175° and was found to contain 9.8% of benzyl alcohol, 80.4% of benzaldehyde, and 9.1% of α-ethylcinnamaldehyde. Benzyl alcohol and α-ethylcinnamaldehyde were separated by preparative glpc and identified by comparison of infrared and nmr spectra with authentic samples.

Registry No.—Boric acid, 10043-35-3; 2-ethyl-2-hexenal, 645-62-5; n-butyl borate, 688-74-4.

(5) H. Steinberg, "Organoboron Chemistry," Vol. I, Wiley, New York, N. Y., 1964, p 31.

(6) The aldehydes used were the best commercial grades and were purified by fractionation through a 36-in. helices packed column. Heptane and cyclohexane were Phillips Petroleum Co. Pure Grade materials and were used as received. Boric acid and fused boric oxide were obtained from Mallinckrodt.

(7) Autoclave Engineers, Inc., Erie, Pa.

(8) J. R. Johnson and S. W. Tompkins, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 106.

Communications

See Editorial, J. Org. Chem., 38, No. 19, 4A (1972)

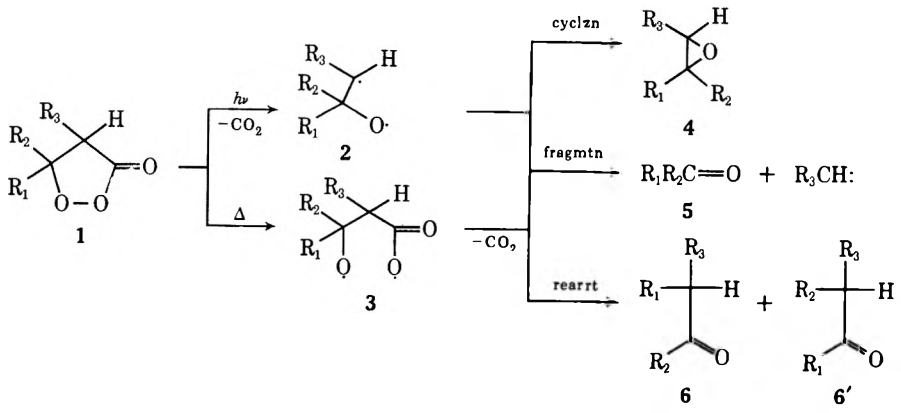
1,3 Diradicals *via* Thermolysis of 1,2-Dioxolanes[1]

Summary: Stereochemical and kinetic results suggest direct deketonation of 1,2-dioxacyclopentanes on thermal activation affording 1-oxatrimethylene, which suffers a novel ring expansion.

Sir: From stereolabeling experiments[2] we rationalized that 1,2-dioxolan-3-ones **1** photodecarboxylate (eq 1) directly into the 1-oxatrimethylene diradical **2**, which serves as precursor to epoxide **4**, fragmentation ketone **5**, and the pair of rearrangement ketones **6** (~R_1) and **6′** (~R_2). However, in the thermal decomposition of **1** (eq 1), stereolabeling[3,4] and kinetic[5] experiments suggest that the 1,5-dioxa-2-oxopentamethylene diradical **3**

(1) Paper XXVII in the Cyclic Peroxide Series. For previous paper, *cf.* W. Adam and H. C. Steinmetzer, *Angew. Chem.*, **84**, 590 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 540 (1972).

(2) W. Adam and G. Santiago Aponte, *J. Amer. Chem. Soc.*, **93**, 4300 (1971).



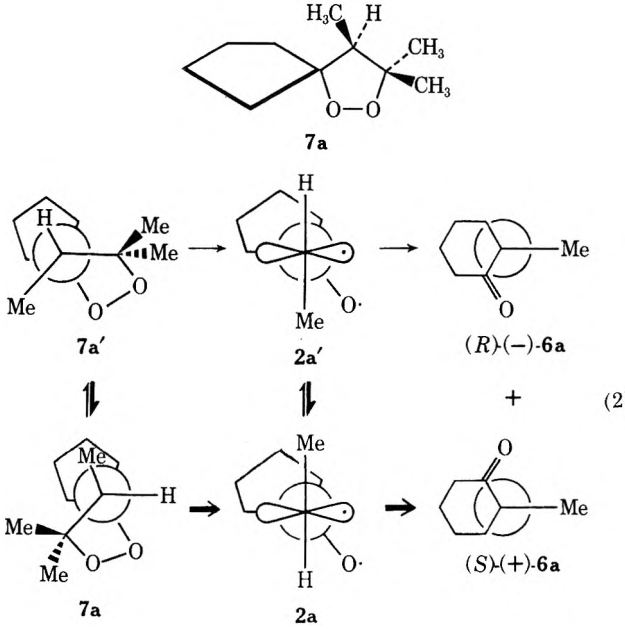
(1)

intervenes, which suffers principally stereospecific rearrangement into **6** and **6'**. Since 1,2-dioxolanes **7** deketonate thermally[6] and photochemically[7] into the same types of products, it was of mechanistic interest to examine the stereochemistry and kinetics of this deketonation process, and presently we wish to report our results.

For the stereochemical study we employed (*S*)-(+)-3,3,4-trimethyl-1,2-dioxaspiro[4.4]nonane (**7a**), bp 57–58° (0.9 mm), $\alpha^{20}D$ +1.58° (*c* 4.47, CCl_4), which was prepared *via* a stereospecific route starting with 88.9% optically pure (*R*)-(−)-*n*-butyl lactate, $\alpha^{20}D$ −11.9° (neat) [lit.[8] $\alpha^{20}D$ +13.4° (neat)]. First, double Grignard addition of 1,4-dibromobutane afforded (*R*)-(+)-1-(1-hydroxycyclopentyl)ethanol, bp 84–85° (0.7 mm), $\alpha^{25}D$ +0.6° (neat). Treatment of this 1,2-diol with benzenesulfonyl chloride in pyridine, followed by sodium hydride in THF,[2] gave (*S*)-(+)-2-methyl-1-oxaspiro[2.4]heptane, bp 74–75° (86 mm), $\alpha^{25}D$ +14.9° (*c* 3.44, CCl_4). Reaction of this epoxide with 2-lithio-2-methyl-1,3-dithiane in THF at −30° and careful hydrolysis with $HgCl_2/HgO$ in aqueous methanol[9] led to (*R*)-(−)-3-(1-hydroxycyclopentyl)-2-butanone, bp 77–78° (1.3 mm), $\alpha^{25}D$ −24.4° (*c* 4.64, CCl_4). Addition of this β-keto alcohol to excess methylmagnesium bromide in ether produced (*S*)-(−)-3-(1-hydroxycyclopentyl)-2-methylbutan-2-ol, mp 86–87°, $\alpha^{20}D$ −22.1° (*c* 9.77, CCl_4), which was cyclized into the desired (*S*)-(+)-**7a** with 98% H_2O_2 (*CAUTION!*). As a control, (*S*)-(+)-**7a** was reduced catalytically over Pd/C back to the (*S*)-(−)-diol in over 90% yield, mp 86–87°, $\alpha^{20}D$ −22.2° (*c* 1.82, CCl_4), and therefore the 1,2-dioxolane **7a** is assumed to be 88.9% optically pure (*S*)-(+) isomer.[10]

Thermolysis of (*S*)-(+)-**7a** in benzene at 170° for 17 hr and collection by glpc[11] afforded (*S*)-(+)-2-methylcyclohexanone (**6a**), $\alpha^{25}D$ +0.29 ± 0.07° (c 1.69, C_6H_6), which corresponds to $\alpha^{25}D$ +0.33 ± 0.08° after correction for 88.9% optical purity of (*S*)-(+)-**7a**. Authentic (*S*)-(+)-**6a** of 23.3% optical purity,[12] $\alpha^{25}D$ +0.91° (*c* 1.43, C_6H_6), was prepared by kinetic resolution of **6a** with di-3-pinanylborane[13] and collected by glpc.[11] Control experiments indicated that the rearrangement ketone (*S*)-(+)-**6a** did not racemize when submitted to the thermolysis conditions in the presence of 1,2-dioxolane **7a**, nor on glpc collection.[11] Thus, (*S*)-(+)-**6a** was formed with 8.4 ± 2.0% net retention of configuration[12] directly in the thermolysis of (*S*)-(+)-**7a** and was not racemized in secondary reactions.

To accommodate this stereochemical result of the novel ring expansion in the thermodeketonation of **7a**, we propose that diradical **2a** is the precursor to **6a** (eq 2). Diradical **2a** suffers extensive racemization either by bond rotation between rotamers **2a'** and **2a** or possibly through conformational effects dictated already in the 1,2-dioxolane rotamers **7a** and **7a'**. In contrast, it should be recalled that 1,2-dioxolan-3-ones **1** undergo thermodecarboxylation with quantitative inversion at the 4 position (migration terminus), which obliged us to propose that the 1,5 diradical **2** and not the 1,3 diradical



(2)

(3) W. Adam, Y. M. Cheng, C. W. Wilkerson, and W. A. Zaidi, *J. Amer. Chem. Soc.*, **91**, 2111 (1969).

(4) W. Adam and C. Wilkerson, *J. Chem. Soc., Chem. Commun.*, 1509 (1971)

(5) W. Adam and Y. M. Cheng, *J. Amer. Chem. Soc.*, **91**, 2009 (1969).

(6) W. Adam and N. Durán, *J. Chem. Soc. Chem. Commun.*, 279 (1972).

(7) W. Adam and N. Durán, *Tetrahedron Lett.*, 1357 (1972).

(8) C. F. Wood, J. E. Such, and F. Scarf, *J. Chem. Soc.*, 1928 (1936).

(9) D. Seebach, University of Giessen, private communication; D. Seebach, *Synthesis*, **1**, 35 (1969).

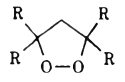
(10) In this assignment it is assumed that no partial racemization occurred during any of the steps of the stereospecific preparation of **7a**, since in ref 2 we showed that such an epoxide synthesis takes place with quantitative inversion, while in ref 9 it was shown that epoxide opening by the Seebach–Corey reagent also occurs with quantitative inversion.

(11) For the glpc collection at 20 ft × 0.25 in. copper column packed with 20% FFAP on 80–100 mesh Chromasorb P was used, operated at column, detector, and injector temperatures of 155, 160, and 165°, respectively, and a helium flow of 60 ml/min.

(12) 2-Methylcyclohexanone of 100% optical purity has $\alpha^{25}D$ +12.01° (neat) as reported by D. Mea-Jocheet and A. Horeau, *Bull. Soc. Chim. Fr.*, 4571 (1962). Material of 23.3% optical purity, prepared *via* kinetic resolution, has $\alpha^{25}D$ +2.80° (neat), +2.50° (*c* 3.5, EtOH), and +0.91° (*c* 1.46, C_6H_6).

(13) J. D. Morton and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1971.

TABLE I
KINETIC DATA FOR THE THERMOLYSIS OF 1,2-DIOXOLANES IN BENZENE[a]



7

	T, (°K)	$k \times 10^5$ (sec^{-1})[b]	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (gibbs/mol)	$\Delta G^{\ddagger}$ at 500° K (kcal/mol)
	463.2	0.553 ± 0.014			
7b (R = Me)	473.2	1.17 ± 0.06	27.0 ± 0.3	−24.8 ± 0.7	34.4 ± 0.3
	491.2	3.20 ± 0.15			
	463.2	9.04 ± 0.5			
7c (R = Ph)	472.7	15.0 ± 0.6	21.7 ± 0.5	−30.8 ± 2.2	37.1 ± 0.5
	492.2	39.0 ± 2.8			

[a] Error limits have been assessed by least-squares analysis of the rate data employing an IBM computer. [b] Averaged over several runs!

3 served as precursor to rearrangement ketones 6 (eq 1).[3-5]

Of course, this stereochemical result cannot decide whether the 1,3 diradical 2a is formed from 7a *via* direct deketonation or whether first simply the peroxide bond in 7a cleaves to give a 1,5 diradical similar to 3, which after loss of ketone results in the 1,3 diradical 2a. For this purpose we examined the kinetics of the thermolysis of 3,3,5,5-tetramethyl- and 3,3,5,5-tetraphenyl-1,2-dioxolanes 7b and 7c, respectively, to see whether $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ exhibit a dependence on structure.[14] The appearance of carbonyl product was monitored by ir and in all runs good first-order rates were obtained for at least two half-lives. The data is summarized in Table I. Furthermore, it was shown that the rate of acetone production from 7b is identical within experimental error in C_6H_6 and CH_3CN. No doubt a homolytic fission of the peroxide bond is involved and a structure-reactivity dependence is clearly evident; *i.e.*, benzophenone as leaving group in 7c helps to lower the activation enthalpy compared to acetone in 7b, but a considerable price must be paid in the activation entropy, implying a two-bond homolysis and thus direct ketone expulsion (eq 2). However, the activation parameters themselves are rather unexpected, particularly the very negative $\Delta S^{\ddagger}$ values, and need further comment.

For comparison, the values for di-*tert*-butyl peroxide are $\Delta H^{\ddagger}$ = 37.8 kcal/mol, $\Delta S^{\ddagger}$ = +13.8 gibbs/mol, and $\Delta G^{\ddagger}$ (500°K) = 31 kcal/mol,[15] revealing that the cyclic analog 7b is by a factor $\sim 3 \times 10^3$ more stable toward thermolysis than di-*tert*-butyl peroxide. The significantly lower $\Delta H^{\ddagger}$ for the cyclic peroxide 7b compared with the acyclic analog is not unreasonable since conformational constraint on the oxygen lone pairs is expected to yield a weaker peroxide bond.[16] However, the $\Delta S^{\ddagger}$ values are without parallel for unimolecular decompositions and certainly cannot be rationalized in terms of two-bond homolysis alone. Excepting the possibility of reduced transmission coefficients in the Eyring equation, possible factors contributing to these unusual $\Delta S^{\ddagger}$ values might be (a) a high rate of reclosure of 1,5 diradicals, implying that its deketonation is rate determining, (b) a need of selective twisting skeletal deformations in unzipping the ketone leaving group *via* two-bond homolysis in 7, and (c) an unusually low rotational entropy for the 1-oxatrimethylene diradicals. In the absence of additionally needed experimental data, at this moment we cannot make any commitments as to which of the above factors contributes predominantly to the very negative activation entropies in the deketonation of 1,2-dioxolanes 7.

(14) P. D. Bartlett and R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958).
(15) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 51.
(16) C. W. Gillies and R. L. Kuczkowski, *J. Amer. Chem. Soc.*, **94**, 6337 (1972).

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(17) Alfred P. Sloan Foundation Fellow, 1968–1972.
(18) On study leave from the Catholic University of Valparaiso, Chile.

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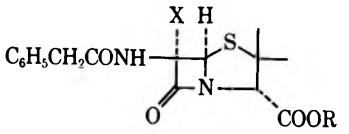
Functionalization of Penicillins at Carbon 6 *via* *N*-Acylimines. 6-Hydroxypenicillin. Substituted Penicillins and Cephalosporins. VIII[1]

Summary: Introduction of 6α-hydroxy, methoxy, benzyloxy, and formyloxy into penicillin G benzyl ester (2e) has been achieved by the addition of the appropriate hydroxy compound to the *N*-acylimine 6, prepared from 2e by halogenation and elimination.

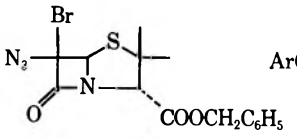
Sir: The finding that a 6(7)α-methoxy group confers β-lactamase stability on penicillins and cephalosporins[2] has stimulated a search for synthetic methods of introducing this and other groups. Particularly sought was 6α-hydroxypenicillin (1a) since its antimicrobial activity might be different from that of 6α-methoxypenicillin (1b), whose potency is lower than that of the parent, penicillin G (1e).[3]

Substituents of many kinds can be introduced into penicillins and cephalosporins at C-6(7) by the addition of nucleophiles to the geminal bromo azide 3.[3] Similarly, electrophilic reagents react at that position with a carbanion which is stabilized by being adjacent to both the β-lactam carbonyl and an azomethine double bond built on the C-6(7)-amino group.[4] Thus, compounds 4

(1) Paper VII: L. D. Cama and B. G. Christensen, *Tetrahedron Lett.*, submitted for publication.
(2) E. O. Stapley, M. Jackson, S. Hernandez, S. B. Zimmerman, S. A. Currie, S. Mochales, J. M. Mata, H. B. Woodruff, and D. Hendlin, *Antimicrob. Ag. Chemother.*, **2**, 122 (1972); T. W. Miller, R. T. Goegelman, R. G. Weston, I. Putter, and F. F. Wolf, *ibid.*, 132 (1972); A. K. Miller, E. Celozzi, B. A. Pelak, E. O. Stapley, and D. Hendlin, *ibid.*, 281 (1972).
(3) L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Amer. Chem. Soc.*, **94**, 1408 (1972).
(4) R. Reiner and P. Zeller, *Helv. Chim. Acta.*, **51**, 1905 (1968); E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **93**, 4324 (1971); R. A. Firestone, N. Schelechow, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972); W. A. Spitzer, T. Goodson, R. J. Smithey, and I. G. Wright, *Chem. Commun.* 1139 (1972); D. B. R. Johnston, S. M. Schmitt, R. A. Firestone, and B. G. Christensen, *Tetrahedron Lett.*, 4917 (1972).



1, R = Na
2, R = $CH_2C_6H_5$
1,2a X = OH
b X = OCH_3
c X = OCHO
d X = $OCH_2C_6H_5$
e X = H



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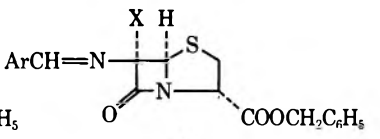

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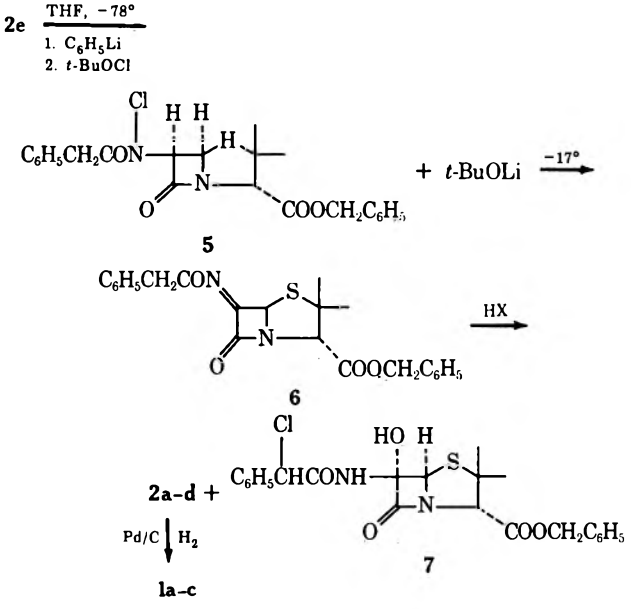
have been prepared in which X is alkyl,[4] hydroxyalkyl,[4] Br,[1] and (by exchange with Br) OCH_3,[1] F,[5] N_3,[5] and NC.[6]

When X is a good leaving group, however, the yields of N-acylated penicillins **2** are sometimes poor because X is easily lost during reduction of the azide or hydrolysis of the Schiff base.[1,3,4] Since electronegative 6 substituents become stabilized once the amino group is acylated, a method was sought for their introduction into the intact penicillin G benzyl ester molecule (**2e**).

This was achieved by the method depicted in the Scheme I. Treatment of **2e** (0.25 mmol) in 5 ml of

SCHEME I



THF with PhLi (0.25 mmol) at −78° under N_2 afforded the *N*-lithio derivative, which was chlorinated to **5** at −78° with 35λ *tert*-butyl hypochlorite (0.29 mmol). The by-product, lithium *tert*-butoxide, effected dehydrohalogenation of **5** during warming to −17°, producing *N*-acylimine **6**, benzyl 6-(*N*-phenylacetyl)iminopenicillanate, the key intermediate.[6] Conjugation of the azomethine linkage with the exocyclic carbonyl was expected to confer electrophilic nature on C-6, and attack on the planar site from the less hindered α direction was anticipated.

Addition of 1 ml of methanol at −17° afforded, after chromatography on silica gel with 4:1 $CHCl_3$–EtOAc, 6α-methoxypenicillin G benzyl ester (**2b**), identical with an authentic sample[3] and different from its 6 epimer. Similarly, with water there was obtained the 6α-hydroxy derivative **2a**: ir (μ) 2.9, 5.63, 5.72, 5.92; nmr (δ, $CDCl_3$) 4.37 (s, 3-H), 5.47 (s, 5-H); mass spectrum *m/e* 440, 250. With triethylammonium formate the 6α-formyloxy compound **2c** was obtained: ir (μ) 2.9, 5.63, 5.72, 5.92; nmr (δ, $CDCl_3$) 4.37 (s, 3-H), 5.55 (s, 5-H); mass spectrum *m/e* 468, 250. Compounds **2a** and **2c** are assigned the 6α configuration by analogy with **2b**.

Low yields of **2a**, and sometimes **2c**, were always obtained, no matter which reagent was added to **6**; evidently the reactivity of **6** toward water is exceptionally great. Presumably **2c** arises from decomposition of *tert*-butyl hypochlorite to acetone, which undergoes the haloform reaction to give formate ion or its equivalent. A major by-product always formed is assigned the structure **7** on the basis of its ir, nmr, and mass spectra. Another minor by-product often seen by nmr was once isolated in low yield and identified as the 6α-benzyloxy derivative **2d**, identical with an authentic sample.[7] This can only come from addition to **6** of benzyl alcohol formed by base attack on the benzyl ester.

Hydrogenolysis[8] of **2a** with an equal weight of 10% Pd/C and equimolar $NaHCO_3$ in 4:1 MeOH–H_2O for 1 hr at 40 psi afforded 6α-hydroxypenicillin G (**1a**): nmr (δ, D_2O) 1.35 (s), 1.46 (s) (*gem*-dimethyl), 3.65 (s, $C_6H_5CH_2CO$), 4.23 (s, 3-H), 4.67 (s, HDO), 5.33 (s, 5-H), 7.25 (s, C_6H_5); mass spectrum of Me ester (from CH_2N_2) *m/e* 364. In similar fashion[8] was obtained 6α-formyloxypenicillin G (**1c**): nmr (δ, D_2O) 4.11 (s, 3-H), 4.55 (s, HDO), 5.35 (s, 5-H); mass spectrum of Me ester *m/e* 392. The antimicrobial activities of **1a** and **1c** were markedly lower than that of **1b**.

Acknowledgment.—We are grateful to Dr. L. Cama for many helpful discussions during the course of this work.

(5) Unpublished results from these laboratories.

(6) With triethylamine as base, and (presumably) at ambient temperature, the sulfur atom is chlorinated and the thiazolidine ring opened: J. C. Sheehan in "Molecular Modification in Drug Design," American Chemical Society, Washington, D. C., 1964, p 22.

(7) Prepared by Mr. W. J. Leanza by the method of ref 3.

(8) These experiments were performed by Miss N. Schelechow.

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Improved Routes to Methyl 4-Methylimidazole-2-carboxylate and Methyl 5-Methyl-1,2,4-triazole-3-carboxylate[1]

Summary: Triethyloxonium tetrafluoroborate and methyl fluorosulfate alkylate the sulfur atom of ethyl 2-thiooxamate. The alkylation products (**2a** and **2b**) contain nucleophilic nitrogen atoms and good leaving

(1) Full experimental details will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-1437.

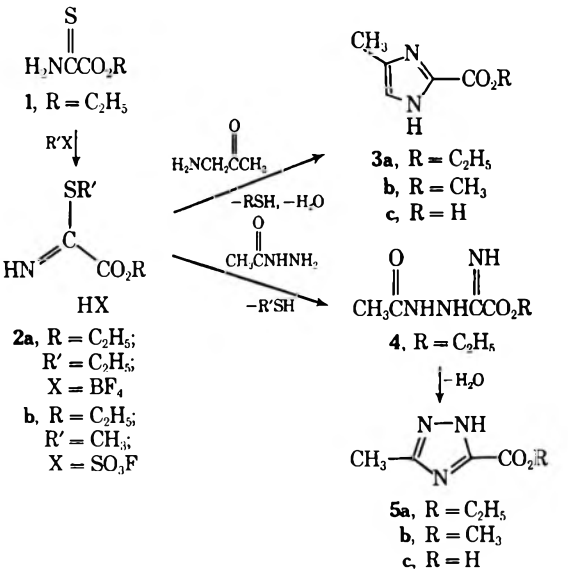
groups, and are thus useful precursors for heterocyclic carboxylates. For example, reaction of **2a** with aminoacetone provided ethyl 4-methylimidazole-2-carboxylate directly, and reaction of **2a** with acethydrazide gave **4** which was cyclodehydrated to ethyl 5-methyl-1,2,4-triazole-3-carboxylate.

Sir: The identification of methyl 4-methylpyrrole-2-carboxylate as a volatile component of the trail pheromone of the leaf-cutting ant, *Atta texana* (Buckley),[2a] prompted us to examine a number of structurally related pyrroles[2b] and similarly constituted pyrazoles, imidazoles, and triazoles.

Surprisingly, there appear to be no general methods for preparing either imidazole-2-carboxylic acid or 1,2,4-triazole-3-carboxylic acid derivatives. Ethyl 4- (or 5-) methyl-2-imidazolecarboxylate **3a** has been prepared by a Radziszewski synthesis involving the condensation of cinnamaldehyde with pyruvaldehyde and ammonia, followed by barium permanganate degradation of the resulting 2-styryl-4- (or 5-) methylimidazole to the carboxylic acid **3c**, and esterification of **3c** to **3a** with EtOH–HCl at 110°.[3] The yields were not reported, but the Radziszewski method is known to afford complex mixtures frequently and poor yields of the desired imidazoles.[4] 5-Methyl-1,2,4-triazole-3-carboxylic acid was recently reported,[5] but again the carboxyl function was generated by a permanganate oxidation, in this case by the selective oxidation of one of the methyl groups of 3,5-dimethyl-1,2,4-triazole. We here report new syntheses of 4-methylimidazole carboxylates **3a** and **3b** and 5-methyltriazole carboxylates **5a** and **5b** from a common precursor, **2**.

Ethyl 2-thiooxamate (**1**)[6] was alkylated[7] with triethyloxonium tetrafluoroborate in CH_2Cl_2 to provide **2a** as a pale yellow oil which we were unable to crystallize and therefore did not characterize.[8] Treatment of **2a** with aminoacetone hydrochloride[9] (1 equiv) and NaOAc (2 equiv) in HOAc at 90–100° provided the imidazole carboxylate **3a** in a single step (77% from **1**), mp 115–116°; its nitrate had mp 125.5–126° (lit.[3] mp 124°). The reaction proceeded equally well in Me_2CO with aqueous Na_2CO_3. Transesterification with $NaOCH_3$–CH_3OH gave the desired methyl ester **3b** (30%, mp 143–145°) (Scheme I).

SCHEME I



Reaction of **2a** with acethydrazide in CH_2Cl_2 containing Et_3N provided **4** in 77% yield (from **1**), mp 196.5–197.5°. Cyclization of **4** to **5a** was effected by heating **4** at 210–215° for 15 min (44%, mp 185–185.5°). Transesterification with $NaOCH_3$–CH_3OH gave the methyl ester **5b** (48%, mp 231°).

The thiooxamate **1** could also be alkylated with methyl fluorosulfate to give **2b**, and **2b** was converted to both **3a** and **4** under conditions similar to those described for the reactions of **2a**. Although the yields were slightly lower in these cases, the possibility of optimizing conditions and the ready availability of methyl fluorosulfate could make this reagent the alkylating agent of choice in some cases. Similarly, since the yields in the transesterification reactions were rather low, other esters of 2-thiooxamic acid might profitably be employed as starting materials.

Since our goal was simply the preparation of **3b** and **5b**, we have not further investigated the scope of these reactions, but it appears that each should be readily adaptable to the preparation of other members of each ring system wherein the methyl group could be replaced by a variety of other substituents. Furthermore, **2** should be a useful starting material for a number of other heterocyclic carboxylates.

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(4) K. Hofmann "Imidazole and Its Derivative," Vol. 6, in the series in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1953, pp 33–38.

(5) T. N. Vereshchagina and V. A. Lopyrev, *Khim. Geteotsikl., Soedin.*, 1695 (1970); *cf. Chem. Abstr.*, **74**, 99951y (1971).

(6) W. R. Boon, *J. Chem. Soc.*, 601 (1945). We found that the use of pyridine as the solvent for the addition of H_2S to ethyl cyanoformate greatly facilitated the reaction and **1** was thus obtained in essentially quantitative yield.

(7) Ethyl 2-thiooxamate (**1**) was rather resistant to alkylation and did not react with methyl iodide in refluxing acetone (15 min); with MeI in refluxing CH_3CN the color rapidly darkened, the odor of methyl mercaptan was evident, and no pure product was obtained.

(8) Except for **2a** and **2b** the structures of all new compounds were confirmed by analytical as well as spectral data.

(9) *Org. Syn.*, **45**, 1 (1965).

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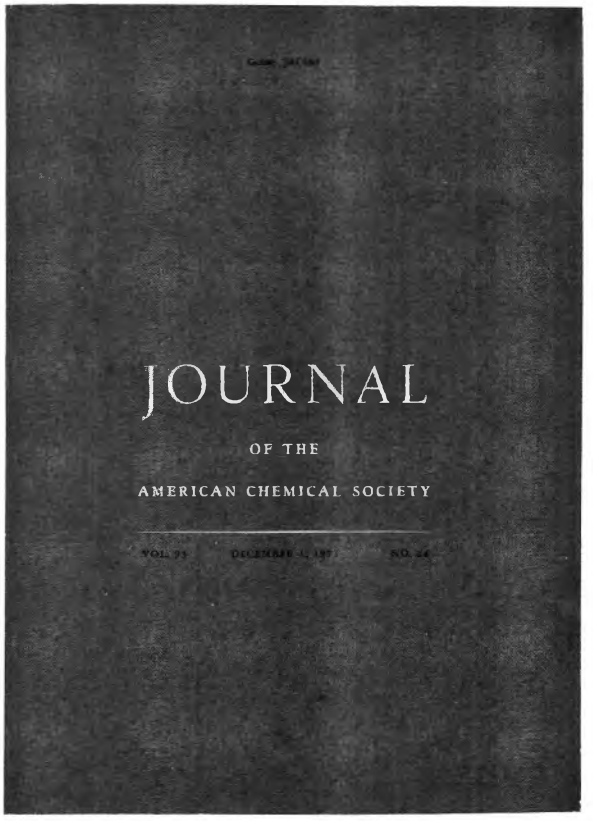

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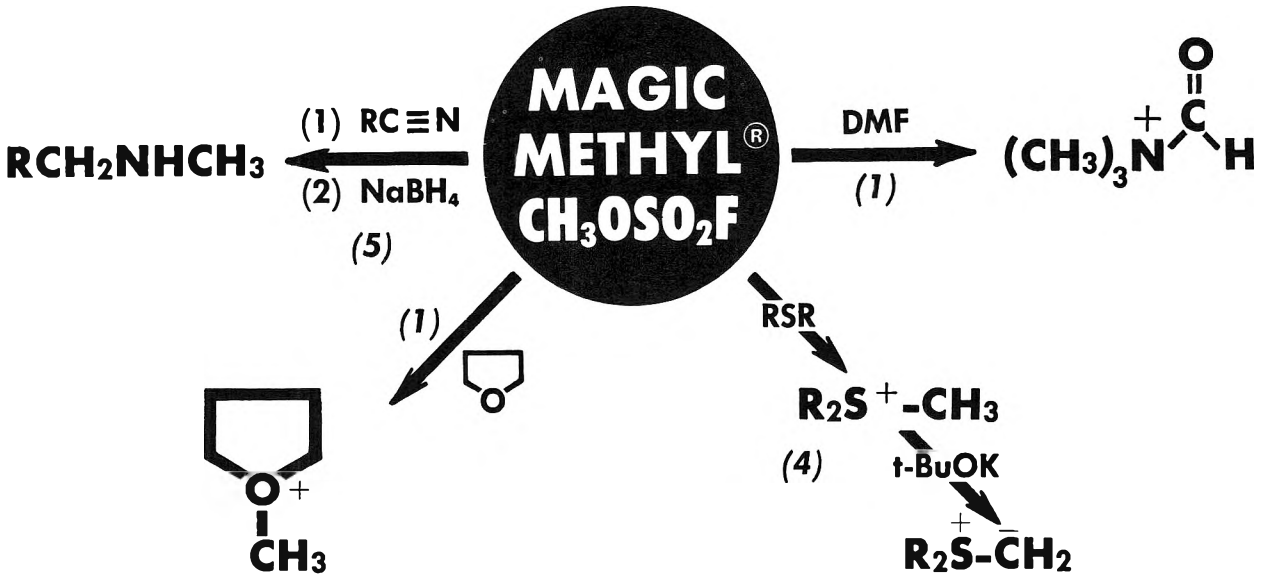

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