VOLUME 43 JANUARY 6, 1978 NUMBER 1 JOCEAH

THE JOURNAL OF Organic Chemistry

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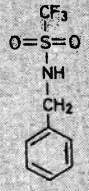
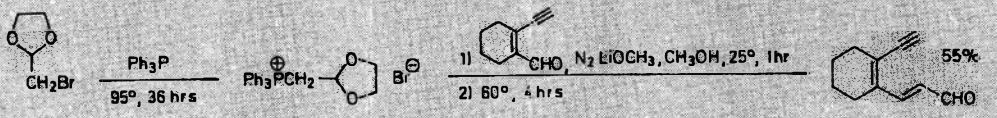
13960 N-Benzyl trifluoromethanesulfonamide purum MP 45-47 (N-Benzyl-triflamide) 5 g sFr. 32.— US$ 16.00
$CF_3SO_2NHC_7H_7$ $C_8H_8F_3NO_2S$ MW 239.22



Reagent for a new "Gabriel" synthesis of primary amines. 25 g sFr. 135.— US$ 62.50
J.B. Hendrickson et al., Tetrahedron (1975) 31, 2517

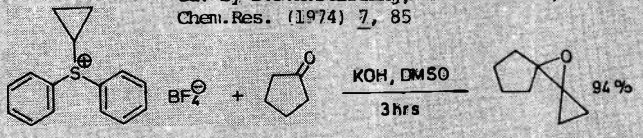
17618 2-Bromomethyl-1,3-dioxolane pract. BP_{12} 65-67°; n_D^{20} 1.4798 1 lt ≈ 1.61 kg 25 ml sFr. 18.— US$ 9.00
$C_4H_7BrO_2$ MW 167.02

Useful synthon for the preparation of α,β-unsaturated aldehydes: T.M. Cresp, M.V. Sargent, P. Vogel, J.Chem.Soc.Perkin I (1974) 39; 100 ml sFr. 65.— US$ 32.50
synthon, for the preparation of 1,4-dialdehyde monoacetals: J.F. Le Borgne, Th. Cuvigny, M. Larchevêque, H. Normant, Tetrahedron Lett. (1976) 1379



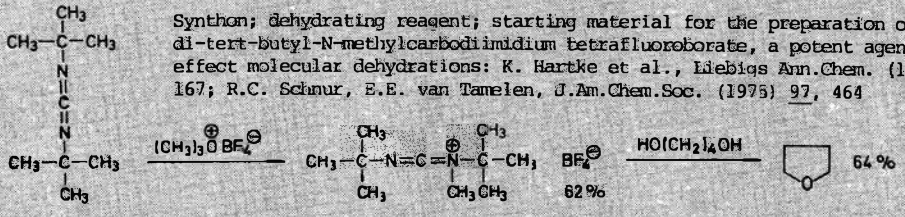
29950 Cyclopropyldiphenylsulfonium tetrafluoroborate pract. MP 135-137° 1 g sFr. 65.— US$ 32.50
$CH_2CH_2CHS(C_6H_5)_2(BF_4)$ $C_{15}H_{15}BF_4S$ MW 314.15

Excellent reagent for the spiroannelation of carbonyl compounds. The ylide derived from this salt effects many different synthetic transformations: M.J. Bogdanowicz, B.M. Trost, Org.Synth. (1974) 54, 27; B.M. Trost, Pure and Appl.Chem. (1975) 43, 563-585; B.M. Trost in "Organic Sulphur Chemistry", ed. by D.J.M.Stirling, Butterworths, London (1975) 237-263; B.M. Trost, Acc. Chem.Res. (1974) 7, 85



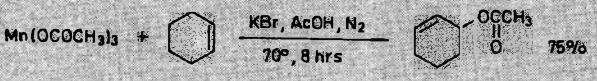
34640 N,N'-Di-tert-butylcarbodiimide purum >99%(GLC); BP_{12} 48-50°; n_D^{20} 1.4298; 1 lt ≈ 0.80 kg 5 ml sFr. 37.— US$ 18.50
$(CH_3)_3C{:}N{:}C(CH_3)_3$ $C_9H_{18}N_2$ MW 140.25

Synthon; dehydrating reagent; starting material for the preparation of N,N'-di-tert-butyl-N-methylcarbodiimidium tetrafluoroborate, a potent agent to effect molecular dehydrations: K. Hartke et al., Liebigs Ann.Chem. (1972) 762, 167; R.C. Schnur, E.E. van Tamelen, J.Am.Chem.Soc. (1975) 97, 464



63538 Manganese (III) acetate pract. (Manganic acetate) 50 g sFr. 50.— US$ 25.00
$Mn(OCOCH_3)_3.2H_2O$ $C_6H_9MnO_6.2H_2O$ MW 268.10

Reagent for the oxidation of olefins and aromatic hydrocarbons: L. Fieser M. Fieser, "Reagents for Organic Synthesis", 2, 263, 4, 318, 6, 355; John Wiley and Sons, Inc.; J.R. Gilmore, J.M. Mellor, J.Chem.Soc. (C) (1971) 2355



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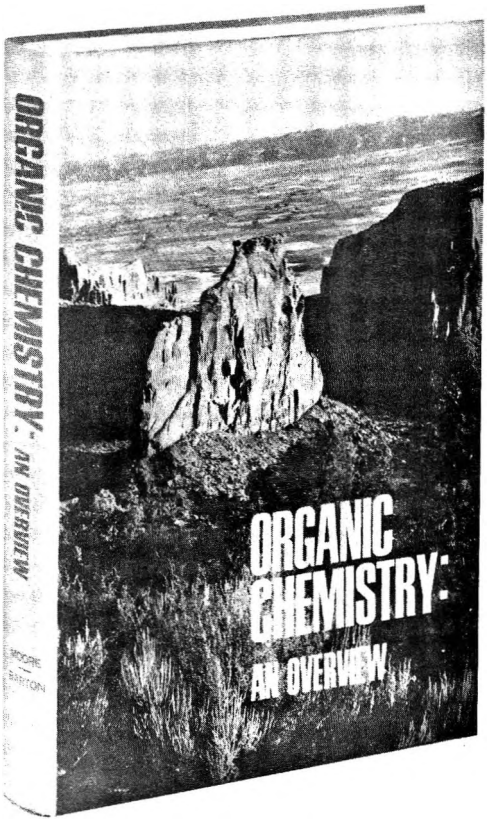

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THE JOURNAL OF Organic Chemistry®

VOLUME 43, NUMBER 1 JANUARY 6, 1978

TRIMETHYLSILYL IODIDE

A new reagent has recently appeared on the scene which promises to show wide application in organic chemistry. Trimethylsilyl iodide has already been shown to dealkylate esters[1] and ethers[2] under neutral conditions and to convert alcohols into iodides.[3]

Quantitative dealkylation occurs when alkyl esters are treated with trimethylsilyl iodide in an aprotic solvent. The free acid is easily obtained by hydrolysis of the trimethylsilyl ester.

$$\mathrm{RCOOR' + Me_3SiI \rightarrow RCOOSiMe_3 + R'I}$$
$$\mathrm{RCOOSiMe_3 \rightarrow RCOOH + Me_3SiOSiMe_3}$$

Alkyl ethers are cleaved in high yield by trimethylsilyl iodide with a high degree of selectivity *e.g.*, aryl alkyl ethers give only the aromatic trimethylsilyl ether and alkyl iodide. When a methyl alkyl ether is cleaved, the overwhelming tendency (95%) is for demethylation to occur. This fact should greatly promote the use of methyl ethers as protecting groups.

$$\mathrm{ArOR + Me_3SiI \rightarrow ArOSiMe_3 + RI}$$
$$\mathrm{ArOSiMe_3 \rightarrow ArOH + Me_3SiOSiMe_3}$$
$$\mathrm{ROMe + Me_3SiI \rightarrow ROSiMe_3 + MeI}$$
$$\mathrm{ROSiMe_3 \rightarrow ROH + Me_3SiOSiMe_3}$$

Primary, secondary and tertiary alcohols, when treated with trimethylsilyl iodide are converted to the corresponding iodides in high yield. If the alcohol contains an acid sensitive group, it may first be converted to its trimethylsilyl ether using hexamethyldisilazane.

$$\mathrm{ROH + Me_3SiI \rightarrow RI + Me_3SiOH}$$
$$\mathrm{ROH \xrightarrow{(Me_3Si)_2NH} ROSiMe_3 \xrightarrow{Me_3SiI} RI + Me_3SiOSiMe_3}$$

Inversion of configuration usually accompanies this reaction.

References

1. M. E. Jung and M. A. Lyster, *J. Am Chem. Soc.*, **99**, 969 (1977).
2. M. E. Jung and M. A. Lyster, *J. Org. Chem.* **42**, 3761 (1977).
3. M. E. Jung and P. L. Ornstein, *Tet. Letters*, 2659 (1977).

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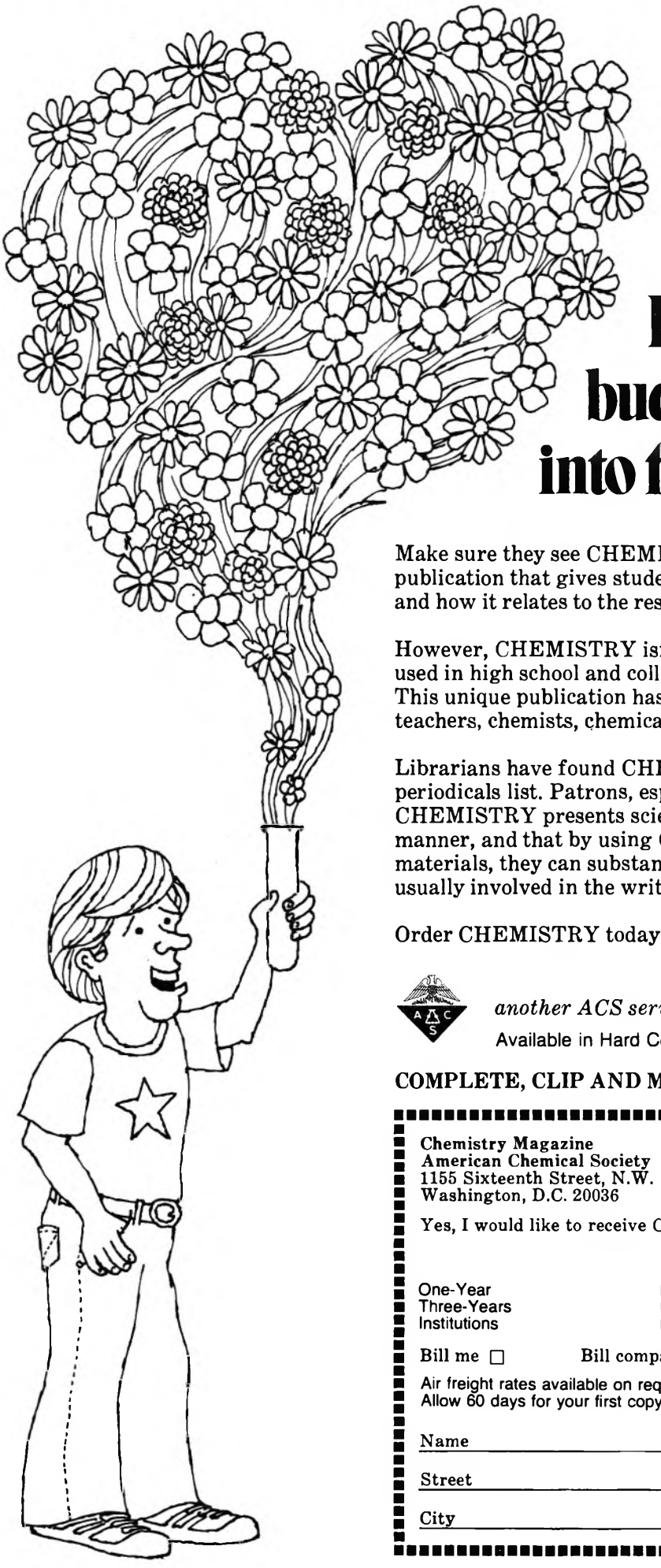

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Patterson, A. M.; Capell, L. T.; Walker, D. F. *Ring Index*, 2nd ed.; American Chemical Society: Washington, D.C., and Supplements I–III, 1963–1965. For rules of carbohydrate nomenclature, see *Biochemistry* **1971**, 10, 3983; for steroid nomenclature, see *J. Org. Chem.* **1969**, 34, 1517. For nomenclature advice, consult Dr. Kurt L. Loening, Director of Nomenclature, Chemical Abstracts Service, P.O. Box 3012, Columbus, Ohio 43210.

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Factors Affecting the Rate of Racemization of Amino Acids and Their Significance to Geochronology[1a]

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Geological samples have been dated on the basis of the degree of racemization of the constituent amino acids by extrapolating rate data from simulated diagenetic studies. The validity of this extrapolation has been questioned, since it is known that, as well as the problem of estimating accurate diagnetic temperatures, factors such as pH and metal ions significantly affect rates of racemization. Results from this study show that further variables affecting the rate of racemization of free amino acids in aqueous solution are ionic strength, the buffer, and buffer concentration. Because of the possible variability in phosphate content in fossil bones, it is significant that racemization increased with increasing concentration of phosphate buffer. Furthermore, since geological matrices vary from sample to sample, and ionic strength may simulate to some extent such matrix changes, it is interesting that, although increasing ionic strength has no effect on racemization rate for a pH of 7.2, at pH 10.0 racemization increases with increasing ionic strength. These data for free amino acids in solution emphasize the necessity to use only the bound amino acid fraction for the dating of fossil specimens. Furthermore, the results suggest that a cautious approach be taken in applying amino acid racemization kinetics of even bound amino acids to geochronology and geothermometry. Concerning the basic mechanism of racemization, our results indicate that steric and proximity effects are equally as important as the inductive strength of the α substituent in determining the relative order of racemization of the amino acids.

Amino acids are ubiquitous and the L-enantiomers of the amino acids have become associated with the presence of life. In recent years there has been a renewed interest in the diagenesis of proteins and, in particular, in the diagenetic racemization of protein amino acids as applied to geochronology and geothermometry. A current investigation of these applications originated in the work of Hare and Abelson[1b] who found increasing proportions of D-amino acids, resulting from the racemization of the constituent L-amino acids, in a series of fossil shells of increasing age. Hare and Mitterer[2] then demonstrated that extrapolation of racemization rate data for L-isoleucine in heated Mercenaria shells agreed well with the data for a series of radiocarbon dated shells at ambient temperatures.

Application of the amino acid dating technique to other geological samples and environments has revealed inherent complications. For the case of deep-sea sediments, it has been shown that the racemization of L-isoleucine does not follow first-order reaction kinetics beyond a few 100 000 years.[3,4] In a study of fossil corals,[5] it was observed that the "D/L ratios in many of the samples investigated did not conform to the concept of increasing racemization being associated with increasing fossil age". Modern contamination was suggested as a problem factor.

The most successful application of amino acid racemization data has been in the dating of fossil bones. In particular, Bada has taken up this application demonstrating the linearity of the kinetics,[6] overcoming the uncertainty of a temperature fluctuation using a "calibration procedure"[7] and presenting evidence for the concordance of the aspartic acid dates so obtained, with known collagen-based radiocarbon dates.[8] Even this data has not been free of criticism, however. Hare has demonstrated the sensitivity of amino acid racemization in bone to water content and has pointed out discrepancies in Bada's results.[9] It was Hare's conclusion that "probably few, if any, of the published amino acid dates are reliable. Some are possibly off by an order of magnitude".[9] Despite such criticism, Bada and Helfman concluded that "because of the close correlation between temperatures calculated from in situ racemization rates (under diverse environmental conditions) and actual mean annual temperatures at various sites throughout the world . . . that factors other than temperature have very small effects on the reaction rate".[10]

In view of the potential problems associated with the technique, we have undertaken to examine more closely parameters which might affect the rate of racemization of amino acids during diagenesis. This involves a two-part study: firstly, with free amino acids in aqueous solution as the simplest system, and, secondly, a study of "protein-bound" amino acids. We here report on the first of these two objectives. We

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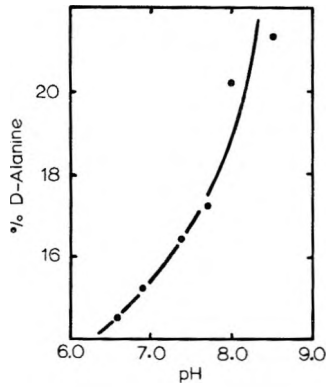

Figure 1. The effect of pH on the racemization of L-alanine at 125 °C, ionic strength 0.20, phosphate buffer 0.03 M.

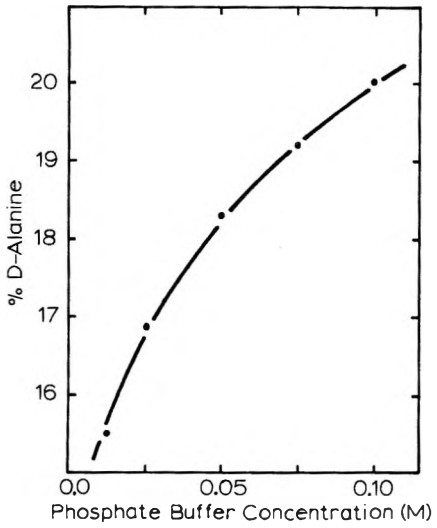

Figure 2. The effect of increasing phosphate buffer concentration on the racemization of L-alanine at 126 °C for 5 days, pH 7.6, ionic strength 0.50.

have attempted to relate our results to geochronology and to a better understanding of the mechanism of amino acid racemization.

Results and Discussion

Kinetics of Amino Acid Racemization. The general racemization reaction for amino acids may be expressed by

$$\text{L-amino acid} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{D-amino acid} \qquad (1)$$

where k_1 and k_2 are the forward and reverse rate constants, respectively. The rate expression for this reaction is

$$\frac{-d[L]}{dt} = k_1[L] - k_2[D] \qquad (2)$$

where [L] and [D] are the respective concentrations of the L and D enantiomers. Equation 2 may be integrated to give eq 3

$$\ln\left(\frac{1 + [D]/[L]}{1 - K'([D]/[L])}\right) = (1 + K')k_1t + C \qquad (3)$$

where $K' = 1/K = k_2/k_1$, and C is the integration constant.

In general, for free amino acids and aqueous solution, k_1 and k_2 and eq 3 reduces to

$$\ln\left(\frac{1 + [D]/[L]}{1 - [D]/[L]}\right) = 2kt + C \qquad (4)$$

However, for L-isoleucine, which racemizes (or more correctly epimerizes) to its diastereomer D-alloisoleucine, $k_1 > k_2$ and thus $K > 1.00$. The importance of the value assigned the isoleucine equilibrium constant will be discussed later in this article.

Table I. Percent D-Alanine Obtained from Racemizing Alkaline Solutions of L-Alanine at Different Ionic Strengths[a]

Sample	% D-Ala			
	μ = 0.2	μ = 0.7	μ = 1.2	μ = 2.2
1	20.8	22.4	25.3	28.6
	20.7	22.3	25.3	28.5
2	21.0	23.2	25.2	28.6
	21.1	23.3	25.3	28.6
3	20.8	23.5	25.1	28.5
	20.8	23.3	25.1	28.5

[a] Conditions: After adjusting the ionic strength of a 0.02 M aqueous solution of L-alanine with sodium chloride, the pH was carefully brought to a pH of 10.0 using 0.05 M phosphate buffer solution. The samples were each heated at 148 °C for 18 h.

Buffer and pH. It has been claimed that in the pH range of 5 to 8 racemization is independent of pH.[11] However, we have found that in the range of 6.5 to 8.5 that there is an increase in racemization with increasing pH for phosphate-buffered alanine (Figure 1). This pH range is that which would most often be encountered during natural diagenetic racemization. Consequently, it has been suggested that by choosing fossil material with either a calcareous or an hydroxylapatite matrix the effects of pH might be minimized, since the matrix would act to buffer the fossil against pH fluctuations.[12] In view of the data illustration in Figure 1, this appears to be a sensible precaution.

Since the racemization reaction is believed to be general-base catalyzed,[26] a study was made on the effect of increasing buffer concentration on the rate of racemization of alanine at constant pH. As the concentration of the phosphate buffer was increased (at constant ionic strength), there was a corresponding increase in racemization of L-alanine (Figure 2). Thus, this data supports the general-base catalyzed mechanism. Furthermore, it lends credence to the possibility discussed by Schroeder and Bada[26] that "various anionic species of carbonate and phosphate may serve as nucleophiles in skeletal material".

At first we also thought that the carbonate–bicarbonate buffer system resulted in a substantial increase in racemization over other buffers. However, it was later realized that the pH was not constant in this study, which further illustrates the sensitivity of amino acid racemization to pH change. Bicarbonate solutions are very unstable and lose carbon dioxide to give carbonate with a resulting increase in pH. Because of the difficulties encountered in maintaining a constant pH, we discontinued further work with the carbonate buffer.

Unbuffered amino acid solutions also do not maintain a constant pH when heated presumably because of some decarboxylation of the amino acid at elevated temperatures. Solutions of leucine were titrated to a pH of 8.0 and 3.7 and then heated to ca. 118 °C for 6 days. The pH was measured again and found to have increased to 8.8 and 8.7, respectively. Solutions of alanine which were treated in the same way also increased in pH to ca. 8.7. An interesting observation, however, was that samples of nonbuffered alanine which were heated under identical conditions as the phosphate-buffered samples of Figure 1 underwent much less racemization. Figure 1 would indicate that at pH 8.7 alanine should racemize to give more than 22% D-alanine. Unbuffered samples were found to form only 13.7% of the D enantiomer. This result is in agreement with the trend evident in Figure 2 for phosphate buffer, and may be of interest in the application of amino acid racemiza-

Table II. Values Reported for the Isoleucine Epimerization Equilibrium Constant, K_{Ile}

K_{Ile}	Temp (°C)	Environment	Reference
1.30	~2	Early Miocene foraminifera	King and Hare[16]
1.40	~2	Miocene sediments	Wehmiller and Hare[3]
1.29	130	6 N HCl	Nakaparksin et al.[17]
1.30	140	Mercenaria shells	Hare[18]
1.25	*a*	Aqueous solution	Hare and Mitterer[2]
1.38	148	Modern bones	Bada[19]
1.28	150	Fossil bone	Dungworth et al.[14]
1.40	*a*	Alkaline solution	Hare and Mitterer[20]
1.40	126	Aqueous solution, pH 7.6, ionic strength 0.50	Smith et al., this paper

[a] Temperature not specified.

Table III. The Effect of K_{Ile} on the Half-Life (τ) Determinations for Isoleucine Racemization[a]

K_{Ile}	$k_1 \times 10^7$ (s^{-1})	τ^b
1.00	143.4	6.7
1.25	50.4	21.2
1.30	48.2	22.6
1.35	46.4	23.8
1.40	44.9	25.0

[a] T = 161.9 °C, pH 7.6, ionic strength 0.50. [b] A general expression for the half-life of amino acid racemization is $\tau = (\ln 2)/[(1 + K')k_1]$.

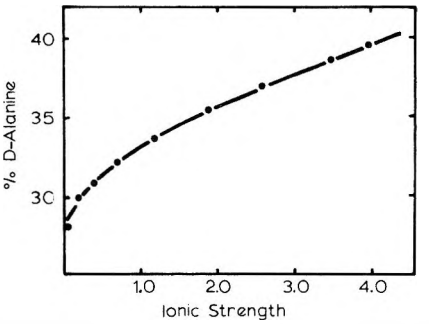

Figure 3. The effect of changes in ionic strength on the racemization of L-alanine at pH 10.7 (unbuffered), at ~130 °C for 3 days.

tion to geochronology. A modern dry bone is ca. 50% calcium phosphate.[13] Since the phosphate content of fossil bones may be changing with time, it might be predicted that the amino acids would initially racemize rapidly in the presence of the high phosphate concentration and then as the percent phosphate decreased so too would the rate of racemization. This expectation may be supported by a report which implies that the racemization rate of alanine in fossil bone is decreasing with time, the decrease being ca. 30% over the time period datable by radiocarbon.[14] (However, we have only established the effect of phosphate on the racemization of "free" alanine. Collagen-bound alanine may not be susceptible to the effects of phosphate. This study has yet to be carried out. For a discussion of the significance of "bound" and "free" amino acids, reference may be made to a recent review by Williams and Smith.)[15]

Ionic Strength. The effect of changes in ionic strength on racemization rates of alanine was studied to partially simulate matrix changes found in the geological environment. The effects were measured at pH 7.2, 10.0, and 10.7. At pH 7 (phosphate buffer) it was thought that the rate decreased with an increase in ionic strength. However, this proved to be a pH effect not an ionic-strength effect. The addition of sodium chloride also changed the pH. When the pH was carefully adjusted to pH 7.2 *after* the sodium chloride was added, no change in the rate was observed with a change in ionic strength. However, at pH 10 and 10.7, the ionic strength altered the racemization rate. At pH 10 (phosphate buffered) an increase in the ionic strength appreciably increased the racemization rate (Table I). Also, at pH 10.7 the same relative result was observed with a greater amount of racemization occurring at the higher pH (Figure 3). These effects are predicted from theory which states that reactions between like-charged ions [in this case $RCH(NH_2)COO^-$ and B^-] proceed more rapidly as the ionic strength increases.

The Effect of *K* on Racemization Rate Data for Isoleucine. It has already been mentioned that, in general, $k_1 = k_2$ and, consequently, $K = 1.0$, but that for the racemization of L-isoleucine to D-alloisoleucine k_1 is greater than k_2 and, hence, $K > 1.0$. Table II lists values for K_{Ile} which have appeared in the literature and the conditions under which they were determined. In other reports using the kinetics of isoleucine racemization, the value of K_{Ile} has been arbitrarily assigned.[5] We wondered if a significant error has been introduced into reported rate data by assuming an incorrect figure for K_{Ile}. The effect of K_{Ile} on the half-life of the isoleucine epimerization at an elevated temperature (161.9 °C) is demonstrated in Table III. Extrapolation of our Arrhenius data to 25 °C gives a half-life of 9000 or 8200 years, depending on whether K_{Ile} is assigned a value of 1.30 or 1.40, respectively. With the scatter in values reported for K_{Ile} (Table II), it is easily evident that isoleucine-derived age estimates have a minimum uncertainty of ca. 10% even if all other parameters are accurately known. The racemization of isoleucine has been used extensively for dating shells and sediments because it is relatively stable against diagenetic degradation,[27,28] has a suitable half-life, and because L-isoleucine may be resolved from D-alloisoleucine by conventional ion-exchange chromatographic procedures. We wish to emphasize the need for an accurate evaluation of K_{Ile} for each system under study to avoid unnecessary errors in age estimations. There is also a need to determine whether K_{Ile} is temperature dependent. We are currently investigating this possibility.

Arrhenius Parameters: Mechanism of Amino Acid Racemization. Amino acid racemization proceeds via base abstraction of the α-proton leading to formation of a planar carbanion, which may be resonance stabilized.[21] This mechanism is supported by the results of deuterium-exchange studies. It has been shown that the rates of racemization and of deuterium-exchange at the α-carbon parallel each other.[22,23]

The observed order of amino acid racemization at elevated temperatures is Asp > Glu > Phe > Ala > Leu > Ile > Val. The electron-withdrawing capacity of the R substituent has been invoked as the principle factor in determining this order by several authors.[6,17] Sato et al.[24] concluded from their base-catalysis studies that the relative susceptibility of a series

Table IV. Reported Arrhenius Parameters for the Racemization of Free Amino Acids in Aqueous Solution

Amino acid	Registry no.	Dungworth et al.[a] (pH 7.0) E_a(kcal/mol)	Dungworth et al.[a] (pH 7.0) A (s^{-1}) × 10^{-9}	Bada[b] (pH 7.6) E_a (kcal/mol)	Bada[b] (pH 7.6) A (s^{-1}) × 10^{-10}	Smith et al.[c] (pH 7.6) E_a (kcal/mol)	Smith et al.[c] (pH 7.6) A (s^{-1}) × 10^{-8}	Nakaparksin et al.[d] (6 N HCl)[b] E_a (kcal/mol)
Asp	6899-03-2			31.0	17.03			
Ala	6898-94-8	29.4	3.15	30.9	4.09	28.5	20.72	25
Val	7004-03-7	29.1	0.69			28.6	8.36	31
Leu	7005-03-0	29.3	2.03			27.7	5.85	25
Ile	7004-09-3	28.9	1.19	31.4	3.03	27.9[c]	4.57	
Phe	3617-44-5			28.6	0.356	24.0	0.173	
α-Ab[d,g]	1492-24-6							25

[a] Reference 16. [b] Reference 11. [c] This paper. [d] Reference 17. [e] A values not reported. [f] For K = 1.40 at all temperatures. [g] α-amino-n-butyric acid.

Table V. The Eyring Parameters for the Racemization of Free Amino Acids in Aqueous Solution

Amino acid	$\Delta H^\dagger$ (kcal/mol)	$\Delta S^\dagger$ (esu)
Phe	23.0 ± 0.3	−28.4 ± 0.8
Ala	28.6 ± 0.4	−16.3 ± 1.0
Leu	27.5 ± 0.3	−19.8 ± 0.8
Ile[a]	27.1 ± 0.6	−21.6 ± 1.4
Val	28.0 ± 0.4	−19.8 ± 1.0

[a] For K_{Ile} = 1.40 at all temperatures.

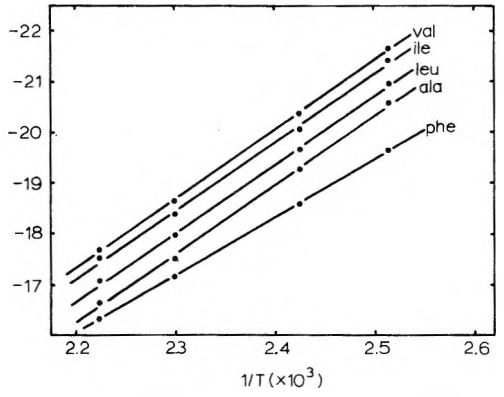

Figure 4. Arrhenius plots for the racemization of valine, isoleucine, leucine, alanine, and phenylalanine, at pH 7.6, ionic strength 0.50 in phosphate-buffered solution (0.05 M).

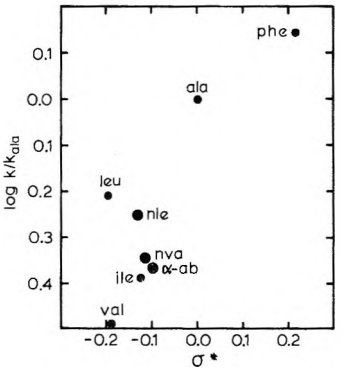

Figure 5. The relationship between the inductive strength (σ^*) of the amino acid side chain and the relative rate constants for the racemization of phenylalanine, leucine, isoleucine, alanine, valine, norvaline, norleucine, and α-amino-n-butyric acid at 161.9 °C, pH 7.6, ionic strength 0.50, and phosphate buffer 0.05 M. The data for norvaline, norleucine, and α-ab are less accurate as indicated.

of N-benzoyl amino acid anilides to racemization "is proportional to the electronegativity of the α-substituent unless the α-substituent exerts a steric effect". A linear result was obtained when log (k/k_{Ala}) was plotted against σ^* for the derivatives of phenylglycine.

The differences in rates of racemization for each amino acid may be attributed to differences in $\Delta H^\dagger$ and/or $\Delta S^\dagger$. If inductive or resonance effects determine the rate, they will be reflected in a change in $\Delta H^\dagger$; if steric considerations are important, they will alter either $\Delta H^\dagger$ or $\Delta S^\dagger$; field effects will change $\Delta H^\dagger$. Finally, any differences in the ordering of the solvent during racemization will effect the relative rates via an entropy contribution.

In order to determine if the electron-withdrawing capacity of the α-substituent accounts for the observed order of amino acid racemization, accurate activation parameters are required. (It should also be emphasized that accurate Arrhenius parameters are essential for amino acid dating, since a 1% error in the activation energy will give a corresponding 20% error in the calculated age.) Since previously reported Arrhenius parameters did not agree well[11,12] (Table IV), we determined activation parameters under carefully controlled conditions of temperature, ionic strength, pH, and buffer concentration. Furthermore, baseline resolution was obtained between the D- and L-enantiomeric peaks for all amino acids studied. Consequently, we believe this data to be reliable. Our results (Figure 4, Tables IV and V) indicate that the order of amino acid racemization cannot be accounted for simply by inductive effects.

For phenylalanine $\Delta H^\dagger$ is the determining factor in the racemization rate overcoming the large negative entropy. In this case, the electron-withdrawing strength of the benzyl group apparently accounts for the high comparative rate constant. However, for the other amino acids this is not the case. For leucine, isoleucine, and valine (whose σ^* values are very similar), both the $\Delta H^\dagger$ and $\Delta S^\dagger$ values are the same within experimental error, and it is by no means clear what determines the rate. For alanine, which appears to have a slightly higher $\Delta H^\dagger$, the rate must be determined by its comparatively lower $\Delta S^\dagger$, since alanine actually racemizes more rapidly than leucine, isoleucine, and valine. Although phenylalanine shows the fastest racemization rate of the amino acids studied, its rate is not as fast as it would be expected from the value of its $\Delta H^\dagger$ alone. The bulk of the $PhCH_2^-$ group apparently alters the $\Delta S^\dagger$ value. It was found to be the most negative of all the amino acids studied (Table V).

Although the reason for the observed order of racemization is not completely clear, it is apparent that to account for this order on the sole basis of the inductive strength of R is unrealistic. A plot of log (k/k_{Ala}) against σ^* for six amino acids (161.9 °C; Figure 5) shows no correlation, further emphasizing this point. (Recently published σ^* values have again been questioned. Therefore, plots of σ^* may not necessarily be significant.[29]) Racemization rates of the amino acids are de-

termined by a complex combination of inductive, resonance, steric, proximity, and solvent effects.

Conclusions

It is clear from this study of factors affecting the rate of racemization of free amino acids in aqueous solution that diagenetic racemization involves a complex interaction of many variables.

We have identified ionic strength, pH, buffer, and buffer concentration as factors which influence racemization rates. These data help explain why, for example, linear first-order kinetics are only observed over short ranges for total sediment hydrolysates. The results for free amino acids also show why it is essential to examine only the racemization of the bound amino acid fraction of fossil specimens. Furthermore, although bound amino acids should be less susceptible to variation of some of these parameters, the results suggest that a cautious approach be taken in applying amino acid racemization kinetics of even bound amino acids to geochronology and geothermometry.

This study supports the contention that the order of racemization of amino acids is not only determined by the inductive strength of the α-substituent, but also by steric, proximity, and solvent effects.

Of importance to the use of isoleucine for amino acid dating is the value assigned to K_{Ile}. This should be accurately defined for each system studied to avoid unnecessary errors in fossil age estimations. There is a need for an investigation of whether or not there is any temperature dependence of K_{Ile} for protein-bound isoleucine.

Experimental Section

Temperature Control. Temperatures of the samples were controlled to ±0.2 °C by immersion in thermostatically controlled baths of heavy-duty motor oil. The baths were regulated via proportional temperature controllers (RFL Industries, Inc., Model 70-115).

Sample Preparation. The amino acid solutions were prepared such that the final buffer concentration was 0.05 M and the ionic strength was brought to 0.50 using sodium chloride solution (5.00 M). The pH was adjusted by the addition of an appropriate volume of sodium hydroxide or hydrochloric acid solution. Aliquots (1.00 mL) of the amino acid solutions were sealed in glass tubing and heated in the oil bath for the required times. The tubes were cooled and opened, and the water was evaporated under a nitrogen stream at 80–90 °C. The last traces of moisture were removed by azeotroping with dichloromethane and by then placing the tubes in a vacuum oven (30 min, 80 °C) or by keeping them over anhydrous calcium chloride in a vacuum dessicator overnight.

Sample Derivatization. *N*-Trifluoroacetylamino Acid Isopropyl Esters. To each dried amino acid residue was added 2-propanol/HCl (4 N; 600 μL). The tubes were sealed, ultrasonicated (70 °C, 20 min) and heated in an oil bath (120 min, 100 °C). The 2-propanol was removed under a stream of nitrogen, dichloromethane was added, and the solvent was evaporated again. Derivatization was completed by the addition of trifluoroacetic anhydride (200 μL) and dichloromethane (200 μL). After 2 h at room temperature, the reagent was removed as previously, and the residue was taken up in dichloromethane (0.5 mL) and transferred to the GLC vials.

Gas Chromatography. GLC analyses were run under appropriate isothermal conditions using stainless-steel capillary columns (150 ft × 0.02 in.), coated with the optically active liquid-phase *N*-lauroyl-L-valyl-*tert*-butylamide.[25] In all cases, baseline resolution was obtained for the D- and L-enantiomeric amino acid peaks. The gas chromatograph was an HP 5830A with an HP automatic injector and electronic integration.

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References and Notes

(1) (a) Presented in part at the 172nd National Meeting of the American Chemical Society, San Francisco, Sept. 3, 1976, Paper Orgn 226. (b) P. E. Hare and P. H. Abelson, *Carnegie Inst. Washington, Yearb.*, **66**, 526 (1967).
(2) P. E. Hare and R. M. Mitterer, *Carnegie Inst. Washington, Yearb.*, **67**, 205 (1968).
(3) J. F. Wehmiller and P. E. Hare, *Science*, **173**, 907 (1971).
(4) J. L. Bada and R. A. Schroeder, *Earth Planet. Sci. Lett.*, **15**, 1 (1972).
(5) J. F. Wehmiller, P. E. Hare, and G. A. Kujala, *Geochim. Cosmochim. Acta*, **40**, 763 (1976).
(6) J. L. Bada, K. A. Kvenvolden, and E. Peterson, *Nature (London)*, **245**, 308 (1973).
(7) J. L. Bada and R. Protsch, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 1331 (1973).
(8) J. L. Bada, R. A. Schroeder, R. Protsch and R. Berger, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 914 (1974).
(9) P. E. Hare, *MASCA Newslett.*, **10**, 1 (1974).
(10) J. L. Bada and P. M. Helfman, *World Archael.*, **7**, 160 (1975).
(11) J. L. Bada, *Adv. Chem. Ser.*, **No. 106**, 309 (1971).
(12) G. Dungworth, N. J. Vincken, and A. W. Schwartz, *Adv. Org. Geochem., Proc. Int. Meet., 6th, 1973*, 689 (1974).
(13) R. Berger, A. G. Horney, and W. F. Libby, *Science*, **144**, 999 (1964).
(14) G. Dungworth, A. W. Schwartz, and L. van de Leemput, *Comp. Biochem. Physiol. B*, **53**, 473 (1976).
(15) K. M. Williams and G. G. Smith, *Origins Life*, **8**, 91 (1977).
(16) K. King and P. E. Hare, *Science*, **175**, 1461 (1972).
(17) S. Nakaparksin, E. Gil-Av, and J. Oró, *Anal. Biochem.*, **33**, 374 (1970).
(18) P. E. Hare, in "Organic Geomchemistry: Methods and Results", G. Eglington and M. T. J. Murphy, Ed., Springer-Verlag, New York, N.Y.
(19) J. L. Bada, *Earth Planet Sci. Lett.*, **15**, 223 (1972).
(20) P. E. Hare and R. M. Mitterer, *Carnegie Inst. Washington, Yearb.*, **65**, 362 (1966).
(21) A. Neuberger, *Adv. Protein Chem.*, **4**, 297 (1948).
(22) H. Matsuo, Y. Kawazoe, M. Sato, M. Ohnishi, and T. Tatsuno, *Chem. Pharm. Bull.*, **15**, 391 (1967).
(23) H. Matsuo, Y. Kawazoe, M. Sato, M. Ohnishi, and T. Tatsuno, *Chem. Pharm. Bull.*, **18**, 1788 (1970).
(24) M. Sato, T. Tatsuno, and H. Matsuo, *Chem. Pharm. Bull.*, **18**, 1794 (1970).
(25) B. Feibush, *J. Chem. Soc. D*, 544 (1971).
(26) R. A. Schroeder and J. L. Bada, *Earth-Sci. Rev.*, **12**, 347 (1976).
(27) J. R. Vallentyne, *Geochim. Cosmochim. Acta*, **28**, 157 (1964).
(28) J. R. Vallentyne, *Geochim. Cosmochim. Acta*, **33**, 1453 (1969).
(29) F. G. Bordwell, G. E. Drucker, and G. J. McCollum, *J. Org. Chem.*, **41**, 2786 (1976).

Effect of Substituents on Ring Size in Radical Cyclizations. 1. Methyl vs. Phenyl[1]

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Mechanisms in cyclization of radicals (e.g., those involved in cyclopolymerization of 1,6-dienes) have been examined. The products obtained from the reactions of tributyltin hydride (Bu_3SnH) with 5,6-unsaturated hexyl radicals substituted at the 5 position were studied. The 2-allyloxyethyl radicals substituted at the 5 position were studied. The 2-allyloxyethyl radical gave 3-methyltetrahydrofuran as the only cyclic product; the 2-methallyloxyethyl radical cyclized to give up to 3% 3-methyltetrahydropyran in addition to 3,3-dimethyltetrahydrofuran and ethyl methallyl ether; 3-phenyltetrahydropyran was the predominant cyclic product from the 2-(2-phenylallyloxy)-ethyl radical. These observations support a mechanism involving classical radical cyclizations. The kinetic treatment for a reaction scheme involving competition between irreversible cyclization and abstraction of hydrogen by the initially formed radical satisfactorily fits the data. The irreversibility of the cyclization reactions was shown by generating the corresponding radical from 3-phenyl-3-bromomethyltetrahydrofuran to yield 3-phenyl-3-methyltetrahydrofuan as the only product. Thus, the kinetic treatment is also in agreement with a simple competition between irreversible cyclization reactions and abstraction of hydrogen by the acyclic radical. The rate constants and activation energies for the competing reactions were obtained from the kinetic data.

Introduction

Radical cyclizations via intramolecular attack of a radical species on an olefinic double bond have been known and studied since the initial observation was made[2] that certain 1,6-dienes polymerized via free-radical initiators to yield soluble, linear, and saturated polymers. These results could be accounted for reasonably only on the basis of an alternating intra–intermolecular chain propagation.[3] This proposal is consistent with "head to tail" enchainment in radical-initiated polymerization of vinyl monomers.[4] However, in 1961 Miyake[5] reported that the cyclic polymer obtained from poly(divinylformal) via hydrolysis contained considerable 1,2-glycol content, a structure which could reasonably arise only through five-membered rings produced via "head to head" enchainment. Subsequently, many reports of radical cyclizations which apparently proceed via the less stable radical intermediate and produce the less stable cyclic structure have appeared.[6,7]

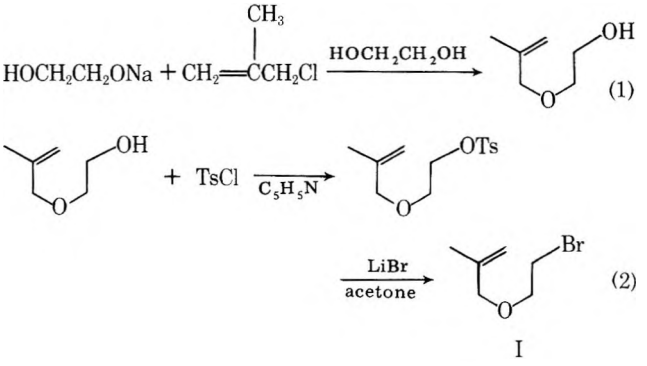
At present, no single, totally satisfactory mechanism is available which can adequately account for all of the experimental observations in these radical cyclizations.[6] Justification for apparent preference for the less-favored cyclization has been based on both electronic[8a,9] and steric[8b,10,11] factors.

Recent evidence which supports the existence of an electronic interaction in 1,5-hexadiene is based upon a photoelectron spectroscopic study[12] in which it was shown that a conformation in which the two double bonds are crossed is more stable by 2.3 kcal/mol than the open chain conformation.

Results and Discussion

It was a major purpose of this investigation to generate 5-substituted-5-hexenyl radicals in which the 5 substituent was selected from among those highly radical-stabilizing groups present in well-known vinyl monomers and to determine the ratio of five- to six-membered ring formed. Thus, 2-phenylallyl 2-bromoethyl ether, 2-methylallyl 2-bromoethyl ether, and the products which could arise from generation of the corresponding radicals in the presence of tributyltin hydride were synthesized.

Synthesis of Reactants and Predicted Products—2-Methylallyl 2-Bromoethyl Ether (I). This compound was synthesized via the reaction sequence in eq 1 and 2 utilizing well-established procedures.



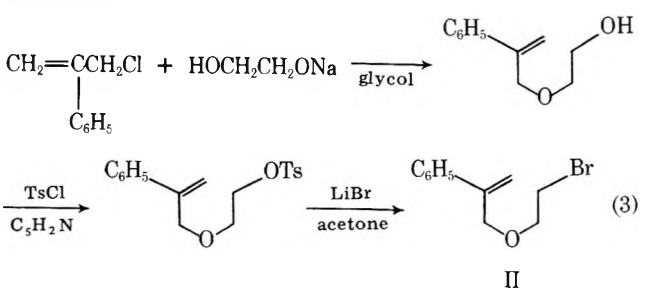
I

Ethyl methallyl ether (Ia) was prepared by treating sodium ethoxide with methallyl chloride in ethanol.

3,3-Dimethyltetrahydrofuran (Ib) was prepared from 2,2-dimethylsuccinic acid which was converted to the diethyl ester, followed by reduction of the ester to 2,2-dimethyl-1,4-butanediol with lithium aluminum hydride (LAH). The diol was converted to Ib by reaction with 60% sulfuric acid at 100 °C.

3-Methyltetrahydropyran (Ic) was prepared via a similar series of reactions beginning with 2-methylglutaric acid.

2-Phenylallyl 2-Bromoethyl Ether (II). This compound was synthesized in a manner analogous to the 2-methylallyl ether (eq 3).



II

Ethyl 2-phenylallyl ether (IIa) was prepared from the reaction of sodium ethoxide with 2-phenylallyl chloride in ethanol.

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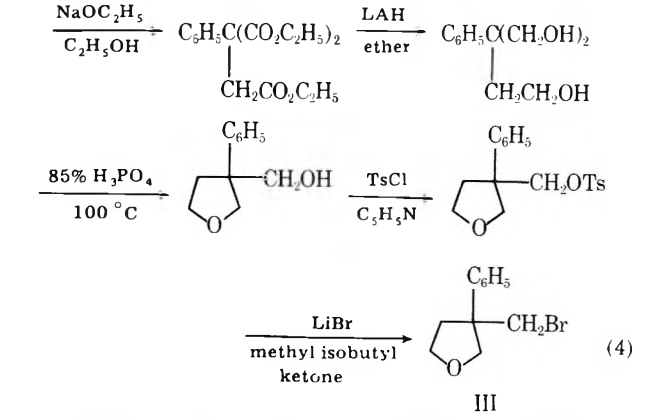
The other two expected products, 3-methyl-3-phenyltetrahydrofuran (IIb) and 3-phenyltetrahydropyran (IIc), were obtained by reacting equimolar portions of 2-bromoethyl 2-phenylallyl ether and tributyltin hydride in benzene solution in an autoclave at 130 °C. At this temperature the main products were IIb and IIc.

In order to establish the irreversibility of the reactions leading to products IIb and IIc, it was necessary to synthesize an unequivocal radical precursor to one of the radicals leading to IIb or IIc. Although cyclization of the 5-hexenyl radical had been shown to be irreversible[9,10] as well as cyclization of the 2-allyloxyethyl radical,[15] in a study of cyclization of 1-substituted 5-hexenyl radicals[7] it was shown that the cyclization reactions were reversible when C-1 was disubstituted (two –CN or $-COOC_2H_5$ groups). It was also shown[7] that as substitutions on C-1 by radical stabilizing groups (one or two –CN or $-COOC_2H_5$ groups) gradually increased, the mixture of products changed from nearly pure cyclopentane to nearly pure cyclohexane derivatives. The reaction sequence[13] in eq 4 was employed for the synthesis of 3-phenyl-3-(bromomethyl)tetrahydrofuran (III).



(4)

Tributyltin hydride (Bu_3SnH) was prepared according to the procedure of Kuivila and Buenel[14] by reaction of tributyltin chloride with LAH.

Generation and Reactions of Radicals. The 2-Methylallyloxyethyl Radical. The techniques involved in generating the radicals and analyzing the resulting products were modeled after previously published procedures.[15,16] In all cases the molar ratio of the bromide to Bu_3SnH in the reaction mixtures was about 3:1. The amount of AIBN was 1.5 mol % based on Bu_3SnH concentration. The solutions prepared are described in Table IV. Quantitative determinations of the concentration of products resulting from the reactions of the radicals with Bu_3SnH were made by GC. The product concentrations resulting from these reaction solutions are given in Table IX. The yield percentages of the products based on the initial concentrations of the Bu_3SnH are listed in Table X. The ratio of 3,3-dimethyltetrahydrofuran to 3-methyltetrahydropyran formed at each temperature was approximately the same for all three concentrations of reactants. The ratios observed at the three reaction temperatures are listed in Table I. The results obtained with this ether are consistent with those subsequently obtained from 2-methyl-6-bromo-1-hexene.[17]

The 2-(2-Phenylallyloxy)ethyl Radical. The procedure, molar ratios of reactants, and methods of analysis were analogous to those used for the previous system.

Table XI shows the compositions of the solutions prepared to study the reactions of the 2-(2-phenylallyloxy)ethyl radical with Bu_3SnH. The product concentrations resulting from these reaction mixtures are listed in Table XII. The yield percentages of the products based on the initial concentrations of the tributyltin hydride are listed in Table XIII.

Table I. Ratios of 3,3-Dimethyltetrahydrofuran to 3-Methyltetrahydropyran Produced

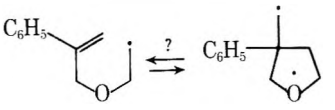
Temp, °C	[Ib]:[Ic]
40	43 ± 1.5
90	30 ± 1.0
125	24 ± 1.0

Table II. Ratios of 3-Phenyltetrahydropyran to 3-Phenyl-3-methyltetrahydrofuran Produced

Temp, °C	[IIc]:[IIb]
40	1.82 ± 0.04
90	1.92 ± 0.04
130	2.00 ± 0.05

The ratio of 3-phenyltetrahydropyran to 3-phenyl-3-methyltetrahydrofuran formed at each temperature was approximately the same for all three concentrations of reactants. The ratios observed at the different reaction temperatures are listed in Table II.

The (3-Phenyl-3-tetrahydrofuranyl)methyl Radical. The (3-phenyl-3-tetrahydrofuranyl)methyl radical was generated from 3-phenyl-3-bromomethyltetrahydrofuran under the usual reaction conditions at 90 °C to check the reversibility of its formation from the 2-(2-phenylallyloxy)ethyl radical. It was reasoned that if either of the cyclization reactions of the 2-(2-phenylallyloxy)ethyl radical was reversible, the one



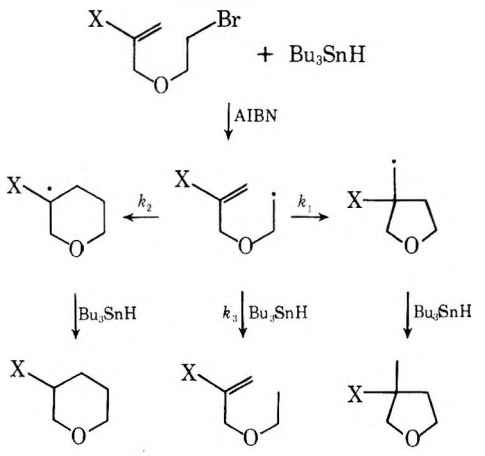
shown should be since the other radical leading to 3-phenyltetrahydropyran should be a more stable benzylic radical. The only product obtained when this bromide was treated with Bu_3SnH under the usual conditions at 90 °C was 3-phenyl-3-methyltetrahydrofuran, which proves the stability of the (2-phenyl-3-tetrahydrofuranyl)methyl radical under these conditions. Thus it appears the radical cyclization reactions of the 2-(2-phenylalloxy)ethyl radical are irreversible processes, just as they were shown to be for the cyclization reactions of the 5-hexenyl radical[9] and subsequently for the 5-methyl-5-hexenyl radical.[17]

Kinetics of the Radical Reactions. The groundwork for studying the kinetics of the reactions of radical systems of the type studied in this work was established by Walling et al.[15] and by Carlsson and Ingold.[18] The first group[15] reported a kinetic treatment for the competing reactions of the 5-hexenyl radical in the presence of Bu_3SnH. The second group[18] established the fact that for the reaction of an alkyl bromide with tributyltin hydride in the presence of a radical initiator, the rate-controlling step is abstraction of hydrogen from the tributyltin hydride by the alkyl radical. Thus, the competing reactions of the alkyl radical can be studied kinetically by this method.

Equation 5 quite satisfactorily fit the data obtained for the reaction products obtained from the 2-methyllyloxyethyl radical and the 2-(2-phenylalloxy)ethyl radical. The equation

$$-\frac{d[Bu_3SnH]}{d\left[\begin{array}{c}X\\ \\ O\end{array}\right]} = \frac{k_1 + k_2 + k_3[Bu_3SnH]}{k_3[Bu_3SnH]} \qquad (5)$$

Scheme I

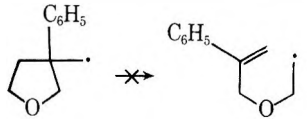


was integrated between the initial and final reaction conditions to yield eq 6.

$$\left[\text{X-cyclic}\right]_F = [Bu_3SnH]_I \frac{k_1 + k_2}{k_3} \ln \frac{k_1 + k_2 + k_3[Bu_3SnH]_I}{k_1 + k_2} \quad (6)$$

Scheme I shows the reactions of the two radical systems studied. It is analogous to the reaction scheme described for the reactions of the 4-(1-cyclohexenyl)butyl radical by Strubble, Beckwith, and Gream.[19a] As they observed a constant ratio of the spiro compound to the decalin formed over a sevenfold change in tributyltin hydride concentration, we observed a constant ratio of tetrahydrofuran derivatives to tetrahydropyran derivative over a fourfold change in tributyltin hydride concentration at each temperature for both of the radical systems studied.

Since the cyclization of the 2-(2-phenylallyloxy)ethyl radical to the 3-(2-phenyltetrahydrofuranyl)methyl radical was shown to be an irreversible process (eq 7), it would seem reasonable to assume that all four cyclic radicals formed in the two radical systems studies were formed irreversibly. The methyl analog of the five-membered cyclic radical should be no more likely to undergo the reverse reaction than the phenyl system, while the two six-membered cyclic radicals, one being tertiary and the other benzylic, should be less likely to undergo the reverse reaction.



(7)

The lack of reversibility of the radical cyclizations coupled with the constant ratios of cyclic products at each temperature supports the proposed reaction scheme, whereby the cyclic products arise from irreversible radical cyclizations whose rates are independent of the tributyltin hydride concentration. Thus the ratio of k_1 to k_2 is just the constant ratio of tetrahydrofuran derivative to tetrahydropyran derivative formed at that temperature as shown in eq 8.

$$\frac{k_1}{k_2} = \frac{[\text{X-cyclic}]}{[\text{X-cyclic}]} \quad (8)$$

Using this relationship between k_1 and k_2 it was possible to solve eq 6 by trial and error for a value of k_3/k_1 or k_3/k_2 which would fit each set of data. The values of k_3/k_1 or k_3/k_2 which gave the best fit for the products obtained from the 2-methyllyloxyethyl radical and the 2-(2-phenylallyloxy)ethyl radical, respectively, are listed in Table III. Also listed in Table III are the values of $[Ia]_{calcd}$ and $[IIa]_{calcd}$, the calculated values of the concentration of uncyclized product, which are obtained when the k_3/k_1 or k_3/k_2 which best fits the data is plugged into eq 3.

Table III. Values of k_3/k_1 or k_3/k_2 Which Best Fit the Data According to Eq 6

2-Methallyloxyethyl Radical System

Solution	Temp, °C	$[Ia]_{obsd}$	k_3/k_1	$[Ia]_{calcd}$
41	40	0.0042	16.4	0.0043
42	40	0.0134	16.4	0.0132
43	40	0.0400	16.4	0.0402
91	90	0.0028	9.9	0.0027
92	90	0.0088	9.9	0.0090
93	90	0.0300	9.9	0.0298
121	125	0.0020	7.6	0.0020
122	125	0.0077	7.6	0.0074
123	125	0.0250	7.6	0.0252

2-(2-Phenylallyloxy)ethyl Radical System

Solution	Temp, °C	$[IIa]_{obsd}$	k_3/k_2	$[IIa]_{calcd}$
401	40	0.0021	10.4	0.0021
402	40	0.0070	10.4	0.0069
403	40	0.0242	10.4	0.0244
901	90	0.0016	7.6	0.0016
902	90	0.0055	7.6	0.0054
903	90	0.0195	7.6	0.0197
131	130	0.0012	5.9	0.0012
132	130	0.0050	5.9	0.0050
133	130	0.0155	5.9	0.0157

Table IV. Composite of Rate Constant Ratios

Radical	Temp, °C	k_1/k_2	k_3/k_1	k_3/k_2
2-Methallyloxyethyl	40	43	16.5	710
	90	30	9.9	297
	125	24	7.6	182
2-(2-Phenylallyloxy)ethyl	40	0.55	18.9	10.4
	90	0.52	14.6	7.6
	130	0.50	11.8	5.9

From Table III it can be seen that a single value of k_3/k_1 or k_3/k_2 gives a good fit of the data to eq 3 at each temperature. The particular value of k_3/k_1 or k_3/k_2 which best fits the results from a single reaction solution to eq 3 is no more than 3% away from the value which gives the best overall fit for the data at that temperature.

The values of k_1/k_2, k_3/k_1, and k_3/k_2 which were obtained for the two radical systems at each of the three reaction temperatures are collected in Table IV.

Applying the Arrhenius equation to these ratios of rate constants gives eq 9 and 10.

$$k_1/k_2 = (A_1/A_2) \exp\left(\frac{E_{A_2} - E_{A_1}}{RT}\right) \quad (9)$$

$$\ln (k_1/k_2) = \ln (A_1/A_2) + \frac{E_{A_2} - E_{A_1}}{RT} \quad (10)$$

Plots of $\ln (k_1/k_2)$ vs. $1/T$ gave straight lines with slopes of $(E_{A_2} - E_{A_1})/R$ and intercepts of $\ln (A_1/A_2)$. The values of the various activation energy differences and frequency factor ratios obtained from the slopes and intercepts are listed in Table V. The margins of error listed in the table were obtained

Table V. Activation Energy Differences and Frequency Factor Ratios

Property	2-Methallyloxyethyl radical	2-(2-Phenylallyloxy)ethyl radical
$E_{A_2} - E_{A_1}$ (kcal/mol)	1.7 ± 0.15	0.26 ± 0.05
$E_{A_1} - E_{A_3}$ (kcal/mol)	2.2 ± 0.15	1.3 ± 0.25
$E_{A_2} - E_{A_3}$ (kcal/mol)	3.9 ± 0.3	1.6 ± 0.25
A_2/A_1	0.35 ± 0.08	2.8 ± 0.2
A_3/A_1 (L/mol)	0.44 ± 0.07	2.3 ± 0.8
A_3/A_1 (L/mol)	1.3 ± 0.55	0.85 ± 0.25

graphically from the two most extreme lines which could be drawn through the limits of the three points. The ranges of the points were determined from the ranges of the rate constant ratios which gave the best fit of the data to eq 6, considering the product concentrations in the reaction mixtures were within about 2% of the measured values.

The product distributions from the 2-methallyloxyethyl radical (Table X) show that up to 3% of 3-methyltetrahydropyran (Ic) was formed in addition to the two major products. In the case of the 2-(2-phenylallyloxy)ethyl radical, 3-phenyltetrahydropyran (IIc) was the predominant cyclic product, indicating that the increased stability of the benzylic radical intermediate is the major controlling factor in the product distribution.

The kinetic results show that Scheme I quite adequately describes the reactions of the two radicals studied in this research. Equation 6, which was derived from this scheme, gave a good fit to the data for both radical systems at all three temperatures. The formation of the cyclic products can be accounted for by irreversible cyclizations of the initially formed radicals—processes whose rates are independent of the Bu_3SnH concentrations. The irreversibility of the cyclizations was checked by generating the (3-phenyl-3-tetrahydrofuranyl)methyl radical from the corresponding bromide. 3-Phenyl-3-methyltetrahydrofuran was the only product formed.

From the kinetic results it was possible to get an estimate of the activation energies for the cyclization reactions relative to the activation energy for the abstraction of hydrogen from Bu_3SnH by a primary alkyl radical. Wilt, Massie, and Dabek[16] have calculated the activation energy for this hydrogen abstraction process to be between 6.8 and 8.2 kcal/mol using rate constants reported by Carlsson and Ingold.[18] The comparisons of the rate constants for the cyclization reactions to that for the hydrogen abstraction from Bu_3SnH by the initially formed primary alkyl radicals were presented in Table V. The rate constants for hydrogen abstraction by the 2-methyloxyethyl and the 2-(2-phenylallyloxy)ethyl radical should be very nearly the same. Thus it is possible to compare the activation energies for the cyclization reactions leading to the four cyclic products in the two radical systems. The order of activation energies for the four cyclizations is presented in Table VI in relation to E_A(H), the activation energy for the hydrogen abstraction by the initially formed primary radicals.

These values show that the activation energy for the cyclization of the 2-(2-phenylallyloxy)ethyl radical to form 3-phenyltetrahydropyran is about 2.3 kcal/mol less than the activation energy for the cyclization of the 2-methyllyloxyethyl radical to form 3-methyltetrahydropyran. This helps to explain why formation of the six-membered cyclic product competes so much more favorably in the phenyl system than in the methyl system.

The relationships between the three rate constants in both of the radical systems were established. Approximate values of the rate constants for the cyclization reactions of the two radicals were obtained from the rate constant relationships and the reported value[18] of the rate constant for abstraction

Table VI

Product	$E_A - E_A$ (H), (kcal/mol)
3-phenyl-3-methyltetrahydrofuran	1.3 ± 0.25
3-Phenyltetrahydropyran	1.6 ± 0.25
3,3-Dimethyltetrahydrofuran	2.2 ± 0.15
3-Methyltetrahydropyran	3.9 ± 0.3

Table VII

Product	k_c, s^{-1} at 40 °C
3-Phenyltetrahydropyran	9.6×10^4
3,3-Dimethyltetrahydrofuran	6.1×10^4
3-Phenyl-3-methyltetrahydrofuran	5.3×10^4
3-Methyltetrahydropyran	1.4×10^3

of hydrogen from tributyltin hydride by the 1-hexyl radical ($k = 1.0 \times 10^6$ M^{-1} s^{-1} at 25 °C). Comparing this value to the ratios reported in Table IV gives the values listed in Table VII for the rate constants of the four cyclization reactions at 40 °C.

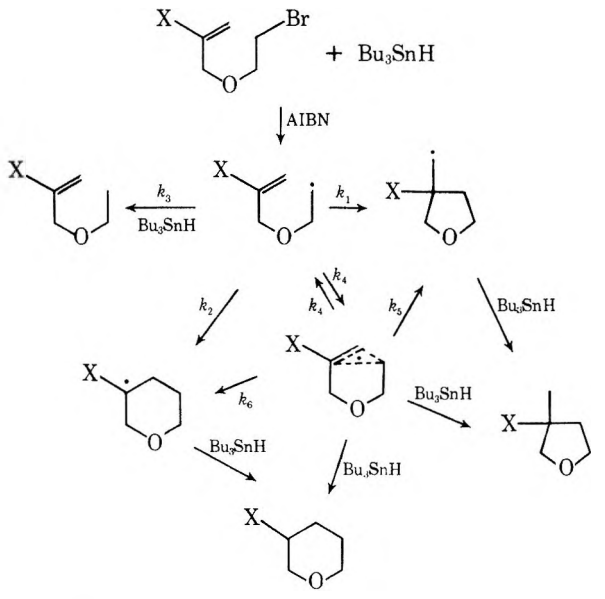
The total rate constant for cyclization in either of the two radical systems would be simply $k_1 + k_2$, the sum of the two rate constants for the cyclization reactions. The approximate values for the methyl and phenyl systems studied in this work are 6.2×10^4 and 1.5×10^5 s^{-1}, respectively. The fact that this total rate constant for cyclization is more than twice as great for the phenyl system as for the methyl system appears to arise from the differences in rate constants for cyclization to the tetrahydropyran derivatives. The rate constants for formation of the tetrahydrofuran derivatives are nearly the same. This big difference is likely due to the greater stability of the benzylic radical leading to 3-phenyltetrahydropyran compared to the tertiary radical leading to 3-methyltetrahydropyran

Carlsson and Ingold[18] determined the rate constants for cyclization at 40 °C for the 1-hexenyl radical studied by Walling et al.[15] and for the 4-(1-cyclohexenyl)butyl radical reported by Strubble, Beckwith, and Gream[19a] by comparing the reported rate constant ratios with the rate constant for hydrogen abstraction from Bu_3SnH by the 1-hexyl radical at 25 °C. The values of k_c obtained were 1×10^5 s^{-1} for the 5-hexenyl radical and 4×10^4 s^{-1} for the 4-(1-cyclohexenyl)butyl radical. In a recent elegant paper by Lal et al.,[20] the rate constant k_c for the 1-hexenyl radical was confirmed by an EPR spectroscopic technique. They compared these constants with the rate constant for addition of an ethyl radical to 1-heptene at 40 °C, 1×10^3 M^{-1}, and stated that the "effective double bond concentration" for the intramolecular cyclization of such radicals is about 40 to 100 M. Such a comparison with the cyclization rate constant for the 2-methyllyloxyethyl radical yields a value of 62 M. For the 2-(2-phenylallyloxy)-ethyl radical the value would be 150 M, but a more accurate basis for comparison would be with the rate constant for addition of a primary radical to an α-alkyl styrene, which should have a value greater than 1×10^3 M^{-1} s^{-1} at 40 °C.

This enhanced "effective double bond concentration" for reaction of the initial radical with the double bond to give a cyclic radical, coupled with the increased steric hindrance to approach of another monomer molecule when the initial radical is part of a growing polymer chain, should be sufficient to explain why so many 1,6-dienes undergo free-radical polymerization to yield polymers composed entirely of cyclic repeating units. Propagation by reaction of the initial radical with another molecule of monomer simply cannot compete with the cyclization processes in most cases.

The products obtained from the reactions of the two radi-

Scheme II



cals studied in this work were consistent with a reaction scheme whereby the cyclic products arise from irreversible radical cyclizations. The kinetic treatment further supports this explanation. Equation 6, when applied to the data of Strubble, Beckwith, and Gream[19a] for the products from reactions of the 4-(1-cyclohexenyl)butyl radical with tributyltin hydride at 40 °C, gave a good fit for $k_3/(k_1 + k_2) = 40$. Equation 6 also gave a good fit to the data reported by Beckwith and Gara[19b] for the reactions of the 2-(3-butenyl)phenyl radical with Bu_3SnH with $k_3/k_c = 2.0$. The data of Walling et al.[15] for the reactions of the 5-hexenyl radical with Bu_3SnH at 40 °C were satisfied by eq 6 with $k_3/k_c = 10$. Only Walling's data at 130 °C, which showed no distinct trend in product distribution, failed to satisfactorily fit eq 6.

From our results and the results of other studies on similar radical systems, it would appear that a reaction path involving a complex between the radical and the double bond is not necessary to explain the formation of the cyclic products. Scheme I involving a competition between the simple irreversible radical reactions leading to the cyclic and noncyclic products satisfactorily explains the observed product distributions. However, the possibility of the presence of a radical-π complex at some point in the reaction cannot be ruled out. Participation of such a complex is considered in Scheme II. It is possible that a complex is formed reversibly from the uncyclized radical and then collapses irreversibly to the cyclic radicals. The fact that 3-phenyl-3-methyltetrahydropyran was the only product obtained from the (3-phenyl-3-tetrahydrofuranyl)methyl radical shows that such a transformation from a complex to the cyclic radical, if it is involved, is irreversible. A direct route from complex to cyclic products is possible if the rate-determining step is formation of the complex rather than attack of the complex by the tributyltin hydride. The steric factors, if important enough in view of the electronic factors involved, would discount the last possibility since the products obtained were not those expected from attack on a complex by the hydride at the more accessible position. Beckwith et al.[21] have recently studied the effects of substituents at C-6 on the rate of 1,6-cyclization of radicals. However, these authors point out that their data do not permit the effects to be accurately assessed, but they do state that "it appears that steric factors are much more important than electronic factors in influencing the rate of intramolecular addition." Some of these problems might be answered by a study of a similar system with a bulky alkyl group on the double bond.

The fact that the cyclic radicals were found to form irreversibly discounts the possibility of the cyclized radicals being in equilibrium with a complex. If such a complex were low in energy relative to the cyclic radicals, one might expect the cyclic radicals to revert to the complex form and partition themselves between the two cyclic products and perhaps also the uncyclized product. The results of Kochi and Krusic[22] also cast some doubt as to the formation of a nonclassical radical species in radical cyclizations of this type. By ESR studies they were able to see the 5-hexenyl radical and the cyclopentylmethyl radical but no other in between. However, more recent ESR results on this radical by Edge and Kochi[23] have led to the postulate that the drastic line broadening due to the β-proton triplets may be associated with a coiled conformation in which the terminal unsaturated system lies over the radical center, thus supporting the nonclassical radical species or the complex.

The proportions of five-membered and six-membered cyclic products in the two radical systems studied appeared to be dependent upon the activation energies for the competing cyclization reactions and also upon steric factors concerning the ease of approach of the radical to the two ends of the double bond. These effects would also be important in determining the ring size of the repeating units of cyclopolymers. When the initial radicals are stable enough that the radical cyclization reactions are partially or totally reversible, as in the case of some of the radical systems studied by Julia,[7] the stabilities of the cyclized radicals become an additional factor in determining the proportions of five-membered and six-membered cyclic repeating units in cyclopolymers.

Experimental Section

Equipment and Data. All temperatures are reported uncorrected in °C. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian A-60A Analytical NMR spectrometer. Infrared (IR) spectra were obtained with a Beckman IR-8 infrared spectrophotometer. Refractive indices were obtained with a Bausch and Lomb Abbé 34 refractometer equipped with an anchromatic compensating prism. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga., and by PCR, Inc., Gainesville, Fla. Gas chromatographic (GC) analyses were done on a Hy-Fi Aerograph Model 600-D gas chromatograph. Preparative scale GC was done on an F & M Model 775 Prepmaster gas chromatograph. The reactions were run in sealed, degassed tubes in a constant-temperature bath controlled by a Sargent Thermonitor to within ±0.01 °C. Bu_3SnH was prepared according to the procedure of Kuivila and Buemel.[14]

Preparation of 2-Methylallyloxyethanol. The procedure of Hurd and Pollack[24] was followed and the reaction was carried out on a 0.5 mol scale: yields, 45.5 g (82%) of 2-methallyloxyethanol; bp 163 °C (760 mm) (lit.[25] bp 172 °C (760 mm)); n^{24}D 1.4386 (lit.[25] n^{25}D 1.4372). NMR and IR spectra confirmed the proposed structure.

Preparation of I. The above procedure[24] was followed and the reaction was carried out on a 0.25 mol scale: yield, 4.8 g (11%); bp 75–76 °C (25 mm); n^{25}D 1.4655. NMR and IR spectra confirmed the proposed structure.

Anal. Calcd for $C_6H_{11}BrO$: C, 40.24; H, 6.19; Br, 44.63. Found: C, 40.36; H, 6.08; Br, 44.99.

Preparation of 2-Methyllyloxyethyl *p*-Toluenesulfonate. The procedure of Ansell[26] was used: yield, 39.0 g (74%). This previously unreported compound was identified by its IR and NMR spectra.

Preparation of I from 2-Methyllyloxyethyl *p*-Toluenesulfonate. The procedure reported by Wilt, Massie, and Dabek[16] was employed on a 0.14 mol scale: yield, 17.1 g (68%); bp 70–71 °C (20 mm); n^{26}D 1.4651. The product was shown to be pure by GC. The structure was confirmed by refractive index, IR, and NMR.

Preparation of Ia via the Williamson Synthesis. Ia was prepared according to a literature procedure[27] on a 1.0 mol scale: yield, 55.0 g (55%); bp 86.5 °C (760 mm) (lit.[27] bp 84.8–86.8 °C (760 mm)); n^{25}D 1.3970 (lit.[27] n^{20D} 1.4067). GC, NMR, and IR confirmed purity and structure.

Preparation of Diethyl 2-Methylglutarate. A procedure in "Organic Syntheses"[28] for the esterification of dicarboxylic acids was used on a 0.33 mol scale: yield, 64.1 g (96%); bp 128 °C (20 mm) (lit.[29] bp 125 °C (20 mm)); n^{26}D 1.4230 (lit.[29] n^{20D} 1.4265). NMR and IR confirmed the structure.

Preparation of Diethyl 2,2-Dimethylsuccinate. The procedure in ref 28 was used on a 1.0 mol scale: yield, 54.0 g (81%); bp 107 °C (15 mm) (lit.[30] bp 101 °C (15 mm)); n^{25}D 1.4201 (lit.[30] n^{20}D 1.4233). NMR and IR confirmed the structure.

Preparation of 2-Methyl-1,5-pentanediol. A procedure in Vogel's "Textbook of Practical Organic Chemistry" [31] for reducing esters to alcohols was followed on a 0.25 mol scale: yield, 19.9 g (68%); bp 135–136 °C (6 mm) (lit.[29] bp 140 °C (20 mm)); n^{25}D 1.4524 (lit.[29] n^{20}D 1.4545). NMR (D_2O) and IR confirmed the structure.

Preparation of 2,2-Dimethyl-1,4-butanediol. The procedure for preparing 2-methyl-1,5-pentanediol[31] was used on a 0.25 mol scale by reduction of diethyl 2,2-dimethylsuccinate: yield, 12.3 g (42%); bp 163 °C (15 mm) (lit.[30] bp 117 °C (8 mm)); n^{25}D 1.4436 (lit.[30] n^{20}D 1.4513). NMR (D_2O) and IR confirmed the structure.

Preparation of Ic. Into a pressure bottle were charged 30 g of 60% sulfuric acid and 10.0 g (0.085 mol) of 2-methyl-1,5-pentanediol. The liquids were heated to 100 °C for 1 h, then cooled overnight. The bottle was opened and the contents were diluted with 30 mL of water and distilled. The product and water distilled as an azeotrope, and 7.5 g of crude product was obtained which was dried over 3A molecular sieves. After two distillations through a 60-cm spinning-band column with Teflon band the yield was 3.8 g (45%) of a clear, colorless, volatile liquid: bp 108 °C (760 mm) (lit.[29] bp 109 °C (733 mm)); n^{25}D 1.4194 (lit.[29] n^{20}D 1.4210). NMR, IR, and GC confirmed the identity and purity. An impurity present in the original mixture was identified by NMR to be 2,2-dimethyltetrahydrofuran, which could have resulted from a 1,2-hydride shift to form a tertiary carbonium ion prior to cyclization.

Preparation of Ib. The same general technique as for the synthesis of 3-methyltetrahydropyran was used. From 6.0 g (0.051 mol) of 2,2-dimethyl-1,4-butanediol was obtained 4.8 g (94%) of product: bp 99 °C (760 mm) (lit.[30] bp 98–99 °C (750 mm)); n^{25}D 1.4102 (lit.[30] n^{20}D 1.4121). GC, NMR, and IR confirmed the purity and identity of the structure.

Preparation of 2-(2-Phenylallyloxy)ethanol. The procedure of Hurd and Pollack[24] was employed on a 0.5 mol scale: yield, 59.3 g (67%); bp 109–111 °C (0.5 mm); n^{27}D 1.5456. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.96; H, 8.12. NMR and IR confirmed the identity of the structure.

Preparation of 2-(2-Phenylallyloxy)ethyl *p*-Toluenesulfonate. The procedure of Ansell[26] was used on a 0.1 mol scale with slight modifications. The reaction mixture was left at room temperature overnight before being worked up. The product was shown by thin-layer chromatography to consist of two major components. They were separated by column chromatography using silica gel and a solvent system of 85% petroleum ether (65–110 °C) and 15% ethyl ether. The two separated components were identified as the expected *p*-toluenesulfonate and 2-phenylallyl 2-chloroethyl ether. Formation of the chloride is not surprising. It has been stated by Fieser and Fieser[32] that in the presence of pyridinium chloride at room temperature primary tosylates are converted to chlorides. Thus the reaction mixture should not be allowed to exceed 20 °C. The chloride was distilled through a 16-cm Vigreux column: yield, 5.2 g (26.5%); bp 88 °C (0.25 mm); n^{25}D 1.5428. NMR and IR confirmed the identity of the structure. Anal. Calcd for $C_{11}H_{13}ClO$: C, 67.17; H, 6.66; Cl, 18.03. Found: C, 67.23; H, 6.69; Cl, 17.86.

The *p*-toluenesulfonate was obtained in a yield of 6.3 g (19%).

Another procedure[33] provided a good yield of the desired 2-(2-phenylallyloxy)ethyl *p*-toluenesulfonate from the alcohol. The reaction was carried out on a 0.10 mol scale: yield, 29.7 g (89%). NMR and IR confirmed the structure.

Preparation of II via 2-(2-Phenylallyloxy)ethyl *p*-Toluenesulfonate. The procedure of Wilt, Massie, and Dabek[16] was employed on a 0.09 mol scale: yield, 18.9 g (88%); bp 98 °C (0.2 mm); n^{25}D 1.5593. NMR and IR confirmed the assigned structure. Anal. Calcd for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43; Br, 33.14. Found: C, 54.85; H, 5.51; Br, 32.97.

Preparation of IIa via the Williamson Synthesis. The procedure by Baucom[34] was used. The reaction was carried out on a 0.20 mol scale: yield, 14.7 g (45%); bp 99.5 °C (10 mm) (lit.[35] bp 96 °C (10 mm)); n^{25}D 1.5215 (lit.[35] n^{25}D 1.5202). GC, NMR, and IR confirmed the identity and purity of the product.

Preparation of IIb and IIc via Cyclization of II. A solution of 6.03 g (0.025 mol) of 2-bromoethyl 2-phenylallyl ether, 7.55 g (0.026 mol) of Bu_3SnH, and 0.062 g (0.0004 mol) of AIBN in 500 mL of spectrograde benzene was sealed in an autoclave (1-L capacity). The contents were run through three freeze–thaw cycles using a vacuum system (0.02 mm) and a dry ice–isopropyl alcohol bath. Then they were placed in a preheated cavity and heated at 130 °C for 3 h. The contents were allowed to cool and most of the benzene was removed on a rotary evaporator. The remaining benzene was removed by distillation at atmospheric pressure. The residue was distilled at a pressure of 7.5 mm to separate the more volatile products from the tributyltin bromide. The two major products, 3-phenyltetrahydropyran and 3-methyl-3-phenyltetrahydrofuran, were isolated by means of preparative GC using an F & M Model 775 Prepmaster GC with an 8 ft × ¾ in. column of 20% SE-30.

Pure IIb was isolated in 17.5% yield (0.7 g): bp 101 °C (4 mm); n^{25}D 1.5271. NMR and IR confirmed its identity. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.57; H, 8.70.

Pure IIc was isolated in 35% yield (1.4 g): bp 104 °C (4 mm); n^{25}D 1.5295 (lit.[36] n^{25}D 1.5267). NMR and IR confirmed the identity of this structure.

Preparation of Triethyl 2-Phenyl-2-carboxysuccinate. The standard procedure for malonic ester syntheses was used on a 0.61 mol scale: yield, 116.5 g (59%); bp 164–165 °C (1.2 mm); n^{26}D 1.4904. NMR and IR confirmed the identity of this compound. Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.45; H, 6.96.

The by-product, ethyl ethoxyacetate, was obtained as a clear, colorless liquid: bp 34 °C (2.2 mm) (lit.[37] bp 55 °C (11 mm)); n^{25}D 1.4031 (lit.[37] n^{25}D 1.4019); yield, 27 g (33.5%). NMR and IR confirmed the identity of this by-product.

Preparation of 2-Phenyl-2-hydroxymethyl-1,4-butanediol. The procedure described[13] for LAH reductions of esters was employed using 0.276 mol of triethyl 2-phenyl-2-carboxysuccinate: yield, 47.1 g (88%). Distillation was not attempted since it is stated that the triol is not stable to distillation.[13] NMR and IR confirmed the identity of the triol.

Preparation of 3-Phenyl-3-hydroxymethyltetrahydrofuran. The procedure described[13] for the cyclization was used on 26.0 g (0.13 mol) of 2-phenyl-2-hydroxymethyl-1,4-butanediol and 67 g (0.58 mol) of 85% phosphoric acid. Distillation of the crude liquid yielded 12.1 g of a viscous liquid which was shown by IR, NMR, and GC to be a mixture containing about 75% of the desired product. The product was redistilled through a 40-cm heated column packed with saddles, yielding three fractions containing about 80%, 88%, and 92% product according to the gas chromatographs. The yields of these three fractions were 6.0, 3.5, and 0.6 g, respectively (37%). Further purification was not attempted since it was planned to make the tosylate, which could be purified and identified: bp 93–94 °C (0.05 mm) (lit.[13] bp 119–120 °C (0.6 mm)); n^{25}D 1.5496 (lit.[13] n^{25}D 1.5471).

Preparation of 3-(3-Phenyltetrahydrofuranyl)methyl *p*-Toluenesulfonate. The procedure for the preparation of 2-(2-phenylallyloxy)ethyl *p*-toluenesulfonate was followed,[33] using 6.65 g (0.033 mol) of 88% 3-phenyl-3-hydroxymethyltetrahydrofuran, 10.5 g (0.13 mol) of pyridine, and 8.4 g (0.044 mol) of *p*-toluenesulfonyl chloride: yield, 8.5 g (77%); mp 115 °C (lit.[13] mp 104 °C). NMR and IR confirmed the identity of the product. Anal. Calcd for $C_{18}H_{20}SO_4$: C, 65.04; H, 6.06; S, 9.65. Found: C, 64.88; H, 6.19, S, 9.50.

Preparation of 3-Phenyl-3-bromomethyltetrahydrofuran. The procedure[16] described earlier was employed, using 8.3 g (0.025 mol) of 3-(3-phenyltetrahydrofuranyl)methyl *p*-toluenesulfonate and 7.0 g (0.080 mol) of anhydrous lithium bromide in 150 mL of methyl isobutyl ketone: yield, 5.2 g (87%); bp 92–93 °C (0.07 mm); n^{25}D 1.5676. NMR and IR confirmed the identity of the product. Anal. Calcd for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43; Br, 33.14. Found: C, 54.85; H, 5.43; Br, 33.24.

Preparation and Analysis of Reaction Solutions. Reactions of I and Bu_3SnH. The solutions for study of the reactions of 2-bromoethyl methallyl ether with Bu_3SnH were prepared in the following manner: AIBN, which had been recrystallized from methanol, was weighed out first and set aside. Bu_3SnH, freshly prepared and stored in an airtight container under N_2, was weighed in a volumetric flask and diluted with spectrograde benzene. Then the 2-bromomethyl methallyl ether, which was free of impurities according to GC, was weighed in the volumetric flask and the flask was filled to the mark with spectrograde benzene. The AIBN was added and the solution was shaken and transferred to reaction tubes. The tubes were degassed by three freeze–thaw cycles, sealed, and heated at the desired reaction temperature until the reactions had reached completion.

The product distributions resulting from the various reactions were analyzed by GC on a Hy-Fi Aerograph, using a 9-ft β,β'-oxydipropionitrile column at 50–55 °C with the injection temperature at 185 °C. Calibration curves for concentration vs. peak area were prepared for the reaction products using standard solutions of mixtures of the authentic products in benzene. The accuracy of these determinations was checked often by preparing solutions containing the concentrations of the three products in the reaction mixture according to the calibration curve. In this manner slight errors could be corrected and the calibration could be checked often.

Table VIII. Reaction Solutions for Generation and Reactions of 2-Methallyloxyethyl Radical

Solution	Temp, °C	[Bu_3SnH]	[I]	[AIBN]
41	40	0.0262	0.0764	0.0004
42	40	0.0497	0.1495	0.0008
43	40	0.0998	0.3014	0.0015
91	90	0.0262	0.0764	0.0004
92	90	0.0497	0.1495	0.0008
93	90	0.0998	0.3014	0.0015
121	125	0.0248	0.0743	0.0004
122	125	0.0502	0.1484	0.0008
123	125	0.1007	0.3046	0.0017

Table IX. Product Concentrations from Reactions of the 2-Methallyloxyethyl Radical[a]

Solution	Temp, °C	[Ia]	[Ib]	[Ic]
41	40	0.0042	0.0197	0.00045
42	40	0.0134	0.0320	0.00075
43	40	0.0400	0.0470	0.0011
91	90	0.0028	0.0210	0.00070
92	90	0.0088	0.0350	0.0012
93	90	0.0300	0.0550	0.0018
121	125	0.0020	0.0197	0.00080
122	125	0.0077	0.0360	0.0015
123	125	0.0250	0.0590	0.0024

[a] The experimental errors for determining the product concentrations by quantitative gas chromatographic analysis were within 2% of measured concentrations.

Table X. Product Percentages from Reactions of the 2-Methallyloxyethyl Radical

Solution	Temp, °C	% Ia	% Ib	% Ic
41	40	16.0 ± 0.3	75.2 ± 1.5	1.75 ± 0.04
42	40	27.0 ± 0.5	64.6 ± 1.3	1.51 ± 0.03
43	40	40.1 ± 0.8	47.1 ± 1.0	1.10 ± 0.02
91	90	10.7 ± 0.2	80.2 ± 1.6	2.67 ± 0.06
92	90	17.7 ± 0.4	70.4 ± 1.4	2.41 ± 0.05
93	90	30.1 ± 0.6	55.1 ± 1.1	1.80 ± 0.04
121	125	8.1 ± 0.2	79.4 ± 1.6	3.22 ± 0.07
122	125	15.3 ± 0.3	71.7 ± 1.4	2.99 ± 0.06
123	125	24.8 ± 0.5	58.6 ± 1.2	2.38 ± 0.05

All solutions prepared in this manner are shown in Table VIII. Duplicate reactions were run to check the accuracy, and in each case both reaction mixtures showed the same product concentrations. The product concentrations and yield percentages from the reaction solutions listed in Table VII are given in Tables IX and X. The ratios of Ib to Ic at the various temperatures are shown in Table I.

Reactions of II and Bu_3SnH. The procedure from the preceding section for preparing the reaction solutions listed in Table IV for the 2-methyllyloxyethyl radical was again employed to prepare the reaction solutions for the 2-(2-phenylallyloxy)ethyl radical, which are described in Table XI.

The product analyses were carried out as before on a Hy-Fi Aerograph, using standard solutions of the authentic products to calibrate a 5-ft 30% SE-30 Column at 190 °C with the injection port at 290 °C. The product concentrations and yield percentages determined for the reaction solutions listed in Table XI are given in Tables XII and XIII. The ratios of IIc to IIb at the various temperatures are shown in Table II.

Reaction of 3-Phenyl-3-bromomethyltetrahydrofuran with Bu_3SnH. Again the same procedures for preparaing and analyzing the samples employed in the preceding experiments were used. A solution was prepared 0.1 M in Bu_3SnH, 0.1 M in 3-phenyl-3-bromomethyltetrahydrofuran, and 0.0017 M in AIBN. The degassed reaction tube was heated at 90 °C for 4 h and then analyzed. The only product of the reaction was 3-phenyl-3-methyltetrahydrofuran. No ethyl 2-phenylallyl ether or 3-phenyltetrahydropyran was observed.

Table XI. Reaction Solutions for Generation and Reactions of the 2-(2-Phenylallyloxy)ethyl Radical

Solution	Temp, °C	[Bu_3SnH]	[II]	[AIBN]
401	40	0.0261	0.0757	0.0004
402	40	0.0500	0.1490	0.0008
403	40	0.1023	0.3022	0.0015
901	90	0.0261	0.0757	0.0004
902	90	0.0500	0.1490	0.0008
903	90	0.1023	0.3022	0.0015
131	130	0.0250	0.0759	0.0004
132	130	0.0538	0.1505	0.0008
133	130	0.1000	0.3016	0.0017

Table XII. Product Concentrations from Reactions of the 2-(2-Phenylallyloxy)ethyl Radical[a]

Solution	Temp, °C	[IIa]	[IIb]	[IIc]
401	40	0.0021	0.0065	0.0119
402	40	0.0070	0.0114	0.0208
403	40	0.0242	0.0204	0.0370
901	90	0.0016	0.0066	0.0127
902	90	0.0055	0.0119	0.0228
903	90	0.0195	0.0213	0.0409
131	130	0.0012	0.0065	0.0129
132	130	0.0050	0.0125	0.0251
133	130	0.0155	0.0217	0.0433

[a] The experimental errors for determining the product concentrations by gas chromatography were within 2% of the measured concentrations.

Table XIII. Product Percentages from Reactions of the 2-(2-Phenylallyloxy)ethyl Radical

Solution	Temp, °C	% IIa	% IIb	% IIc
401	40	8.0 ± 0.2	24.9 ± 0.5	45.6 ± 0.9
402	40	14.0 ± 0.3	22.8 ± 0.5	41.6 ± 0.8
403	40	23.7 ± 0.5	19.9 ± 0.4	36.2 ± 0.7
901	90	6.1 ± 0.15	25.3 ± 0.5	48.7 ± 1.0
902	90	11.0 ± 0.2	23.8 ± 0.5	45.7 ± 0.9
903	90	19.1 ± 0.4	20.8 ± 0.4	40.0 ± 0.8
131	130	4.8 ± 0.10	26.0 ± 0.5	51.6 ± 1.0
132	130	9.3 ± 0.2	23.2 ± 0.5	46.7 ± 0.9
133	130	15.5 ± 0.3	21.7 ± 0.5	43.3 ± 0.9

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Registry No.—I, 64010-97-5; Ia, 24309-28-2; Ib, 15833-75-7; Ic, 26093-63-0; II, 64010-98-6; IIa, 7534-41-0; IIb, 15833-78-0; IIc, 16765-32-5; 2-methylallyloxyethyl radical, 64011-05-8; 2-(2-phenylallyloxy)ethyl radical, 64010-99-7; 2-methallyloxyethanol, 5175-48-4; 2-methallyloxyethyl *p*-toluenesulfonate, 64011-00-3; diethyl 2-methylglutarate, 18545-83-0; diethyl 2,2-dimethylsuccinate, 39155-16-3; 2-methyl-1,5-pentanediol, 42856-62-2; 2,2-dimethyl-1,4-butanediol, 32812-23-0; 2-(2-phenylallyloxy)ethanol, 64011,01-4; 2-(2-phenylallyloxy)ethyl *p*-toluenesulfonate, 64011-02-5; 2-phenylallyl 2-chloroethyl ether, 3916-99-2; triethyl 2-phenyl-2-carboxysuccinate, 64011-03-6; ethyl ethoxyacetate, 817-95-8; 2-phenyl-2-hydroxymethyl-1,4-butanediol, 64011-04-7; 3-phenyl-3-hydroxymethyltetrahydrofuran, 15833-68-8; 3-(3-phenyltetrahydrofuranyl)methyl *p*-toluenesulfonate, 15833-70-2; 3-phenyl-3-bromomethyltetrahydrofuran, 15833-79-1; 3-phenyl-3-tetrahydrofuranyl methyl radical, 64011-06-9; *p*-toluenesulfonyl chloride, 98-59-9.

References and Notes

(1) Taken from the Ph.D. Dissertation of T. W. Smith, University of Florida, 1972; presented in part before the Romanian–U.S. Seminar on Polymer Chemistry, Jassy, Romania, Sept 1976.
(2) (a) G. B. Butler and R. L. Bunch, *J. Am. Chem. Soc.*, **71**, 3120 (1949); (b) G. B. Butler and F. L. Ingley, **73**, 895 (1951).
(3) (a) G. B. Butler, A. H. Gropp, R. J. Angelo, W. J. Huck, and E. P. Jorolan, Fifth Quarterly Report, U.S. Atomic Energy Commission Contract AT-(40-1)-1353, Sept 15, 1953; (b) G. B. Butler, Gordon Research Conference on Ion Exchange, June 15, 1955 [Science, **121**, 574 (1955)]; (c) G. B. Butler and R. J. Angelo, *J. Am. Chem. Soc.*, **79**, 3128 (1957); (d) G. B. Butler, A. Crawshaw, and W. L. Miller, *ibid.*, **80**, 3615 (1958).
(4) R. W. Lenz, "Organic Chemistry of Synthetic High Polymers", Interscience, New York, N.Y., 1967, p 342 ff.
(5) T. Miyake, *Kogyo Kagaku Zasshi*, **64**, 1272 (1961).
(6) G. B. Butler in "Proceedings of the International Symposium on Macromolecules, Rio de Janerio July 26–31, 1974", Elsevier, Amsterdam, 1975, pp 57–76.
(7) M. Julia, *Acc. Chem. Res.*, **4**, 386 (1971).
(8) (a) G. B. Butler, *J. Polym. Sci.*, **48**, 279 (1960); (b) G. B. Butler and M. A. Raymond, *ibid.*, **A3**, 3413 (1965).
(9) R. C. Lamb, P. W. Ayers, and M. K. Toney, *J. Am. Chem. Soc.*, **85**, 3483 (1963).
(10) C. Walling and M. S. Person, *J. Am. Chem. Soc.*, **86**, 2262 (1964).
(11) W. E. Gibbs and J. M. Barton, "Vinyl Polymers", Vol. I, Part I, G. E. Ham, Ed., Marcel Dekker, New York, N.Y., 1967.
(12) J. C. Bunzli, A. J. Burak, and D. C. Frost, *Tetrahedron*, **29**, 3735 (1973).
(13) J. C. Colonge and Y. Infarnet, *C. R. Acad. Sci. Paris (C)*, **264**, 894 (1967).
(14) H. G. Kuivila and O. F. Beumel, Jr., *J. Am. Chem. Soc.*, **83**, 1246 (1961).
(15) C. Walling, J. H. Cooley, A. A. Pouaras, and E. F. Racak, *J. Am. Chem. Soc.*, **88**, 5361 (1966).
(16) J. W. Wilt, S. N. Massie, and R. B. Dabek, *J. Org. Chem.*, **35**, 2803 (1970).
(17) C. Walling and A. Cioffari, *J. Am. Chem. Soc.*, **94**, 6059 (1972).
(18) D. J. Carlsson and K. U. Ingold, *J. Am. Chem. Soc.*, **90**, 7047 (1968).
(19) (a) O. L. Strubble, A. L. J. Beckwith, and D. E. Gream, *Tetrahedron Lett.*, 3701 (1968); (b) A. L. J. Beckwith and W. B. Gara, *J. Am. Chem. Soc.*, **91**, 5691 (1969).
(20) D. Lal, D. Griller, S. Husband, and K. U. Ingold, *J. Am. Chem. Soc.*, **96**, 6355 (1974).
(21) A. L. J. Beckwith, I. A. Blair, and G. Phillipou, *Tetrahedron Lett.*, **No. 26**, 2251 (1974).
(22) J. K. Kochi and P. J. Krusic, *J. Am. Chem. Soc.*, **91**, 3940 (1969).
(23) D. J. Edge and J. K. Kochi, *J. Am. Chem. Soc.*, **94**, 7695 (1972).
(24) C. D. Hurd and M. A. Pollack, *J. Am. Chem. Soc.*, **60**, 1905 (1938).
(25) R. I. Meltzer, A. D. Lewis, and A. Fischman, *J. Org. Chem.*, **24**, 1763 (1959).
(26) M. F. Ansell, *J. Chem. Soc.*, 539 (1961).
(27) M. Tamele, C. J. Ott, K. E. Marple, and G. Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941).
(28) "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 264.
(29) E. Hanschke, *Chem. Ber.*, **88**, 1048 (1955).
(30) Y. K. Yur'ev, G. Y. Kondrat'eva, and N. K. Sndovaya, *J. Gen. Chem. USSR*, **23**, 883 (1953); *Chem. Abstr.*, **48**, 3955*i* (1954).
(31) A. I. Vogel, "Textbook of Practical Organic Chemistry", 3rd ed, Longmons, London, 1959, p 879.
(32) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", 1968, p 965.
(33) "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 366.
(34) K. B. Baucom, Ph.D. Dissertation, University of Florida, June 1971.
(35) W. C. Keith, U.S. Patent 3 230 205; *Chem. Abstr.*, **64**, 8497*c* (1966).
(36) G. Descotes and A. Laily, *Bull. Soc. Chim. Fr.*, 2989 (1967).
(37) A. Schoenberg and K. Praefcke, *Chem. Ber.*, **99**, 196 (1966).

Nature of the Ortho Effect. Reactivity Correlations of the Acidic and Alkaline Hydrolyses of Ortho-Substituted *N*-Methylbenzohydroxamic Acids[1]

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Rates of acidic and alkaline hydrolyses of a series of ortho-substituted *N*-methylbenzohydroxamic acids have been determined at moderate acidity and very high basicity. The data are correlated by Taft's ortho polar and steric substituent constants. The results provide support for this method of correlation of quantitative data as well as support for the qualitative picture of ortho-substituent effects as described by McCoy and Riecke.

Introduction

The nature and quantitative treatment of the "ortho effect" has long interested chemists and is still unresolved.[2-4] The ratio of rate constants or equilibrium constants for similarly substituted *o*- and *p*-benzene systems[2] has been taken as a measure of ortho effects. Taft's separation of polar and steric ortho substituent effects is the best known treatment of ortho effects and has had some success in the correlation of data.[2,4] Equation 1 (Pavelich–Taft) quantitatively relates the log of the rate or equilibrium constants, k (k_0 is the constant for reaction of the compound with the reference substituent, methyl), to the polar (σ_0^*) and steric (E_s) substituent parameters for ortho-substituted benzene systems. ρ^* and δ are the respective reaction system susceptibility constants.

$$\log k = \rho^*\sigma_0^* + \delta E_s + \log k_0 \quad (1)$$

Charton has analyzed a large amount of data by linear regression and come to rather unconventional conclusions regarding the ortho effect,[2,5,6] e.g., that steric effects of ortho groups are minor. Charton represents Taft's steric effect substituent constant as

$$E_s = \alpha\sigma_I + \beta\sigma_R + \psi r_v + h \quad (2)$$

in which σ_I and σ_R are inductive and resonance substituent constants, respectively; r_v is related to the size of the substituent and is evaluated from van der Waals radii; h is an intercept term; α, β, and ψ are susceptibility constants. Charton considers the ψr_v term to be insignificant for ortho E_s values. The development and use of eq 2 and related equations has been criticized.[2,7]

McCoy and Riecke[8] have presented a qualitative picture of the ortho effect which reconciles the more conventional interpretations of proximity effects with those of Charton; in particular they have given a further interpretation to the h term of eq 2 and related equations. These authors consider and qualitatively analyze in some detail the effects of increasing the size of the ortho substituents. In the absence of specific interactions such as hydrogen bonding, the steric effect[8] will be composed of at least three effects: hindrance to solvation and to attack by a reagent, and steric hindrance to resonance. The first two effects will be rate reducing in typical ester reactions, e.g., those used by Taft to define σ^* and E_s, while the last will be a rate enhancing factor—the conjugation of the carbonyl group with the aromatic ring will be reduced in the reactant state compared to a nonhindered substrate, and in either case, the conjugation should be stronger in the

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Table I. Observed and Calculated Results for Acidic Hydrolysis of Ortho-Substituted *N*-Methylbenzohydroxamic Acids at 90 °C in 0.764 M Hydrochloric Acid

Substituent	Registry no.	σ^* [a]	E_s [a]	$-\log k_{obsd}$ [b]	$-\log k_{calcd}$ [c]
CH_3	24962-87-6	0	0	4.359	4.403
OCH_3	63977-15-1	−0.22	0.99	3.964	3.977
Cl	59686-63-4	0.37	0.18	4.585	4.608
Br	63977-16-2	0.38	0	4.713	4.665
I	63977-17-3	0.38	−0.20	4.793	4.720
NO_2	63977-18-4	0.97	−0.75	5.237	5.279

[a] Ortho substituent parameters, ref 4. [b] Average first-order rate constant, s^{-1}. [c] From eq 1, $\rho^* = -0.688$, $\delta = 0.278$.

Table II. Observed and Calculated Results for Alkaline Hydrolysis of Ortho-Substitued *N*-Methylbenzohydroxamic Acids at 90 °C in 7.31 M Sodium Hydroxide

Substituent	$-\log k_{obsd}$ [a]	$-\log k_{calcd}$ [b]
CH_3	6.130	6.178
OCH_3	5.498	5.466
Cl	5.585	5.695
Br	5.915	5.850
I	6.092	6.032
NO_2	5.166[c]	

[a] Average first-order rate constant, s^{-1}. [b] From eq 1, $\rho^* = 0.863$, $\delta = 0.911$. [c] Not included in the correlation by eq 1, see text.

reactant state than in the tetrahedral-like transition state for ester hydrolysis. Depending upon the particular substrate system and reaction chosen, steric effects in an ortho-substituted system could thus be *relatively* large or small.

Results and Discussion

Our present results for the acidic and alkaline hydrolysis of ortho-substituted *N*-methylbenzohydroxamic acids combined with our earlier results for the similar reaction of ortho-substituted benzohydroxamic acids[9] support both McCoy and Riecke's interpretation of ortho effects and the usefulness of eq 1 as a first approximation to a quantitative description of the ortho effect. Data are listed in Tables I and II. The calculated data are from eq 1 with ρ^*, δ, and $\log k_0$ determined by least-squares multiple regression. The mechanisms of the hydrolysis reactions have been reported.[10]

Statistical measures[11] of the validity of the correlations in Tables I and II are the correlation coefficient, the *F* test, which allows for the number of degrees of freedom in the correlation, and the residuals or the differences between observed and calculated values. For the correlation by eq 1 for the acid-catalyzed hydrolysis, the correlation coefficient is 0.989 with the *F* test indicating the correlation to be significant within the 1% level (a highly significant correlation). Correlation with σ^* alone (eq 1 with $\delta = 0$) is poorer than with σ^* and E_s together, even though the *F* test is within the 1% level, since the average residual for correlation with σ^* alone is almost twice the average residual for the correlation with σ^* and E_s together. Correlation with E_s alone (eq 1 with $\rho^* = 0$) is also poorer (correlation coefficient 0.934; *F* test, 1% level), since not only is the average residual more than twice the average residual for correlation with σ^* and E_s together, but particularly because the calculated value for k_0 (the value for the reference compound) is significantly in error, by a factor of 1.89.

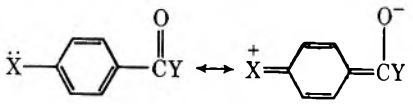
Correlation of the alkaline hydrolysis data by eq 1 is fairly good provided the datum for the nitro compound is omitted. The correlation coefficient is 0.928, the *F* test indicating significance not quite within the 5% level. Omission of the nitro compound is justified, since the reaction of the nitro compound appears to be abnormal because *o*-nitrobenzoic acid could not be isolated from the reaction mixture. In this connection it is worth noting that the ionic strength and base concentration were very high in the alkaline hydrolyses. Correlation of the data (nitro compound excluded) with σ^* or E_s parameters *alone* is very poor or nonexistent; the correlation coefficients are 0.448 and 0.743, respectively. Although the confidence level for the correlation of the alkaline hydrolysis rate data by eq 1 is a little lower than that for the correlation of the acid hydrolysis rate data, the correlation is evidently real. A graph of $\log k_{obsd} - \rho^*\sigma^*$ vs. E_s is acceptable, reproducing the trend of the data, and shows no curvature.

The results given above show the usefulness of eq 1 for the correlation of ortho effects in rather crowded systems. In addition it is worth noting that the correlation of the alkaline hydrolysis rate data involves a system with *very high* base concentration and ionic strength well above those usually employed in most studies. Furthermore, the observed rate constants in the alkaline hydrolysis are a sum of two contributing terms,[10] one for attack by water and the other for attack by hydroxide ion on the *N*-methylarylhydroxamate ion. The substituent effects on these two pathways must be similar or porportional, as is reasonable, in order for the observed correlation to occur.

Support for McCoy and Riecke's[8] qualitative picture of the ortho effect arises from the comparison of the correlation obtained with eq 1 for the present study (acid-catalyzed hydrolysis of ortho-substituted *N*-methylbenzohydroxamic acids) with the similar correlation for our earlier study[9] on the acid-catalyzed hydrolysis of the less hindered ortho-substituted benzohydroxamic acids. Both studies were carried out under comparable conditions and the results are well correlated by eq 1. A comparison of the ratios of the susceptibility constants, δ and ρ^*, indicates the *relative* importance of steric and polar substituent effects. Thus in the more hindered *N*-methyl series (space-filling models confirm the greater hindrance and conformational restrictions in this series) δ/ρ^* is 0.404 and in the less hindered series δ/ρ^* is 0.874. That is, steric effects appear to be *relatively less important in the more hindered system.* This result is quite consistent with McCoy and Riecke's qualitative description of the ortho effect (briefly summarized in the Introduction) in which the contributions of the *various components* of the steric ortho effect vary as a function of the reaction and the skeletal makeup of the substrate.

The above interpretations depend upon the concept that E_s represents steric or bulk effects of substituents which are reaction independent. This question has been discussed in some detail.[2,4] Two pieces of evidence indicate that E_s is a good measure of the steric effect for the substituents in Table I. First, E_s values for symmetrical ortho substituents parallel their van der Waals radii.[2] Secondly, the resonance contribution to E_s values for the substituents, except methoxy, in Table I can be shown to be negligible as follows: substituents which are electron releasing by resonance can exhibit a direct resonance interaction with the carbonyl group of the esters used to define E_s. A similar resonance interaction is included

in Hammett substituent constants, eq 3. An "insulated" para substituent constant[3,12] has been defined which eliminates



(3)

the resonance contribution shown in eq 3. Comparison of the Hammett para substituent constants[3] with these "insulated" constants[12] shows essentially no difference between the two scales for the substituents in Table I except for methoxy. Thus the resonance contribution to E_s values analogous to eq 3 is negligible except for methoxy. The resonance contribution to the E_s value for methoxy may, in reality, be smaller than anticipated by the above comparison. Taft[4] has shown for the saponification of ethyl *p*-dimethylaminobenzoate that only part of the resonance interaction of the *p*-dimethylamino group with the carbonyl group is lost in going from the ester to the saponification transition state. It is only this fraction of the resonance interaction lost which contributes to the E_s value.

The ρ^* values for the catalyzed hydrolysis of ortho-substituted benzamides,[4] benzohydroxamic acids,[9] and *N*-methylbenzohydroxamic acids are 0, −0.868, and −0.688, respectively, for similar but not identical reaction conditions. A negative ρ^* value for the hydrolysis of the benzohydroxamic acids compared to the zero value for benzamides is consistent with the greater electronegativity of *N*-hydroxyl compared to NH in changing from amides to hydroxamic acids,[9] provided that the polar effect upon the protonation step in the mechanism is greater than the polar effect on nucleophilic attack by water on the protonated intermediate. Substitution of a methyl group for the *N*-hydrogen on the hydroxamic acids should offset somewhat the effect of the substitution of hydroxyl for the *N*-hydrogen of the amide and thus reverse the *trend* in the ρ^* values.

Experimental Section

The 2-substituted *N*-methylbenzohydroxamic acids were synthesized by adaptations of the method used previously for the preparation of the 2-chloro and 2-methyl derivatives.[10] ^{1}H NMR and IR spectra are consistent with the structures listed. Satisfactory analyses (C, H, N; maximum difference between calculated and observed analysis (%): C, 0.21; H, 0.20; N, 0.16) were obtained for all new compounds and were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 2-Substituent and melting point: methoxy, 138.5–139.2 °C; bromo, 135.0–135.8 °C; iodo, 145.1–145.8 °C; nitro, 170.8–171.6 °C dec.

Kinetic measurements were accomplished using the methods and procedures described previously.[10]

References and Notes

(1) Abstracted from Ph.D. dissertation of I. E. Ward, Western Michigan University, 1977.
(2) J. Shorter in "Advances in Linear Free Energy Relationships", J. Shorter and N. B. Chapman, Ed., Plenum Press, New York, N.Y., 1972, Chapter 2.
(3) O. Exner in ref 2, Chapter 1.
(4) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, Chapter 13.
(5) M. Charton, *J. Org. Chem.*, **40**, 407 (1975), and references cited therein.
(6) M. Charton, *Prog. Phys. Org. Chem.*, **8**, 235 (1971).
(7) Reference 3, pp 39, 46.
(8) L. L. McCoy and E. E. Riecke, *J. Am. Chem. Soc.*, **95**, 7407 (1973).
(9) D. C. Berndt and I. E. Ward, *J. Org. Chem.*, **39**, 841 (1974).
(10) D. C. Berndt and I. E. Ward, *J. Org. Chem.*, **41**, 3297 (1976).
(11) D. A. Leabo, "Basic Statistics", 4th ed, Richard D. Irwin, Inc., Homewood, Ill., 1972, Chapter 16.
(12) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).

Kinetics of the Reactions of Hydrazine and Acethydrazide with Acetic Acid

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A kinetic study of the reactions of monoacetylhydrazine (MAH) and hydrazine (H) with acetic acid at 61 °C has been made using HPLC separation of salicylaldehyde derivatives. Both reactions involve pseudo-first-order reaction with acetic acid to produce an acetylated base and a rapid disproportionation of MAH to yield diacetylhydrazine (DAH) and hydrazine. The hydrazine acetylation is faster than the MAH acetylation. Mechanisms have been proposed for both series of reactions using approximations, and the predictions are in good agreement with experimental findings.

The reaction of hydrazine (H) with acetic acid was described by Harris and Stone.[2] This kind of reaction, a loss of basicity with time, was also reported by Medwick[3] in a study of various hydrazides. In related work, Posgay[4] found that the basicity of some amino compounds was lost owing to acetylation by acetic acid, and Kadin[5] reported that more than 10% of procainamide was acetylated in acetic acid in a few minutes at room temperature. Both authors attribute the acetylation to unavoidable small traces of acetic anhydride in glacial acetic acid. No careful kinetic study of the H or acethydrazide (MAH) reaction with acetic acid has been reported; Harris and Stone[2] used a spectrophotometric procedure that was inadequate due to the interference of MAH in the H assay.

In the present study, the reactions of H and MAH with acetic acid at 61 °C have been thoroughly investigated using specific analytical procedures. Salicylaldehyde derivatives of H and MAH [and of symmetrical diacetylhydrazine (DAH), after hydrolysis] are formed and can be separated using high-pressure liquid chromatography (HPLC). These compounds offer high molar absorptivities and make measurement of very small quantities possible. These analyses permit measurement of each hydrazine reaction participant and yield data that is used to propose a complex kinetic mechanism. Rate constants are calculated by approximation methods based on the experimental data. The findings of this study have been applied to some hydrazine derivatives that are useful analytically and medicinally.

Results and Discussion

The analytical procedure used in this study effectively separated the salicylaldehyde derivatives of MAH (retention time r_t 5.0 min) and H (r_t 16.3 min) and salicylaldehyde (r_t

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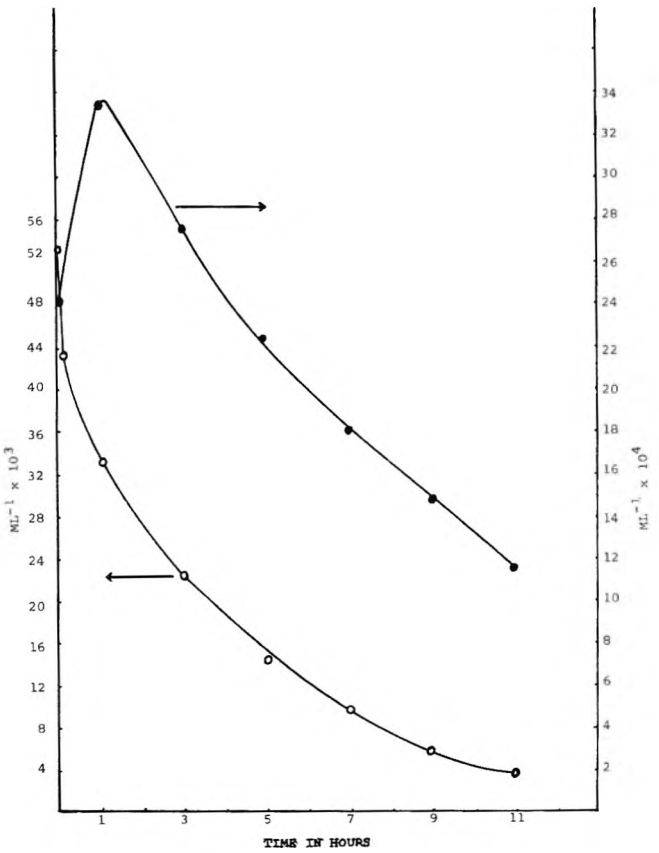

Figure 1. Kinetic behavior of MAH in acetic acid at 61 °C: (○) concentration of MAH at indicated time; (●) concentration of H at indicated time.

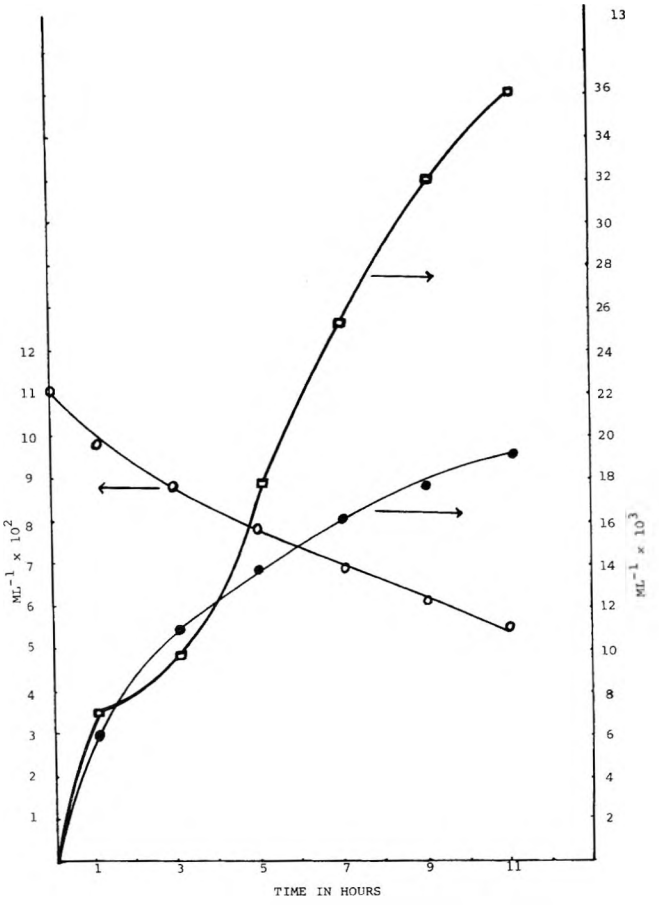

Figure 2. Kinetic behavior of H in acetic acid at 61 °C: (○) concentration of H at indicated time; (●) concentration of MAH at indicated time; (□) concentration of DAH at indicated time.

8.5 min) as may be noted from the different retention times.

The salicylaldehyde reactions with MAH (concentration range 0.20–0.80 mg/mL) and with H (concentration range 0.10–0.60 mg/mL) were complete and well behaved, since, in both cases, the chromatographic response was linear (correlation coefficients 0.99999 and intercepts essentially 0). The minimum detectable quantities of both MAH and H were 5×10^{-5} M.

The temperature chosen for this study, 61 °C, was a choice dictated by the nature of the MAH and H reactions with salicylaldehyde. In both cases, the reactions are practically instantaneous at 61 °C, thus introducing no temperature disturbances through analytical necessity. Due to the presence of both consecutive and parallel bimolecular reactions in the suggested mechanisms, difficulties were encountered in integrating the differential rate equations. Mathematical treatments reported by Chien[10] and later by Pearson et al.[11] for solving less-complicated mechanisms using transforms and the introduction of Bessel functions were investigated; however, the solution was complicated in this case due to the presence of the H loop (i.e., its regeneration from the MAH disproportionation). Although an exact solution for this complicated mechanism may still be possible, an approximation was used. Linear least-squares lines were obtained for the MAH and H concentration vs. time profiles seen in Figures 1 and 2. This permitted use of slopes for derivatives, i.e., $d[A]/dt \simeq \Delta[A]/\Delta t$ and $d[B]/dt \simeq \Delta[B]/\Delta t$. When concentrations of A and B were required, the values on the least-squares line at 5 h, approximately the midpoint representing a point where deviation of the least-squares point from experimental values would be at least, were chosen.

Reactions of MAH with Acetic Acid. The reaction profiles of H and MAH are presented in Figure 1. The concentration of MAH decreases regularly, whereas H is seen to decrease only after an initial increase. The mechanism that is proposed must account for the presence of H and explain its concentration profile.

The compounds present as well as their change with time suggested the following reactions:

$$\mathrm{MAH} + \mathrm{MAH} \xrightarrow{k_1} \mathrm{DAH} + \mathrm{H} \quad (1)$$

$$\mathrm{H} + \mathrm{HOAc} \xrightarrow{k_2} \mathrm{MAH} + \mathrm{H_2O} \quad (2)$$

$$\mathrm{MAH} + \mathrm{HOAc} \xrightarrow{k_3} \mathrm{DAH} + \mathrm{H_2O} \quad (3)$$

If A = H, B = MAH, and C = DAH and recognizing the invariant status of HOAc, then the reactions may be written explicitly in order to respect the implied stoichiometries.

$$2\mathrm{B} \xrightarrow{k_1} \mathrm{C'} + \mathrm{A} \quad (4)$$

$$\mathrm{A} \xrightarrow{k_2} \mathrm{B'} \quad (5)$$

$$\mathrm{B'} \xrightarrow{k_3} \mathrm{C''} \quad (6)$$

These equations are described by the following rate expressions.

$$\frac{d[B]}{dt} = -2k_1[B]^2 + k_2[A] - k_3[B] \quad (7)$$

$$\frac{d[A]}{dt} = k_1[B]^2 - k_2[A] \quad (8)$$

$$\frac{d[C]}{dt} = k_1[B]^2 + k_3[B] \quad (9)$$

A mass balance equation on total B-derived materials may be solved for 2B:

$$[2B] = M_B - ([C] + [A] + [B'] + [C'']) \quad (10)$$

where M_B is the total concentration of all B-related species. Equation 10 may be differentiated:

$$\frac{2d[B]}{dt} = -\left(\frac{d[C']}{dt} + \frac{d[A]}{dt} + \frac{d[B']}{dt} + \frac{d[C'']}{dt}\right)$$

$$qc = -(k_1[B]^2 + k_1[B]^2 - k_2[A] + k_2[A] + k_3[B] - k_3[B])$$

$$= -2k_1[B]^2 \quad (11)$$

Equation 11 leads to eq 12 and 13.

$$\frac{d[B]}{dt} \simeq \frac{\Delta[B]}{\Delta t} = -k_1[B]^2 \quad (12)$$

$$k_1 = \frac{-\Delta[B]/\Delta t}{[B]^2} \quad (13)$$

From eq 13, $k_1 = 1.96 \times 10^{-3}\ M^{-1}\ s^{-1}$. Equations 7 and 8 show $k_2 = 2.14 \times 10^{-5}\ s^{-1}$ and $k_3 = 4.60 \times 10^{-6}\ s^{-1}$.

The values calculated for k_1, k_2, and k_3 agree with the general statements made by Harris and Stone[2] in that the rate of disproportionation of MAH (eq 1) is significantly faster than the acetylations of both H and MAH.

An examination of some experimental plots made from concentrations of MAH and H shows them to be in keeping with the proposed mechanisms. The rate of disappearance of MAH is pseudo-first-order [correlation coefficient of 0.9997, k (from slope) = $5.68 \times 10^{-5}\ s^{-1}$, intercept of 4.10×10^{-2} M]. This intercept value is lower than the initial value, 5.4×10^{-2} M, seen in Figure 1. But it must be remembered that the rate of disappearance of MAH is a complex process (eq 7) and this deviation indicates the initial importance of the k_1 process. Equation 7 which described the disappearance of MAH can be seen to be a combination of three factors; however, since k_1 is large, B diminishes rapidly making the equation reduce to $k_2[A] - k_3[B]$, a combination of first-order processes producing an overall first-order change.

The disappearance of H is shown to be a first-order process; the log c vs. t plot has a correlation coefficient of 0.9996, a slope of $0.0455\ h^{-1}$, and an intercept of 3.8×10^{-3} M. This finding is in keeping with eq 8 which shows that $k_2[A]$ is the rate-controlling factor, since k_1 is large. In order to check the possibility that the appearance of H in the MAH acetous solution resulted from MAH hydrolysis (reverse of eq 2), another mechanism which involved a k_{-2} rate constant was tested. All the data obtained from such a mechanism did not correlate with any of the experimental data.

Reaction of Hydrazine with Acetic Acid. The concentration–time profiles for H and MAH are presented in Figure 2. The disappearance of H is characterized by a short induction period. Taking into account the nature of the products and their concentration–time profiles, the following mechanism is proposed using the symbols previously introduced.

$$A \xrightarrow{k_2} B \quad (14)$$

$$B \xrightarrow{k_3} C' \quad (15)$$

$$2B \xrightarrow{k_1} C'' + A' \quad (16)$$

(14) + (15) + (16) $\rightarrow k_2$

This scheme is complicated by the loop made necessary by the appearance of H in eq 16. As before, however, an approximate solution was accomplished using graphical values. Equations 14, 15, and 16 may be described by the differential equations seen as eq 17, 18, and 19.

$$\frac{d[A]}{dt} = -k_2[A] + 0.5k_1[B]^2 - 0.5k_2[A] \quad (17)$$

$$= -\tfrac{3}{2}k_2[A] + 0.5k_1[B]^2$$

$$\frac{d[B]}{dt} = k_2[A] - k_3[B] - k_1[B]^2 + 0.5k_2[A] \quad (18)$$

$$= \tfrac{3}{2}k_2[A] - k_2[B] - k_1[B]^2$$

$$\frac{d[C]}{dt} = k_3[B] + 0.5k_1[B]^2 \quad (19)$$

In order to specify compounds taking part in different portions of the rate process, a mass balance expression, using M_A to indicate the total concentration of H-related compounds, is written.

$$[A] = M_A - ([B] + [C'] + [C''] + [A'] + 0.5[B]) \quad (20)$$

Differentiating eq 20 and expressing the result as differentials yields the following.

$$\frac{d[A]}{dt} = -\tfrac{3}{2}\frac{d[B]}{dt} + \frac{d[C']}{dt} + \frac{d[C'']}{dt} + \frac{d[A']}{dt} \quad (21)$$

$$\frac{d[A]}{dt} + \tfrac{3}{2}\frac{d[B]}{dt} = -\frac{d[C']}{dt} - \frac{d[C'']}{dt} - \frac{d[A']}{dt} \quad (22)$$

Evaluating differentials from eq 15 and 16 and substituting in eq 22 results in eq 23.

$$\frac{d[A]}{dt} + \tfrac{3}{2}\frac{d[B]}{dt} = -k_3[B] - 0.5k_1[B]^2 - 0.5k_1[B]^2 + 0.5k_2[A]$$

$$= -k_3[B] - k_1[B]^2 + 0.5k_2[A] \quad (23)$$

Subtracting eq 13 from 23 results in eq 24 from which k_2 may be evaluated.

$$\frac{d[A]}{dt} + 0.5\frac{d[B]}{dt} = -k_2[A] = \frac{\Delta[A]}{\Delta t} + 0.5\frac{\Delta[B]}{\Delta t} \quad (24)$$

Using graphical values from Figure 2 for $d[A]/dt$ and $d[B]/dt$, $k_2 = 2.04 \times 10^{-5}\ s^{-1}$. This value used in eq 17 together with [A] and [B] shows that $k_1 = 2.11 \times 10^{-3}\ L\ mol^{-1}\ s^{-1}$. Similarly, eq 18 yields $k_3 = 1.26 \times 10^{-5}\ s^{-1}$.

Since it may be seen from eq 17, 18, and 19 that $\Delta[C]/\Delta t = \Delta[A]/\Delta t + \Delta[B]/\Delta t$, a corroboration of the validity of the calculated rate constants may be attempted. The experimental value for $\Delta[C]/\Delta t$, $3.19 \times 10^{-3}\ M\ h^{-1}$, compares very well with the calculated result $3.22 \times 10^{-3}\ M\ h^{-1}$. The agreement of k_1 and k_2 values from the MAH and H studies is good; only in the case of k_3 is a large variation experienced.

The experimental data shows that H disappearance is pseudo-first-order [correlation coefficient = 0.9985, k (from slope) = $1.70 \times 10^{-5}\ s^{-1}$ (predicted $2.04 \times 10^{-5}\ s^{-1}$), intercept = 10.6×10^{-2} M (predicted 10.0×10^{-2} M)]. These values are in good agreement and indicate that the proposed mechanism is valid, since eq 17 becomes a first-order process ($k_1 \gg k_2$).

Experimental Section

Materials and Solutions. All chemicals used were reagent grade unless otherwise specified. The following chemicals were used as obtained: hydrazine (97%, anhydrous) and hydrazine hydrate (64%), Matheson, Coleman and Bell; spectranalyzed grade methanol, ethanol, 2-propanol, chloroform, and acetonitrile (99 mol %), Fisher. Salicylaldehyde (from bisulfite compounds), Eastman White Label, was redistilled immediately before use. Glacial acetic acid was distilled three times before use and exhibited no impurities by HPLC when examined using the system used in the kinetic studies. The distilled acetic acid was stored in and delivered from an all-glass delivery system to offer protection from moisture. TLC silica plates (Eastman) were 100-μm thick silica layer coated on a plastic support, 12.5-in. square.

Mobile Phase for HPLC Analysis. The mobile phase consisted of acetonitrile (52 ± 2%, v/v) and 0.14 M aqueous potassium dihydrogen phosphate (48 ± 2%, v/v). The mobile phase was filtered and degassed under vacuum before use.

Standard MAH Solution and Standard H Solution. Separate solutions of MAH and H in 2-propanol were prepared (2 mg/mL each). For each solution the following dilutions were made: to three low-actinic glass 10-mL volumetric flasks, 4-, 2-, and 1-mL volumes were pipetted, followed by 0.4, 0.2, and 0.1 mL of acetic acid, respectively. These diluted standard MAH and H solutions were then processed together with the respective sample solutions and treated exactly in the same manner.

Salicylaldehyde Reagent Solution. Fifty milliliters of salicylaldehyde was diluted to 100 mL with 2-propanol.

Instrumentation. The 61 °C temperature used in the kinetic study was maintained by means of a Lauda/Brinkmann circulator Model K-2/RD.

The modular liquid chromatograph used consisted of a Laboratory Data Control (LDC) Model 2396 minipump, an LDC Model 709 pulse dampener, and an LDC Model 1285 UV monitor operated at 254 nm. A sample injection valve (Chromatronix HPSV-20) with a fixed volume of 20 μL (nominal) was used for sample introduction onto the chromatograph. The detector response was displayed on a 10-mV recorder. The analytical HPLC column used was a 30-cm long by 4-mm i.d. stainless-steel tube packed with spherical siliceous microbeads 5–10 μm to which is chemically bonded a monomolecular layer of octadecyltrichlorosilane (μ Bondapak C_{18}, Waters Assoc.). A flow rate of 1.2–1.4 mL/min (at 1000 psig) was maintained at room temperature.

Synthesis of MAH. To 19.5 g of hydrazine hydrate, 27.5 g of ethyl acetate was added, gradually and with continuous stirring, followed by 20 mL of absolute alcohol. The mixture was refluxed for 48 h and dried in vacuo until a paste was obtained. The paste was shaken twice with ether and the supernatant liquid was decanted and discarded. The residue was heated on a water bath at 60 °C until all the ether evaporated, and then cooled immediately in a freezing mixture of ice and salt where a deliquescent solid was obtained. The product was pressed between two filter papers and dried for 48 h in a vacuum desiccator. The melting point of the dried MAH crystals (yield 79.5%) was 63.9 °C [lit.[6,7] 62–64 °C].

The purity of the MAH crystals was checked by both TLC and HPLC. The TLC system consisted of a mobile phase composed of 7.5% 2-propanol in chloform and a silica thin-layer plate. The MAH crystals were dissolved in alcohol, spotted on the plate, and developed for about 2 h after which the plate was sprayed with Ehrlich's reagent and viewed under short-wavelength (254 nm) UV light. Only a single purple spot, R_f 0.40, was noticed when compared with other plates on which H and MAH had been run and treated similarly (H appeared as a yellow spot R_f 0.05). The MAH showed no trace of H when analyzed by the HPLC system used in the kinetic study. To detect the presence of any traces of DAH in the MAH, a second plate was spotted and developed in the TLC system described above for 2 h after which the plate was sprayed with aqueous alcoholic hydrochloric acid and heated at 80 °C for 10 min, and then the plate was sprayed again with the Ehrlich's reagent and viewed under short wavelength UV light. Again only a single yellow spot (DAH hydrolyzed to H, R_f 0.58) was noticed when compared with other plates on which MAH and DAH had been treated similarly.

Synthesis of DAH. To 100 mL of pyridine contained in a 250-mL flask, 8.3 g of anhydrous hydrazine was added slowly and with continuous shaking. The mixture was transferred gradually and with continuous mixing to another 250-mL flask containing 52.5 g of acetic anhydride; the DAH started to precipitate immediately. The suspension was left overnight at room temperature, filtered, and recrystallized twice, first from acetone and then alcohol (yield 75%). The melting point, 137.5 °C, agreed with the literature.[8,9]

The purity of the DAH so obtained was checked using the TLC system described for MAH. Only a single yellow spot was observed, R_f 0.58, and no trace of H or MAH was seen.

Kinetic Study. All kinetic runs were conducted in duplicate. **(a) MAH.** A quantity, 0.989 g, of MAH was transferred to a 250-mL low-actinic volumetric flask containing about 100 mL of acetic acid. After mixing, the solution was brought to volume with acetic acid (MAH concentration, 5.346×10^{-2} M). For a few minutes, nitrogen was bubbled through the solution and the top of the flask was flushed with nitrogen. The flask was stoppered, sealed with aluminum foil, and placed in a water bath at 61.00 ± 0.01 °C. At specified times, 2-mL aliquots were withdrawn and transferred to a 10-mL low-actinic volumetric flask which was immediately stoppered, sealed, and stored in a freezer where the acetous solution froze. After all the samples were collected, they were removed from the freezer and 0.04 mL of the salicylaldehyde reagent calculated to be approximately 50% in stoichiometric excess was added to each flask. All the flasks were transferred to a 55 °C water bath for 5 min to ensure complete derivatization. The flasks were removed from the water bath and 5 mL of chloroform was added to each. Finally, all the solutions were brought to volume with methanol and were subjected to chromatographic analysis.

(b) H. A quantity, 0.822 g, of anhydrous H was weighed and transferred using a syringe to a 250-mL low-actinic volumetric flask (H concentration, 1.09×10^{-1} M). The solution was treated as described for the MAH kinetic study except for the fact that 0.18 mL of the salicylaldehyde reagent was added to each flask.

Calculation of the quantity in grams of MAH or H in each sample solution was done using the formula

$$(H_u/H_s)W_sP$$

where H_u is the height of a specific component in the sample solution, H_s is the height of the corresponding peak in the standard chromatogram, W_s, is the weight in grams of that standard component initially taken, and P is the purity expressed as a decimal of the standard MAH or H.

(c) MAH and H. For DAH analysis, a separate 2-mL volume of the kinetics sample solution was pipetted into a 10-mL low-actinic volumetric flask to which was added 2 mL of aqueous alcoholic HCl acid solution. The flask was immersed in a 60 °C water bath for 5 min and then 0.16 mL of the salicylaldehyde reagent was added. The sample thereafter was treated in the same manner as the MAH and H samples. Calculations of the quantity of DAH in solution was obtained by the difference between the total amount of H after hydrolysis and the amount of H obtained from the nonhydrolyzed sample.

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Registry No.—Hydrazine, 302-01-2; ethyl acetate, 141-78-6; MAH, 1068-57-1; DAH, 3148-73-0; acetic anhydride, 108-24-7; acetic acid, 64-19-7.

References and Notes

(1) Taken, in part, from a thesis submitted by Hamed M. Abdou to the Graduate School, Rutgers University, May 1977, for the Ph.D. degree. Present address: E. R. Squibb & Sons, Inc., New Brunswick, N. J. 08903.
(2) W. C. Harris and K. G. Stone, *J. Org. Chem.*, **23**, 2032 (1958).
(3) T. Medwick, *Diss. Abstr.*, **19**, 1214 (1958).
(4) E. Posgay, *Acta Pharm. Hung.*, **39**, 88 (1969); *Chem. Abstr.*, **71**, 67213f (1969).
(5) H. Kadin, *J. Pharm. Sci.*, **63**, 919 (1970).
(6) T. H. Curtius and T. S. Hofmann, *J. Prakt. Chem.*, **2**, 53, 524 (1896).
(7) A. M. Kost and R. S. Sagitullin, Jr., *Zh. Obshch. Khim.*, **27**, 3338 (1957); *Chem. Abstr.*, **52**, 9071 (1958).
(8) L. B. Turnbull, A. S. Yard, and H. McKennis, Jr., *J. Med. Pharm. Chem.*, **5**, 1327–1334 (1962).
(9) H. McKennis, Jr., A. S. Yard, J. H. Weatherby, and J. A. Hagy, *J. Pharmacol. Exp. Ther.*, **126**, 109 (1959).
(10) J. Y. Chien, *J. Am. Chem. Soc.*, **70**, 2256 (1948).
(11) R. G. Pearson, L. C. King, and S. H. Langer, *J. Am. Chem. Soc.*, **73**, 4149 (1951).

Side-Chain Kinetic Acidities of 4-Alkyl-1-methylpyridinium Ions. Opposing Resonance and Charge Neutralization Effects on Reactivity

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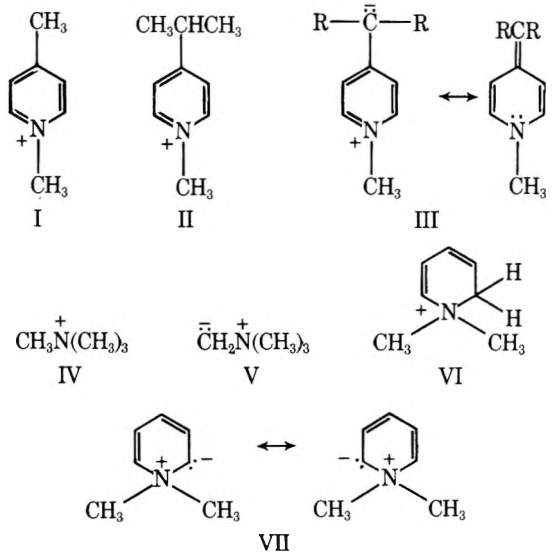
Hydrogen–deuterium exchange of the methyl and methine protons of 1,4-dimethylpyridinium and 4-isopropyl-1-methylpyridinium ions at 75 °C in D_2O is subject to general base catalysis with Brønsted coefficients of 0.74 and 0.72, respectively. Steric hindrance is encountered with 2,6-dimethylpyridine bases; lyate ion is about 10^2 less reactive than predicted by the Brønsted correlation. The isopropyl is 7.3 times less reactive than the methyl carbon acid when lyate ion is the catalyst. This difference in reactivity decreases as the basicity of the catalyst decreases, being a factor of 2.0 toward acetate ion, the weakest base examined. The transition state for deprotonation is believed to be pyramidal, having considerable delocalization of charge from the chain into the ring. Comparisons with nonaromatic ammonium ions reveal the effect of a reduction in resonance energy in a transition state on reactivity, and the extent to which this is offset by charge neutralization.

Nonaromatic ions having a quaternized nitrogen atom have played an important role in developing an understanding of the effects which influence the acidity of carbon acids.[1,2] By contrast, little quantitative information is available concerning the acidities of aromatic ions containing a similar quaternized site. We report the results of a study involving the kinetic acidities of pyridinium ions which undergo deprotonation at the carbon side chain bonded to position 4. Comparison of results for the nonaromatic ions with our new data provides a most revealing glimpse into the interplay of resonance and charge neutralization effects which dominate the reactivity of the heteroaromatic carbon acids.

We have determined the kinetic acidities of 1,4-dimethyl- (I) and 1-methyl-4-isopropylpyridinium ion (II) carbon acids



which give conjugate bases III (R = H and CH_3) on deprotonation. Particularly instructive is a comparison of the reactivities of I and II with those of tetramethylammonium ion (IV) which gives ylide V on proton removal[1] and with 1,1-dimethyl-1,2-dihydropyridinium ion (VI).[2] The reactivity of a methyl group of IV is essentially determined by the inductive and electrostatic effects of the adjacent positively charged site; a charge localized ylidic intermediate forms when a proton is eliminated. Nonaromatic ion VI gives anionically delocalized ylide VII on proton loss; charge delocalization constitutes an additional factor enhancing the reactivity of VI.

Deprotonation of I and II is expected to be influenced by similar inductive, electrostatic, and charge delocalization effects. However, two different and important effects operate when III is produced: (a) charge neutralization occurs, providing additional stabilization not available to bases V and VII, and (b) a reduction in resonance delocalization energy impedes proton removal. The comparisons provide considerable insight into the acidities of other positively charged heteroaromatic carbon acids as well as of I and II.

Results

Rate constants for deprotonation of the 4-methyl protons of I and the methine proton of II in D_2O at 1.0 M ionic strength were obtained using an NMR method of analysis. Deprotonation is catalyzed by OD^- and by buffer bases; i.e., deprotonation is subject to general base catalysis. The deuteration of I in $NaOD-D_2O$[3] and in CH_3OD[4] has been reported.

Isotope exchange was observed when a saturated solution of $Ca(OD)_2$ was employed as the catalyzing base. Pseudo-first-order rate constants, k_ψ, were obtained at several temperatures (Table I). In the case of I, hydrogen isotope exchange proceeded too rapidly at 75 °C, and with II it proceeded too slowly at 25 °C for convenient study; convenient rates were found for both compounds at 50 °C.

Several buffers were employed as catalysts at 75 °C. Under these conditions deprotonation is brought about by the action of both the buffer base and deuteroxide ion; i.e., k_ψ is given by eq 1 where B is the buffer base, k_{OD} and k_B are second-

$$k_\psi = k_{OD}[OD^-] + k_B[B]_{tot}\frac{K_a}{[D^+] + K_a} \quad (1)$$

order rate constants associated with catalysts OD^- and B, respectively, and K_a is the dissociation constant of buffer acid. The contribution of lyate ion to the total observed rate constant is sufficiently large using phenol and 4-amino-2,6-dimethylpyridine buffers in the case of I so that an accurate value can be obtained for k_{OD}. The values 0.438 and 0.475 M^{-1} s^{-1} derived with these two buffers, respectively, are in good agreement. Only the former buffer was examined with II, giving a k_{OD} value of 5.86×10^{-2} M^{-1} s^{-1} which is in reasonable agreement with the value 6.55×10^{-2} obtained using calcium deuteroxide.

These k_{OD} rate constants obtained at several temperatures give rise to the enthalpies of activation, $\Delta H^\ddagger$, for I and II, 15.6 and 17.8 kcal/mol, respectively, and entropies, $\Delta S^\ddagger$, of −15.5 and −13.2 cal/deg-mol, respectively. The rate constant calculated for II at 25 °C with these values is 6.93×10^{-4} M^{-1} s^{-1}.

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Table I. Conditions and Results for the Hydrogen–Deuterium Exchange of 1,4-Dimethylpyridinium Iodide (I) and 1-Methyl-4-isopropylpyridinium Iodide (II) in D_2O at 1.0 M Ionic Strength and 75.0 °C

Substrate	Buffer	pK_a[a]	pD[a]	Total buffer, M	k_ψ, s^{-1}	k,[b] $M^{-1}\,s^{-1}$	k_B^{Me}/k_B^{Pr}
I	$Ca(OD)_2$		12.24[c]	Satd	9.93×10^{-4}[c]	7.30×10^{-2}[c]	7.34[e]
			12.98[d]	Satd	1.15×10^{-4}[d]	8.68×10^{-3}[d]	
II	$Ca(OD)_2$		11.60	Satd	7.80×10^{-4}	6.55×10^{-2}	
			12.27[c]	Satd	1.16×10^{-4}[c]	7.78×10^{-3}[c]	
I	Phenol	9.99	8.89	0.0204	2.36×10^{-5}	1.27×10^{-2}	3.26
			9.00	0.0202	3.83×10^{-5}	4.38×10^{-1} (OD^-)	
			9.02	0.102	1.37×10^{-4}		
			10.11	0.0147	3.60×10^{-4}		
			10.35	0.0437	6.36×10^{-4}		
II	Phenol	9.99	9.34	0.0545	3.83×10^{-5}	3.90×10^{-3}	
			9.43	0.102	9.50×10^{-5}	5.86×10^{-2} (OD^-)	
			9.89	0.109	1.88×10^{-4}		
			10.37	0.0147	8.37×10^{-5}		
			10.40	0.0436	1.64×10^{-4}		
			10.91	0.0600	4.68×10^{-4}		
			11.09	0.0600	4.30×10^{-4}		
I	4-Amino-2,6-dimethylpyridine	9.50	9.11	0.0511	3.10×10^{-5}	8.05×10^{-4}	
			9.43	0.102	7.42×10^{-5}	4.75×10^{-1} (OD^-)	
			9.63	0.102	1.07×10^{-4}		
			10.50	0.109	5.21×10^{-4}		
I and II	4-Aminopyridine	8.44	9.42	0.200	1.36×10^{-4} (I)	5.50×10^{-4} (I)	2.42
					4.88×10^{-5} (II)	2.27×10^{-4} (II)	
			9.46	0.220	1.36×10^{-4} (I)		
					4.80×10^{-5} (II)		
I and II	Imidazole	6.68	6.65	0.200	2.20×10^{-6} (I)	2.37×10^{-5} (I)	1.20
					1.72×10^{-6} (II)	1.97×10^{-5} (II)	
			7.73	0.228	6.12×10^{-6} (I)		
					4.70×10^{-6} (II)		
II	2,6-Dimethylpyridine	6.50	6.49	0.202	3.19×10^{-8}	2.58×10^{-7}	
I	Pyridine	5.37	6.45	0.206	9.63×10^{-7}	4.96×10^{-6}	
I and II	Acetic acid	5.25	6.27	0.220	7.06×10^{-7} (I)	3.39×10^{-6}	1.97
					3.51×10^{-7} (II)	1.72×10^{-6}	

[a] Measured at 75 °C. [b] For buffer base and/or OD^- as indicated. [c] 50.0 °C. [d] 25.0 °C. [e] For OD^- base.

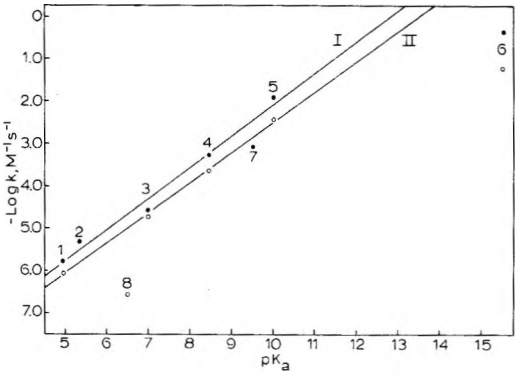


Figure 1. Brønsted plots for the deprotonation of I and II in D_2O at 75.0 °C and 1.0 M ionic strength. Bases include: (1) acetate ion, (2) pyridine, (3) imidazole, (4) 4-aminopyridine, (5) phenolate ion, (6) deuteroxide ion, (7) 4-amino-2,6-dimethylpyridine, and (8) 2,6-dimethylpyridine. Statistical corrections have been made.

In order to obtain a more extensive comparison of the reactivities of I and II and to construct a Brønsted plot the kinetic effects of several other buffers were examined. They include 4-aminopyridine, imidazole, 2,6-dimethylpyridine, pyridine, and acetic acid. Because the reactivities of both substrates are so similar it was convenient at times to examine both in the same mixture. Overlap of the signals for the methyl group of I and the methyl protons of 2,6-dimethylpyridine prevented an analysis of the reactivity of I with this base.

The results obtained at 75 °C summarized in Table I indicate that I and II have very similar reactivities under all the conditions examined. Thus, toward deuteroxide, ion I is only 7.3 times more reactive than II; this relative reactivity, given as k_B^{Me}/k_B^{Pr} in Table I, decreases for the other bases. Toward phenoxide ion, 4-aminopyridine, imidazole, and acetate ion it is 3.3, 2.4, 1.2, and 2.0, respectively. With the exception of the value for imidazole there appears to be a trend suggesting that relative kinetic carbon acidity decreases as the basicity of the catalyzing base decreases. These results may also be expressed in terms of a linear free energy relationship, eq 2

$$\log k_B^{Me} = 1.14 \log k_B^{Pr} - 0.92 \qquad (2)$$

(correlation coeefficient, $r = 0.997$), which shows that I undergoes slightly larger changes in reactivity than II as basicity is varied. Although these results are interesting because they run counter to the idea that selectivity decreases as reactivity increases, the variations are not large. By comparison, a similar but larger change in relative reactivity was reported for the rates of deprotonation of nitromethane and 2-nitropropane. Here relative reactivity decreased from a factor of 29 toward hydroxide ion to about a factor of 2–4 toward acetate and chloroacetate ions.[5,6]

The range in the second-order rate constant from the least (acetate ion) to the most basic (lyate ion) catalyst is a factor of 1.3×10^5 for I and 3.6×10^4 for II. The reactivity of each substrate toward the catalysts may be expressed in terms of a Brønsted plot. Such a plot is shown in Figure 1. Statistical corrections have been made for the number of acidic and basic sites in a buffer.[7] Acetate ion, pyridine, and phenoxide ion bases all appear to fall on a common line. However, points associated with 2,6-dimethyl- and 4-amino-2,6-dimethylpy-

ridine and also deuteroxide ion all lie below the line generated by the other bases. Eliminating these deviant points gives rise to Brønsted lines described by eq 3 and 4.

$$\log k_B^{Me} = 0.74pK_a - 9.49 \quad (r = 0.991) \quad (3)$$

$$\log k_B^{Pr} = 0.72pK_a - 9.71 \quad (r = 0.9994) \quad (4)$$

Deuteroxide ion is 230 times less reactive toward I than predicted by the linear relationship; for II the factor is 500. Such negative deviations for lyate ion are not uncommon; they are believed to reflect the absence of a hydrogen bond between this base and the carbon acid and the energetic cost to bring about partial desolvation of the base in the course of proton transfer.[8]

No doubt the deviations associated with the substituted pyridines reflect steric hindrance to general base catalysis. The deviation is greater where the hindrance is larger, a factor of 39 for the isopropyl substrate and a factor of 4.7 for the methyl compound. The rate retarding factor of 39 is greater, for example, than the value of 5[9] reported for 2-nitropropane but less than the factor of about 150 recorded for isobutyraldehyde-2-*d* and the same base.[10]

The NMR spectrum of the conjugate base of II could easily be recorded in liquid ammonia but that from I was time dependent, suggesting decomposition. Others have demonstrated that the conjugate base of I is unstable.[11] Interestingly, the signal for a methyl group of II shifts downfield by about 15 Hz on deprotonation, suggesting the formation of an allylic proton. Moreover, the extent of deprotonation of I and II by ammonia is not unlike that of nitromethane under similar conditions.[12] The results suggest that these carbon acids have similar ionization constants in ammonia, unlike the very large difference which exists in aqueous solution. The pK_a of I in water is 20.25[13] and that of nitromethane under similar conditions is 10.22.[14] This constitutes additional dramatic evidence that relative acidities may be highly dependent on solvent.[15]

Discussion

Before considering a comparison of kinetic carbon acidities, the nature of the transition states in the deprotonation reactions will be examined. Comparisons of kinetic acidities are most informative when transition states closely resemble products because structural effects on rates are magnified. The transition states for the deprotonation of IV and VI are believed to be product-like, i.e., resemble ylide intermediate.[2]

Nature of Transition States. Both the small kinetic effect of methyl substitution on I to give II and the large Brønsted β value suggest product-like transition states. The transition states probably have a pyramidal geometry at the reacting carbon.[16] Considerable charge is delocalized from the side chain into the ring giving rise to a partial exocyclic double bond.

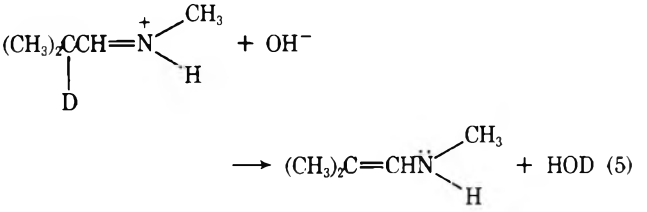
Methyl substitution can be an effective way to probe the hybridization and charge density of a carbanion. When a carbanion has sp^3 or sp^2 hybridization with considerable charge localized on the carbon atom, a methyl substitutent, relative to hydrogen, may exert an electron releasing effect which destabilizes the anion in solution.[20] But a change from an sp^3 to an sp^2 hybridization results in an increase in the strength of the carbon–methyl bond. Depending on the amount of charge on the sp^2 hybridized carbon, either one of the two opposing effects may predominate.[22,23]

The difference in reactivity between I and II ranks among the smallest observed for proton transfer involving related methyl and isopropyl carbon acids. This difference which varies from a factor of 1.2 to 7.3, depending on the catalyzing base, is smaller, for example, than the factor of 29[5,6] found for the deprotonation of nitroalkanes by hydroxide ion where the geometry of the transition state is believed to be pyramidal with a great deal of charge localized at the reactive site.[24,25] Moreover, the difference is markedly less than the factor of 10^4 found for similarly substituted sulfones[26] and sulfides.[27] The small rate retarding effect of the two methyl groups in II reflects the approximate balance between charge destabilization and double bond stabilization in a transition state leading to III.

Although Brønsted β values need to be considered cautiously in attempting to derive information about the extent of proton transfer,[28-31] our large value of 0.7 is consistent with a high degree of transfer. This value is considerably larger than the value of 0.5 recorded for the deprotonation of nitroalkanes by amines[32] but less than the value of 0.9 for the deprotonation of acetone, a carbon acid having a pK_a value similar to that of I.[33]

Reactivity Comparisons. At 75 °C, I and II are about 10^8 times more reactive toward OD^- than IV.[1] This enormous difference is best rationalized in terms of transition states for I and II having considerable delocalization of charge from the side chain into the ring. The reactivity of I serves as a model illustrating the importance of inductive and electrostatic effects free of resonance.

The reactivities of I and II are less than that of VI in the presence of OD^-, having rate constants smaller by factors of 8.2 and 61 at 75 °C,[2] respectively. In transition states and conjugate bases formed from these three acids extensive charge delocalization occurs, but only in the case of base III is charge neutralization possible. Such charge neutralization if it were unopposed by another major effect would enhance greatly the kinetic and equilibrium acidities of I and II over VI. An indication of how effective charge neutralization may be in enhancing kinetic acidities is found in a comparison of the reactivity of IV with that of an iminium ion formed from isobutyraldehyde-2-*d*, eq 5. This iminium ion is roughly 10^{13} times (35 °C) more reactive than IV.[10,34,35]



Another factor must be included in a consideration of the reactivities of I and II. Both of these acids on deprotonation undergo a very large reduction in resonance delocalization energy. Estimates place the magnitude of this thermodynamic barrier for the conversion of I to III at 19.5 ± 4 kcal/mol.[36] Naturally, the change would be somewhat smaller when a transition state rather than intermediate III is formed. Such a very large energy barrier opposes and partially cancels the large beneficial effect associated with charge neutralization. Were it not for the thermodynamic barrier the kinetic and equilibrium acidities of I and II would be vastly greater. A similar conclusion is likely to hold for the great number of heteroaromatic ions related to I and II.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60A instrument. Measurements of pD were made on a Beckman Model 1019 Research pH meter equipped with a Corning (476050) semimicro combination electrode.

Chemicals. All common laboratory chemicals, unless specified to the contrary, were reagent grade. Deuterium oxide (99.8%) was obtained from Columbia Organic Chemicals. Stock solutions of DCl were prepared by diluting concentrated HCl with D_2O and standarized by potentiometric titration. Stock solutions of KOD were prepared by

dissolving KOH in D_2O; solutions were standardized by potentiometric titration using primary standard grade potassium hydrogen phthalate.

Mallinckrodt sodium acetate was used directly. Pyridine obtained from Mallinckrodt Chemical Works and 2,6-dimethylpyridine from Eastman Organic Chemicals were dried over sodium and distilled from zinc powder. Imidazole from Matheson Coleman and Bell was recrystallized from hexane. 4-Aminopyridine from Reilly Tar and Chemical Corp. was purified by vacuum sublimation and recrystallized from benzene (mp 157–160 °C; lit.[37] 158 °C). The method of Evans and Brown[38] was used to prepare 4-amino-2,6-dimethylpyridine which was purified by successive vacuum sublimations (mp 190–191 °C; lit.[38] 191–192 °C). The purification of phenol was accomplished by adding benzene to phenol, liquified reagent, obtained from Matheson Coleman and Bell, and distilling. Calcium hydroxide was prepared by heating well-washed calcium carbonate in a platinum crucible at approximately 1000 °C with a burner for 1-h intervals until a constant weight was obtained.[39] The freshly prepared oxide was then slowly added to water and the solution was heated to boiling, cooled, and filtered. The solid was then oven dried and crushed to a finely granular state. Calcium deuteroxide was prepared by dissolving calcium hydroxide in D_2O. 1,4-Dimethylpyridinium iodide was prepared from 4-methylpyridine and methyl iodide, mp 153–154 °C (lit.[40] mp 153–153.8 °C).

4-Isopropyl-1-methylpyridinium iodide. Liquid 4-isopropylpyridine (K and K Laboratories) was fractionally distilled; the portion distilling at 181–182 °C was collected. The distillate was then dissolved in methanol and heated at reflux with methyl iodide. After cooling and evaporation to dryness, the crude salt was dissolved in excess ethanol at room temperature. Crystallization was induced by slowly adding small portions of ethyl ether, mp 125.5–128.5 °C (lit.[40] 117–120 °C dec).

Anal. Calcd for $C_9H_{14}NI$: C, 41.08; H, 5.36; N, 5.32; I, 48.23. Found: C, 41.09; H, 5.38; N, 5.28; I, 48.24.

Preparation of Reaction Mixtures. Substrate was weighted along with a corresponding molar amount of internal standard in a 30- or 10-mL volumetric flask. A weighed amount of buffer and/or a known volume of stock solution was added with a Hamilton microliter syringe. In the case of 4-amino-2,6-dimethylpyridine a stock solution of this buffer in D_2O–DCl was employed. Ionic strength was maintained at 1.0 M using KCl.

Kinetic Procedure for H–D Exchange. Kinetics were obtained by two methods. The first method, by which a majority of the work was done, involved the preparation of 3 mL of solution. Approximately 1 mL of this solution was transferred to an NMR tube whch was then flushed with nitrogen and sealed. The remainder of solution was stored under nitrogen for later comparison and pD measurements. A ^1H NMR spectrum was recorded and the NMR tube was then immersed in a constant-temperature bath set at the desired temperature using a National Bureau of Standards certified thermometer. Periodically, the NMR tube was removed and quenched in ice water, and the ^1H NMR spectrum was recorded.

In mixtures with a high deuteroxide concentration, a second method was employed. From 10 mL of stock solution, a 2-mL aliquot was stored under nitrogen for pD measurements. The remaining solution in a 10-mL volumetric flask fitted with a rubber septum was immersed in the bath. Periodically, 0.9 mL of solution was withdrawn and injected into a test tube containing 0.1 mL of a 1.2 M DCl quench solution. The NMR spectrum of this neutralized solution was recorded.

Reactions were followed a minimum of 1.5 half-lives by measuring the change in the integrated area of the NMR signal of the proton(s) of interest with respect to that of a nonexchanging proton in the reaction mixture. The integrals of proton signals were measured in a minimum of five successive sweeps and the average value was taken. Substrate concentrations were 0.40 to 0.45 M.

Usually an internal standard external to the substrate was used. For runs involving the 1,4-dimethylpyridinium iodide, tetramethylammonium bromide was added as an internal standard. In a few instances both substrates were present in the same mixture and so it was necessary, due to peak overlap, to change to sodium acetate as an internal standard. Although acetate ion promotes exchange, it does so slowly. Once a rate constant was obtained for acetate ion, its contribution to the rate could be easily calculated out of the total rate. Catalysis by acetate ion internal standard was significant only in the case of imidazole buffer where it made a contribution to the total rate of ≤12%. In the case of 2,6-dimethylpyridine acting as buffer it was necessary to use the ring protons of the substrate as an internal standard since catalysis by acetate ion was greater than by 2,6-dimethylpyridine. In the case of $Ca(OD)_2$ a small amount of this solid was present to avoid supersaturation and to maintain a constant concentration of base in solution.

From each kinetic run a plot was made of the quantity log $(A/A_{std})_t$ vs. time where $(A/A_{std})_t$ is the ratio of the integrated area of the reacting proton(s) to the area of the internal standard at time t. A pseudo-first-order rate constant, k_ψ, was then calculated from each plot constructed by visually fitting the best straight line through the points.

pD Measurements. Standardization buffers were prepared as recommended by Bates.[41] Prior to measurements at 50.0 and 75.0 °C, the electrode was thermally equilibrated for at least 20 min in 4 M KCl. By rinsing and storing the electrode in solutions maintained at the desired temperature, the electrode was not allowed to cool.

Since the pH meter was standardized and linearized with proteo buffers, it is necessary to add a correction to the meter readings to arrive at accurate pD values. For pD measurements at 25 °C, the pD value is obtained by adding 0.41 to the meter reading.[42] For pD measurements at 75 °C, this factor is 0.35.[43] At 50 °C, a value of 0.38 is obtained by simple interpolation. The apparent activity of deuteroxide ion was calculated using the relationship $pOD = pK_w^D - pD$. The values used for pK_w^D, the dissociation constant for deuterium oxide, are 14.869 (25 °C), 14.103 (50 °C), and 13.526 (75 °C);[44] they are not corrected for small salt effects.[45]

The pK_a of a buffer was calculated from the measured pD at 75 °C and the known buffer ratio for reaction mixtures containing substrate. Considerable scatter was found for phenol buffers. Twelve determinations gave a value of 9.97 with a standard deviation of 0.23. Repeated measurements of four solutions of phenol buffer of the same ionic strength but without substrate gave a pK_a of 9.99 with a standard deviation of 0.09. The latter value was taken as the pK_a.

As the electrolyte solution in the reference electrode contains silver ion, a precipitate of AgI forms in the porous frit at the liquid function, resulting in drifts in pD measurements. Elimination of this drift was accomplished by washing the electrode with thiosulfate solution.

Control Runs. Although the presence of an internal standard, agreement of pD measurements on original and recovered solutions, and the linearity of the pseudo-first-order kinetic plots indicated the absence of important complicating factors, control runs were carried out to determine the stability of both the 4-methyl- and 4-isopropylpyridinium iodides under various conditions.

The two pyridinium iodides were first dissolved in 0.10 M DCl solutions with an acetic acid internal standard and heated at 75 °C to determine their stability and, if possible, measure any exchange catalyzed by D_2O acting as the buffer base. No exchange, as evidenced by the broadening of the 4-methyl singlet or the emerging of a singlet between the 4-isopropyl *gem*-dimethyl doublet, could be detected in the NMR after heating for several days. These NMR spectral changes are a more sensitive indication of initial deuterium substitution than change in the integral ratios.

The same solutions were heated again until the change in the NMR area ratios of substrate to internal standard reached 10%. A precipitate formed but there were none of the above-mentioned spectral changes indicative of isotope exchange. The change in the integral ratio is, therefore, attributed to degradation of substrate. For the 4-methyl compound, heating for a period of 7 days produced the 10% degradation while for the 4-isopropyl compound, heating for a period of 14 days was required to produce this same percent change.

Proteo control runs were then carried out at 75 °C to verify the stability of the two pyridinium iodides in basic solution. The compositions of previously used buffer solutions were duplicated using H_2O in place of D_2O and the mixtures were heated for the equivalent of ten half-lives. For each buffer, the most basic conditions employed in the kinetic study were the conditions duplicated for the control runs. Although kinetic runs were not carried out with the 4-isopropyl compound in 4-amino-2,6-dimethylpyridine buffer, a control run was made using this buffer. Using calcium hydroxide, I was heated for 20 min and II for 140 min. With 4-amino-2,6-dimethylpyridine, I was heated for 220 min and II for 2000 min. In all cases the change in pH (measured at 25 °C) between heated and unheated samples was ≤0.04. Degradation of substrate as measured by loss of the signal for the 4-alkyl group relative to the signal of acetate ion internal standard was less than 10% in all cases.

NMR Spectra of the Conjugate Bases of 1-Methyl-4-Substituted Pyridinium Iodides in Ammonia. To either 1,4-dimethylpyridinium iodide or 1-methyl-4-isopropylpyridinium iodide and benzene internal standard in an NMR tube was added about 1 mL of ammonia. The tubes were sealed and spectra were recorded at probe temperature, about 30 °C. The solution of the 4-methyl compound was opaque and dark green; only the spectrum of starting material was evident, even a day later. The solution of the 4-isopropyl com-

pound was a clear orange; its NMR spectrum consisted of that due to starting material and conjugate base, estimated by integration to constitute about 10% of the mixture.

The experiments were repeated but this time powdered KOH was added as well. The spectrum of the dark green solution of the 4-methyl substrate at −35 °C showed that approximately 20% had been converted to conjugate base. Warming this solution to probe temperature resulted in an increase in the amount of conjugate base but the material appeared to be unstable as the signals slowly disappeared. Only the ring proton signals could be readily characterized: H-3,5, δ 5.55 and H-2,6, δ 6.22, taking benzene as δ 7.40.

Similarly, in the presence of KOH the 4-isopropyl carbon acid at −35 °C gave 30% conjugate base; only conjugate base was observed at probe temperature. The spectrum of the clear orange solution was unchanged after standing overnight: CH_3, δ 1.55, NCH_3, 2.93, H-3,5, 5.37 and H-2,6, 6.02. This spectrum is similar to that reported for 1-carbethoxy-4-isopropylidene-1,4-dihydropyridine in carbon tetrachloride.[46]

Registry No.—I, 2301-80-6; II, 18136-37-3; 4-isopropylpyridine, 696-30-0; deuterium, 16873-17-9.

References and Notes

(1) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **77,** 521 (1955).
(2) M. Saunders and E. H. Gold, *J. Am. Chem. Soc.*, **88,** 3376 (1966).
(3) Y. Kawazoe, M. Ohnishi, and Y. Yoshioka, *Chem. Pharm. Bull.*, **15,** 1255 (1967).
(4) N. N. Zatsepina, A. V. Kirova, and I. F. Tupitsyn, *Reakt. Sposobn. Org. Soedin.*, **5,** 70 (1968); N. N. Zatsepina, I. F. Tupitsyn, and L. S. Efros, *Zh. Obshch. Khim.*, **34,** 4065 (1964).
(5) R. P. Bell and D. M. Goodall, *Proc. R. Soc. London, Ser. A,* **294,** 273 (1966).
(6) A statistical correction has been applied to reflect the three equivalent protons of the reactive methyl group.
(7) R. P. Bell and P. G. Evans, *Proc. R. Soc. London, Ser. A,* **291,** 297 (1966).
(8) A. J. Kresge, *Chem. Soc., Rev.*, **2,** 475 (1973); A. J. Kresge and A. C. Lin, *J. Chem. Soc., Chem. Commun.*, 761 (1973).
(9) E. S. Lewis and L. H. Funderburk, *J. Am. Chem. Soc.*, **89,** 2322 (1967).
(10) J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **87,** 5050 (1965).
(11) W. Schneider, K. Gaertner, and A. Jordan, *Ber.*, **57,** 522 (1924).
(12) J. A. Zoltewicz and J. K. O'Halloran, *J. Org. Chem.*, **39,** 89 (1974).
(13) R. A. Cox, R. Stewart, M. J. Cook, A. R. Katritzky, and R. D. Tack, *Can. J. Chem.*, **54,** 900 (1976).
(14) R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, **75,** 2439 (1953).
(15) C. D. Ritchie in "Solute–Solvent Interactions", J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N.Y., 1969, Chapter 4; W. S. Matthews, J. E. Bares, J. F. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.*, **97,** 7006 (1975).
(16) Electron withdrawing groups in the para position of aniline cause the nitrogen pyramid to flatten.[17]
(17) W. J. Hehre, L. Radom, and J. A. Pople, *J. Chem. Soc., Chem. Commun.*, 669 (1972).
(18) A pyramidal site can effectively conjugate with an aromatic ring.[19]
(19) M. J. S. Dewar and P. Rona, *J. Am. Chem. Soc.*, **91,** 2259 (1969).
(20) The question of whether alkyl groups have a significant electron releasing effect and how they interact with electron rich sites is a long-standing one.[21] For a review, see L. S. Levitt and H. F. Widing, *Prog. Phys. Org. Chem.*, **12,** 119 (1976).
(21) R. W. Taft and L. S. Levitt, *J. Org. Chem.*, **42,** 916 (1977); F. G. Bordwell, G. E. Drucker, and G. J. McCollum, *ibid.*, **41,** 2786 (1976); F. G. Bordwell and H. E. Fried, *Tetrahedron Lett.*, 1121 (1977).
(22) A. Streitwieser, Jr., J. R. Murdoch, G. Häfelinger, and C. J. Chang, *J. Am. Chem. Soc.*, **95,** 4248 (1973); A. Streitwieser, Jr., C. J. Chang, and D. M. E. Reuben, *ibid.*, **94,** 5730 (1972); A. Streitwieser, Jr., P. C. Mowery, and W. R. Young, *Tetrahedron Lett.*, 3931 (1971).
(23) Other explanations have been advanced for alkyl group stabilization of carbanions. See C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, **89,** 1721 (1967); K. Bowden and A. F. Cockerill, *J. Chem. Soc., B,* 173 (1970).
(24) F. G. Bordwell, W. J. Boyle, Jr., and K. C. Yee, *J. Am. Chem. Soc.*, **92,** 5926 (1970); F. G. Bordwell and W. J. Boyle, Jr., *ibid.*, **97,** 3447 (1975).
(25) A. J. Kresge, *Can. J. Chem.*, **52,** 1897 (1974).
(26) F. G. Bordwell and M. D. Wolfinger, *J. Am. Chem. Soc.*, **93,** 6303 (1971).
(27) A. I. Shatenshtein and H. A. Gvozdeva, *Tetrahedron,* **25,** 2749 (1969).
(28) F. G. Bordwell and W. J. Boyle, Jr., *J. Am. Chem. Soc.*, **93,** 511 (1971); **94,** 3907 (1972); F. G. Bordwell, W. J. Boyle, Jr., J. A. Hautala, and K. C. Yee, *ibid.*, **91,** 4002 (1969).
(29) A. J. Kresge, *J. Am. Chem. Soc.*, **92,** 3210 (1970).
(30) M. Fukuyama, P. W. K. Flanagan, F. T. Williams, Jr., L. Frainier, S. A. Miller, and H. Schechter, *J. Am. Chem. Soc.*, **92,** 4689 (1970).
(31) J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **99,** 464 (1977).
(32) M. J. Gregory and T. C. Bruice, *J. Am. Chem. Soc.*, **89,** 2327 (1967).
(33) R. P. Bell, "The Proton in Chemistry", Cornell University Press, Ithaca, N.Y., 1959.
(34) The comparison is based on the assumption that the iminium ion is 200 times more reactive than the corresponding aldehyde.
(35) J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **88,** 3367 (1966); J. Hine, J. Mulders, J. G. Houston, and J. P. Idoux, *J. Org. Chem.*, **32,** 2205 (1967).
(36) M. J. Cook, A. F. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.*, **17,** 256 (1974).
(37) "Handbook of Chemistry and Physics", 46th ed., R. C. Weast, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1966.
(38) R. F. Evans and H. C. Brown, *J. Org. Chem.*, **27,** 1329 (1962).
(39) R. G. Bates, V. E. Bower, and E. R. Smith, *J. Res. Natl. Bur. Stand.*, **56,** 305 (1956).
(40) E. M. Kosower and J. A. Skorcz, *J. Am. Chem. Soc.*, **82,** 2195 (1960).
(41) R. Bates, "Determination of pH. Theory and Practice", Wiley, New York, N.Y., 1964.
(42) A. K. Covington, M. Paabo, R. A. Robinson, and R. G. Bates, *Anal. Chem.*, **40,** 700 (1968).
(43) J. A. Zoltewicz and R. E. Cross, *J. Chem. Soc., Perkin Trans. 2,* 1363 (1974).
(44) A. K. Covington, R. A. Robinson, and R. G. Bates, *J. Phys. Chem.*, **70,** 3820 (1966).
(45) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions", 3rd ed., Reinhold, New York, N.Y., 1958, pp 639–643.
(46) G. Graenkel and J. W. Cooper, *J. Am. Chem. Soc.*, **93,** 7228 (1971).

Crystal and Molecular Structure of Pentaaquohexa(diphenyl phosphato)trimagnesium(II), $[(C_6H_5O)_2P(O)O]_6Mg_3(H_2O)_5$, a Hydrated Magnesium Phosphodiester Salt with Penta- and Hexacoordinate Metal Ions

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Anhydrous magnesium diphenyl phosphate is prepared by the reaction of diphenyl methyl phosphate with tris(tetrahydrofuran)magnesium(II) bromide. A solution of the salt in benzene and moist ether deposits triclinic crystals of pentaaquohexa(diphenyl phosphato)trimagnesium(II), space group $P\bar{1}$, with two formula units, $[(C_6H_5O)_2P(O)O]_6Mg_3(H_2O)_5$, in the unit cell ($Z = 2\lambda$) of dimensions: $a = 15.173$ (23); $b = 23.625$ (17); $c = 12.896$ (9) Å; $\alpha = 104.85$ (6); $\beta = 112.56$ (10); $\gamma = 86.23$ (10)°. Reflections were collected on a $P\bar{1}$ diffractometer (Mo Kα) by ω step scan mode. The structure was solved by Patterson superposition methods and by iterative Fourier maps, and refined by full-matrix least-squares methods to a final R factor of 8.3% for 8126 reflections. Average interatomic distances (Å) are: 2.154, 2.111 for Mg–W (water); 2.042, 1.987 for Mg–O (phosphoryl) for coordination numbers 6 and 5, respectively; and 4.702 for Mg···Mg. The compound can be formulated as $[(ArO)_2P(O)O]_2Mg(W)_2 \cdot [(ArO)_2P(O)O]_2Mg(W) \cdot [(Aro)_2P(O)O]_2Mg(W)_2$, where Ar = C_6H_5 and W = H_2O. The structure consists of infinite chains of phosphodiester molecules linked through Mg^{2+} ions and oriented along the z axis. The chains are joined together by the Mg^{2+} ions to give a sequence of eight-membered rings fused in a spiro configuration at the metal, each ring with two Mg, two P, and four O atoms. There are two types of magnesium ions, coordination number 6 and coordination number 5. There are two of the former and one of the latter in the asymmetric unit. Each magnesium ion is coordinated to four oxygen atoms from four different phosphate groups and by one or two water molecules. The geometry about the CN6 Mg atoms is nearly octahedral, but that of the CN5 Mg atom is neither regular trigonal bipyramidal (TBP) nor regular tetragonal pyramidal (TP). The structure suggests models for some possible interactions which may contribute to the conformation of hydrated metal salts of some polynucleotides.

Research on the crystal and molecular structure of esters of phosphoric and polyphosphoric acids, **1** and **2**, has been pursued intensively with the goal of arriving at information on the conformations of such molecules, which are of great importance in biochemistry.

$(R^1O)(R^2O)P(O)OH$ **1** $\qquad$ $(R^1O)(HO)P(O)(PO_3H)_n(OR^2)$ **2**

The structures of simple calcium,[2] sodium,[3,4] and potassium[5] phosphomonoesters (**1**, R^2 = H), and of barium,[6,7] and silver[8] phosphodiesters (**1**), all as hydrates, have been solved by x-ray diffraction analysis. More complicated structures of type **1** (R^2 = H) have been elucidated, namely, calcuim thymidine 5′-phosphate hexahydrate,[9] barium adenosine 5′-phosphate heptahydrate,[10] and the cadmium,[11] cobalt,[11] and manganese[12] salts of cytidine 5′-phosphate hydrates. The following salts of phosphodiesters (**1**) are also known: sodium adenylyl-3′,5′-uridine hexahydrate,[13] and the calcium[14] and sodium[15] salts of guanylyl-3′,5′-cytidine nonahydrate. Sodium guanosine 3′,5′-cyclic phosphate tetrahydrate[16] has been reported. Among ammonium salts triethylammonium uridine 3′-*O*-thiophosphate methyl ester[17] and triethylammonium uridine 2′,3′-*O*,*O*-cyclophosphorothioate,[18] as well as the model compound bis(dicyclohexylammonium) α,β-(2-naphthyl) dipolyphosphate,[19] are known. The structures of two metal ion salts of condensed polyphosphate monoesters (**2**, R^2 = H) have been fully described: rubidium adenosine 5′-dipolyphosphate monohydrate,[20a] and disodium adenosine 5′-tripolyphosphate hexahydrate.[20b]

A number of structures based on formulas **1** (R^2 = H), **1**, and **2** (n = 1), but without any metal ion constituent, have been solved and are referenced in recent articles.[21-23] The structures of three diesters (**1**) in the phospholipid field, L-α-glycerophosphorylcholine[24] and its cadmium chloride trihydrate complex,[25] and 1,2-dilauroyl-DL-phosphatidylethanolamine,[26] are known.

In spite of the essential role played by magnesium in the biochemistry of phosphorus, only two structures of organic phosphate salts of this metal have, to our knowledge, been reported. Ezra and Collin[27] prepared magnesium diethyl phosphate as follows:

$$2(C_2H_5O)_2P(O)OAg + MgCl_2 \xrightarrow{\text{water}} [(C_2H_5O)_2P(O)O]_2Mg + 2AgCl$$

The monoclinic crystals obtained from 95% ethanol and ethyl acetate consist of a polymer of the formula unit $[(C_2H_5O)_2P(O)O]_2Mg$, in which Mg atoms are coordinated to four phosphoryl oxygens in a nearly regular tetrahedral arrangement. In contrast, Schwalbe, Goody, and Saenger[28] observed discrete molecules of tetrapyridinebis(diethylphosphorothioato)magnesium(II), with Mg atoms in octahedral coordination.

The structures of several *inorganic* magnesium phosphates are known, and the coordination number (CN)[29] of their metal atoms varies as follows: 6 in $Mg(HPO_4)(H_2O)$,[30] 4, 5, and 6 in $Mg_3(PO_4)_2$,[31] 6 in $Mg(NH_4)_2(HPO_4)_2(H_2O)_4$,[32] 6 in $Mg_2(PO_4)Cl$,[33] 5 and 6 in α-$Mg_2P_2O_7$,[34] and 6 in $Mg_2P_4O_{12}$[35] (tetrametaphosphate).

The present investigation focuses on the synthesis of anhydrous magnesium diphenyl phosphate (MDP) by the new reaction:[36]

$$2(C_6H_5O)_2P(O)OCH_3 + MgBr_2(C_4H_8O)_3 \xrightarrow{CH_2Cl_2} [(C_6H_5O)_2P(O)O]_2Mg + 2CH_3Br + 3C_4H_8O$$

3 $\qquad$ **4** $\qquad$ **5**

Both the reagent, tris(tetrahydrofuran)magnesium bromide (**4**),[36] and the reaction product, MDP (**5**), are relatively soluble in dichloromethane (3.0 and 0.02 M solutions at 25 °C, re-

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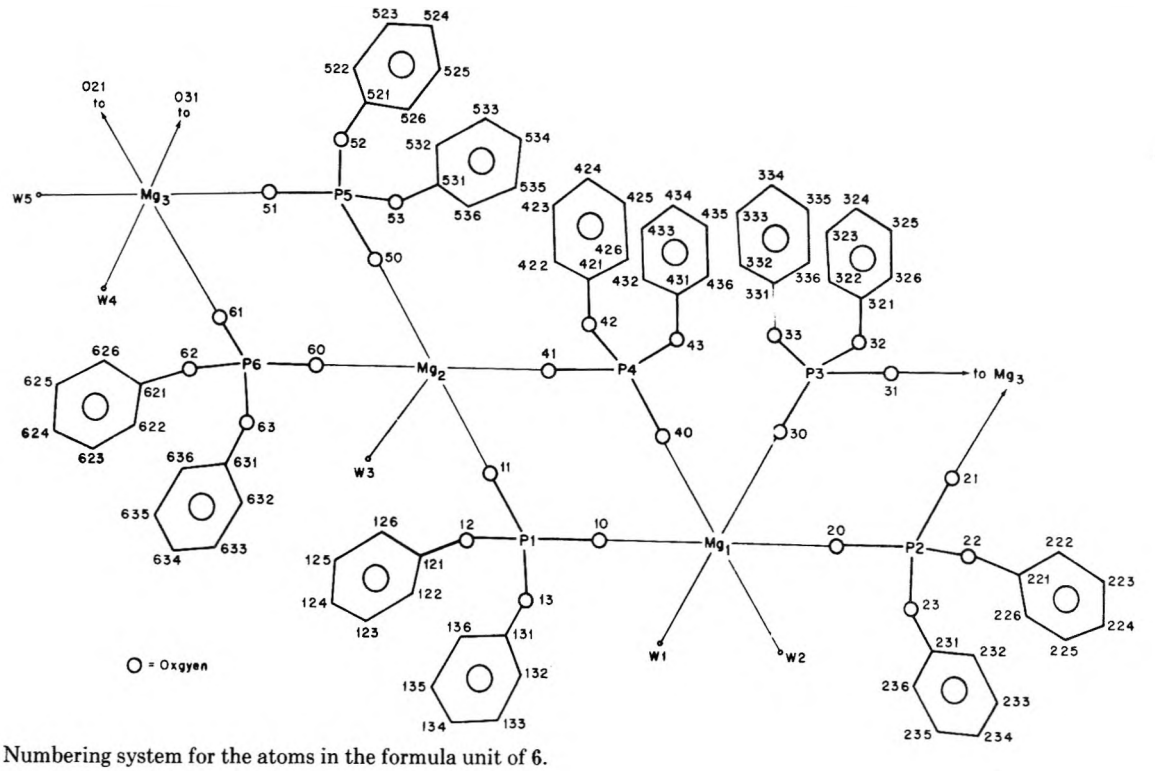


Figure 1. Numbering system for the atoms in the formula unit of **6**.

spectively). The salt **5** prepared in this manner has also a finite solubility in benzene (0.002 M at 25 °C). This method, therefore, permits the introduction of known amounts of aprotic and protic donor molecules into a strictly anhydrous magnesium phosphodiester solution for the purpose of studying the coordination chemistry of these biochemically important complexes.

Experimental Section

Preparation of Magnesium Diphenyl Phosphate (5). A solution of diphenyl methyl phosphate[37] (2.43 g, 9.12 mmol) in anhydrous dichloromethane (3 mL) was added dropwise to a solution of $MgBr_2(C_4H_8O)_3$ (**4**; 1.83 g, 4.56 mmol) in dichloromethane (25 mL) at 25 °C under Ar. The clear solution was stirred for 4 h at 25 °C; no solid phase was observed at this point. The solution was evaporated at 30 °C (30 mm), and the residue was extracted with anhydrous diethyl ether (2 × 10 mL). The resulting power was dried for 45 min at 25 °C (0.1 mm): yield 2.01 g or 85% of the theory based on formula $[(C_6H_5O)_2P(O)O]_2Mg$. For elemental analysis, the sample was washed successively with small volumes of benzene and ether, and was dried as above. Calcd for $C_{24}H_{20}O_8P_2Mg$ (mol wt 522): C, 55.2; H, 3.8; P, 11.8; Mg, 4.6. Found: C, 55.2; H, 4.0; P, 11.8; Mg, 4.5. ^{31}P NMR δ +18.6 ppm in $CDCl_3$ and +9.1 ppm in D_2O (sharp singlets in both cases), from H_3PO_4 = 0. Compound **5** is crystalline according to x-ray powder photographs.

Crystallization of Pentaaquohexa(diphenyl phosphato)trimagnesium(II). (6). A solution of MDP (**5**) in benzene was diluted with moist diethyl ether (5:1, v/v) and kept for several days at 25 °C to allow the slow growth of satisfactory small plates. The crystals, once harvested, were very sensitive to atmospheric moisture; they were handled under a constant flow of Ar in a glove box, and sealed in glass capillaries with a trace of silicon grease to prevent the crystals from slipping. Crystal data: triclinic; space group $P\bar{1}$; a = 15.173 (23); b = 23.625 (17); c = 12.896 (9) Å; α = 104.85 (6); β = 112.56 (10); γ = 86.23 (10)°; V = 4124 Å^3; Z = 2 (one formula unit $C_{72}H_{70}O_{29}P_6Mg_3$ per asymmetric unit). ρ_{calcd} = 1.34 g cm^{-3}; ρ_{obsd} = 1.37 g cm^{-3} (flotation in carbon tetrachloride/hexane). Intensity data were collected on a $P\bar{1}$ diffractometer employing Mo Kα radiation by ω step scan mode. Out of 13 459 unique reflections collected below 2θ = 52°, 8126 reflections with their intensities 2.33 σ above the background were considered to be observed reflections. Lorentz and polarization corrections were applied to the intensity data, but no absorption corrections were applied.

Solution and Refinement. The structure was solved by Patterson superposition methods and by iterative Fourier maps. Sixteen of the peaks selected from the superposition maps performed on the four prominent sharpened Patterson peaks could be judiciously assigned to be atomic peaks, from the criterion that phosphorus has tetrahedral and magnesium octahedral ligands. The first Fourier map calculated with seven of these peaks revealed four other peaks of the 16 selected peaks and from the subsequent Fourier maps all the 110 nonhydrogen atoms were located.

Refinements on observed reflections were by full-matrix least squares, minimizing $\Sigma\omega(\Delta F)^2$ with weights $w = 1/\sigma^2(F)$. In the isotropic refinements the structure was refined in two blocks and in anisotropic refinements it was divided into six blocks and the three magnesium atoms were included in every block. The positions of the hydrogen atoms belonging to phenyl groups were calculated (at 1.0-Å distance) from the molecular geometry. Their parameters were included in the refinements, but they were not refined. Their thermal parameters were the final isotropic terminal parameters of carbon atoms to which they are attached. During the anisotropic refinements those reflections of $\Delta F > 10\ \sigma$ were not included in refinements. In the final difference Fourier map a number of peaks were found around the water oxygen atoms. Seven of these peaks were assumed to be hydrogen atoms belonging to water oxygen atoms, due to their reasonable hydrogen-bond geometries. These were also included in the final structure factor calculation.

After termination of the refinements the positions of the phenyl hydrogen atoms were recalculated from the final coordinates and their thermal parameters were readjusted, respectively. The final structure factor calculated (177 atoms) with all the observed 8126 reflections gave an R value of 0.083 and R_w = 0.128. The scattering factors for nonhydrogen atoms were from International Tables for X-Ray Crystallography,[38] and for H atoms from Stewart et al.[39] The positional and thermal parameters of the atoms with their esd's are given in Table V. Table V is given as supplementary material; see paragraph at end of paper. For consultation of structure factors see also paragraph at end of paper.

Results and Discussion

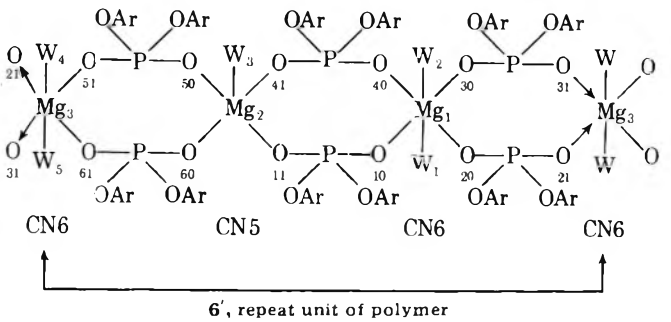
Molecular Structure of Pentaaquohexa(diphenyl phosphato)trimagnesium(II) (6). The atoms are numbered as shown in Figure 1, and one isolated formula unit is illustrated in Figure 2. Tables I and II give the most significant interatomic distances and angles, respectively. Several equations of least-squares planes, the deviations of certain atoms from those planes, and a few dihedral angles between planes related to the geometry about the magnesium are

Table I. Main Interatomic Distances (Å) in 6 and Their Standard Deviations[a]

	Metal–Oxygen	
Mg(1)–O(10) 2.056 (4)	Mg(2)–O(11) 1.987 (3)	Mg(3) ← O(21)[b] 2.073 (4)
Mg(1)–O(20) 2.033 (4)	Mg(2)–O(41) 1.985 (4)	Mg(3) ← O(31)[b] 2.033 (4)
Mg(1)–O(30) 2.075 (3)	Mg(2)–O(50) 1.964 (5)	Mg(3)–O(51) 2.023 (4)
Mg(1)–O(40) 2.019 (4)	Mg(2)–O(60) 2.012 (3)	Mg(3)–O(61) 2.023 (4)
Mg(1)–W(1) 2.176 (4)	Mg(2)–W(3) 2.111 (5)	Mg(3)–W(4) 2.141 (5)
Mg(1)–W(2) 2.129 (4)		Mg(3)–W(5) 2.166 (4)
	Phosphorus–Oxygen	
P(1)–O(10) 1.471 (5)	P(2)–O(20) 1.466 (5)	P(3)–O(30) 1.483 (4)
P(1)–O(11) 1.473 (4)	P(2)–O(21) 1.476 (4)	P(3)–O(31) 1.469 (4)
P(1)–O(12) 1.599 (3)	P(2)–O(22) 1.603 (4)	P(3)–O(32) 1.604 (4)
P(1)–O(13) 1.596 (4)	P(2)–O(23) 1.603 (4)	P(3)–O(33) 1.590 (4)
P(4)–O(40) 1.471 (4)	P(5)–O(50) 1.473 (5)	P(6)–O(60) 1.477 (3)
P(4)–O(41) 1.486 (4)	P(5)–O(51) 1.489 (4)	P(6)–O(61) 1.471 (5)
P(4)–O(42) 1.589 (4)	P(5)–O(52) 1.599 (4)	P(6)–O(62) 1.590 (4)
P(4)–O(43) 1.585 (4)	P(5)–O(53) 1.597 (4)	P(6)–O(63) 1.609 (4)
	Benzene Ring[c]	
Average values	C–C 1.362 (14)	C–O 1.398 (9)
	Metal–Metal	
Mg(1)···Mg(2) 4.720 (3)	Mg(2)···Mg(3) 4.636 (2)	Mg(3)···Mg(1)[b] 4.751 (3)
	Metal–Phosphorus	
Mg(1)···P(1) 3.404 (3)	Mg(2)···P(1) 3.254 (2)	Mg(3)···P(2)[b] 3.311 (2)
Mg(1)···P(2) 3.332 (3)	Mg(2)···P(4) 3.145 (2)	Mg(3)···P(3)[b] 3.471 (2)
Mg(1)···P(3) 3.291 (2)	Mg(2)···P(5) 3.410 (3)	Mg(3)···P(5) 3.264 (2)
Mg(1)···P(4) 3.440 (3)	Mg(2)···P(6) 3.366 (2)	Mg(3)···P(6) 3.303 (2)
	Oxygen(water)–Oxygen(phosphoryl)	
W(1)···O(20) 2.932 (6)	W(2)···O(10) 2.675 (6)	W(3)···O(60) 2.629 (5)
W(1)···O(40) 3.012 (5)	W(2)···O(51) 2.808 (6)[d]	W(3)···O(30) 2.791 (6)
W(1)···O(10) 3.041 (6)	W(2)···O(30) 3.019 (6)	W(3)···O(11) 2.856 (5)
	W(2)···O(20) 3.072 (5)	W(3)···O(41) 3.130 (5)
	W(2)···O(31) 3.131 (6)	
W(4)···O(21) 2.644 (6)[b]		W(5)···O(22) 2.836 (5)[b]
W(4)···O(41) 2.818 (6)		W(5)···O(31) 2.883 (6)[b]
W(4)···O(61) 3.020 (5)		W(5)···O(21) 2.908 (5)[b]
W(4)···O(51) 3.058 (6)		W(5)···O(61) 2.912 (5)
	Oxygen(water)–Oxygen(water)	
W(1)···W(2) 2.890 (6)		W(4)···W(5) 2.984 (5)
	Oxygen(phosphoryl)–Oxygen(phosphoryl)	
O(11)···O(50) 2.826 (5)		O(11)···O(41) 3.019 (5)
O(31)···O(51)[d] 2.891 (4)		O(60)···O(41) 3.049 (5)
O(50)···O(60) 2.904 (5)		O(50)···O(41) 3.095 (5)
O(10)···O(30) 2.913 (5)		O(11)···O(60) 3.933 (5)
O(21)···O(51)[d] 2.942 (5)		O(61)···O(21)[b] 4.078 (5)
O(31)···O(61)[d] 2.964 (5)		O(10)···O(20) 4.084 (5)

[a] Numbers in parentheses are esd's in the least significant digits. [b] Atoms related by $z + 1$. [c] Average values; esd's in parentheses are the larger of an individual deviation. [d] Atoms related by $z - 1$.

gathered in Table VI, submitted as Supplementary Material.



6′, repeat unit of polymer

Compound **6** can be formulated as $[(ArO)_2P(O)]_2Mg(W)_2{\cdot}[(ArO)_2P(O)O]_2Mg(W){\cdot}[(ArO)_2P(O)O]_2Mg(W)_2$. This is best seen in the partial formula **6′**. The structure consists of infinite chains of phosphodiester molecules linked through Mg ions and oriented along the z axis. The chains are joined together by the Mg ions to give a sequence of eight-membered rings fused in a spiro configuration at the metal, each ring with two Mg, two P, and four O atoms. The six phosphodiester molecules in the formula unit of the compound, which is also the asymmetric unit of the crystal, occur as three dimers, one of them bonded by CN5 Mg, and two by CN6 Mg.[40,41] Both types of coordination spheres in the triplet of dimers have four O atoms from four different phosphoryl groups, and the coordination is completed by one or two water molecules, respectively. The geometry about both CN6 atoms is nearly octahedral, but that of the CN5 atoms is neither trigonal bipyramidal (TBP)[29] nor tetragonal pyramidal (TP),[29] although it is closer to the latter; this question is discussed below.

No information is available on the structure of anhydrous

Table II. Main Angles (deg) in 6 and Their Standard Deviations

Mg(1)···Mg(2)···Mg(3)	143.7 (2)	Mg(2)···Mg(1)···Mg(3)[a]	135.6 (2)	Mg(2)···Mg(3)···Mg(1)[b]	137.8 (2)
Mg(1)–O(10)–P(1)	149.2 (2)	Mg(2)–O(11)–P(1)	139.8 (2)	Mg(3)–O(51)–P(5)	136.2 (2)
Mg(1)–O(20)–P(2)	144.0 (2)	Mg(2)–O(41)–P(4)	129.3 (2)	Mg(3)–O(61)–P(6)	141.4 (2)
Mg(1)–O(30)–P(3)	134.7 (2)	Mg(2)–O(50)–P(5)	165.5 (2)	Mg(3) ← O(21)–P(2)[b]	137.2 (2)
Mg(1)–O(40)–P(4)	160.5 (2)	Mg(2)–O(60)–P(6)	149.1 (2)	Mg(3) ← O(32)–P(3)[b]	164.5 (2)
O(11)–Mg(2)–O(60)	159.3 (2)	O(50)–Mg(2)–W(3)	157.0 (2)	O(41)–Mg(2)–O(50)	103.2 (2)
O(41)–Mg(2)–W(3)	99.6 (2)	O(11)–Mg(2)–O(41)	98.9 (1)	O(50)–Mg(2)–O(60)	93.8 (2)
O(10)–Mg(1)–O(20)	174.5 (2)	O(30)–Mg(1)–W(1)	175.5 (2)	O(40)–Mg(1)–W(2)	172.6 (2)
O(10)–Mg(1)–O(30)	89.7 (2)	O(10)–Mg(1)–W(2)	79.5 (2)	O(20)–Mg(1)–O(40)	91.0 (2)
O(20)–Mg(1)–W(1)	88.3 (2)	O(30)–Mg(1)–W(2)	91.8 (2)	O(40)–Mg(1)–W(1)	91.7 (2)
O(51)–Mg(3)–W(5)	177.0 (2)	O(61)–Mg(3)–O(21)	169.4 (2)	O(31)–Mg(3)–W(4)	171.0 (2)
O(51)–Mg(3)–O(21)	91.8 (1)	O(51)–Mg(3)–W(4)	94.5 (2)	O(61)–Mg(3)–W(5)	88.0 (2)
O(61)–Mg(3)–O(31)	93.9 (2)	W(5)–Mg(3)–O(31)	86.7 (2)	O(21)–Mg(3)–W(4)	77.7 (2)

O(metal)–P–O(metal)[c]	120.1 (3)	O(phenyl)–P–O(phenyl)[c]	104.0 (3)
O(i)(metal)–P(j)–O(i + 2)(phenyl)[c]	111.2 (3)	i = 10, 11, 20, 21, . . . 60, 61; j = 1, 2, . . . 6; k = 1 or 3	
O(i)(metal)–P(j)–O(i + k)(phenyl)	104.7 (2)		
C–C–C[c]	119.8 (9)	C–O–P[c]	124.1 (4)
O(ij)–C(ijl)–C(ij2)	121.0 (7)	i = 1, 2, . . . 6; j = 2 or 3	
O(ij)–C(ijl)–C(ij6)	117.0 (7)		

[a] Atoms related by $z - 1$. [b] Atoms related by $z + 1$. [c] Average quantities.

MDP (5). However, little ion-pair dissociation is expected in a benzene solution of 5, and we speculate that the limited amount of water introduced into the benzene/ether solvent allows the partial hydration, and the reorganization of the hydrated ion pairs into the "triplets" present in the formula unit and the polymer crystal.

The distances between phosphoryl oxygens and magnesium are shorter than those between water oxygens and the metal, and any Mg–O distance is shorter when the metal has CN5 than when it has CN6. A decrease in interatomic distance should accompany a decrease in CN, since nonbonded repulsions between ligands should be lower in the lower CN state.[42]

The average Mg(CN5)–O(phosphoryl) distance (1.987 Å) is less than the average Mg(CN6)–O(phosphoryl) distance (2.042 Å); likewise the average Mg(CN5)–W (2.111 Å) is less than the average Mg(CN6)–W (2.154 Å). The average Mg–W (water) distance is larger in the partially hydrated aquo-MDP (6) (2.132 Å) than in the completely hydrated octahedral $MgX_2(H_2O)_6$ (X = Cl, Br)[43] and in several other salts[44-47] (~2.08 Å), and it is closer to the value found in diaquobis(acetylacetonato)magnesuim(II) (2.148 Å).[48] The Mg–O(phosphoryl) distances in 6 are in the range reported for other Mg–O distances (1.990–2.161 Å).[44-48] An exceptionally long Mg–O distance has been recorded (2.40 Å).[33] In compound 6, Mg–O(phosphoryl) < Mg–W, but the reverse is true in some other structures, e.g., magnesium formate dihydrate.[46] Apparently the phosphoryl oxygen in combination with water molecules tends to occupy the coordination sites associated with stronger bonds.

The P–O bonds bridged by Mg atoms are shorter (averages distance 1.475 Å) than those leading to the phenyl rings (average distance 1.597 Å). Resonance delocalization of unshared oxygen electrons into the benzene ring would decrease the extent of p–d π bonding involving those oxygen unshared electrons and the phosphorus, accounting for the observed differences. The distances between consecutive Mg atoms in the formula unit average 4.678 Å, while the distance between metal atoms across formula units is 4.751 Å, indicative of the polymeric nature of the crystal; note also the Mg···P distances, e.g., Mg(3)···P(2) [z + 1] which are similar to, or shorter than, related distances within the formula unit.

With respect to the distances between water oxygens and phosphoryl oxygens, it is noteworthy that, in some instances, e.g., W(3)···O(30) and W(4)···O(41), a water coordinated to one magnesium atom is relatively close to a phosphoryl oxygen

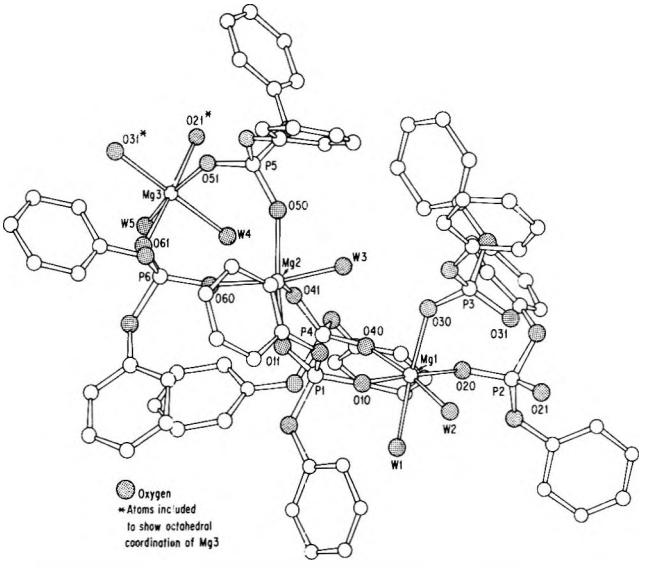


Figure 2. Compound 6 showing the different coordinations for magnesium.

bonded to another Mg atom within the same formula unit. The same is true across formula units, e.g., W(2)···O(51) [z −1], W(4)···O(21) [z + 1], and W(5)···O(31) [z + 1]. In one instance, the water approaches close to one of the *ester* oxygens in the adjacent formula unit, W(5)···O(22) [z + 1] = 2.83 Å. These data suggest significant stabilization of the structure through hydrogen bonding involving water and phosphate oxygens within and across formula units. These phenomena are of interest in connection with models by which hydrated metal ions can contribute to the structure and configuration of hydrated metal salts of polynucleotides.

The three magnesium atoms in the formula unit define an angle of 143.7°, while the related angles involving one Mg atom of the adjacent formula units are 135.6 and 137.8°, respectively. The Mg–O–P angles vary from a minimum of 129.3° to a maximum of 165.5°, and *within a formula unit this extreme range is found about CN5 Mg.* The O–P–O angles are wider (av 120.1°) when both oxygens are coordinated to the metal than when they are covalently bonded to the phenyl rings (av 104.0°). The phosphate groups are distorted tetrahedra.[49]

The skeletal geometry about the two CN6 Mg atoms is that of a distorted octahedron. The maximum deviation from 180°

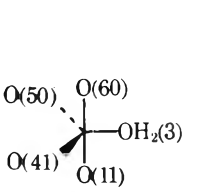
Table III. Deviations from Ideal Trigonal Bipyramid (TBP) and Tetragonal Pyramid (TP) in the Skeletal Geometry of 5-Coordinate Magnesium in 6

Angle	From TBP		From TP	
	Deviation from, deg	Deviation, deg	Deviation from, deg	Deviation, deg
O(11)–Mg–O(60)	180	−20.7	150	+9.3
O(50)–Mg–H_2O(3)	120	+37.0	150	+7.0
O(41)–Mg–O(50)	120	−16.8	105	−1.8
O(41)–Mg–H_2O(3)	120	−20.4	105	−5.4
O(41)–Mg–O(60)	90	+9.4	105	−5.6
O(11)–Mg–O(41)	90	+8.9	105	−6.1
O(50)–Mg–O(60)	90	+3.8	86	+7.8
O(11)–Mg–O(50)	90	+1.3	86	+5.3
O(11)–Mg–H_2O(3)	90	−1.7	86	+2.3
H_2O(3)–Mg–O(60)	90	−10.8	86	−6.8

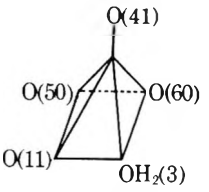
is found in one angle each of Mg(1) (−8°) and Mg)3) (−10°); the maximum deviation from 90° is found in one angle of Mg(1) (−11°) and one of Mg(3) (−12°). The remaining angles are close to the ideal values.

The skeletal geometry about CN5 Mg can be analyzed as follows. (i) The ten bond angles about the metal are considered in the order of their decreasing values, and the deviations from the values to be expected if those ligands are placed on the ideal trigonal bipyramid skeleton are noted. The results are shown in Table III. (ii) The same set of ligands are then placed on the hypothetical ideal trigonal pyramid skeleton which would result from the performance of a permutational isomerization of the TBP structure according to the Berry pseudorotation mechanism;[50] in doing so, the ligand that seems to be closer to being "flagpole" in the resulting TP is chosen as the "pivot" of the pseudorotation. The deviations between observed and ideal TP angles are listed in Table III. (iii) Several significant least-squares planes based on the ideal TBP and TP are calculated (Table VI), and the dihedral angles formed by some of these planes are calculated. (iv) From these considerations it is concluded that the actual geometry about the CN5 Mg deviates sufficiently from the regular TBP and TP geometries so that another more general description of the skeletal geometry is desirable. For reasons previously given,[51–53] the description chosen is that of an $x°$ turnstile rotation ($x°$-TR) configuration. This geometry is derived from the motions of the five ligands during the permutational isomerization of a TBP phosphorane by the TR mechanism.[54] The $x°$-TR is not an ideal geometry; it represents the accommodation of all bond angles and distances in the actual structure to the electronic and steric demands of all the ligands. The $x°$-TR configuration deviates from the ideal 30°-TR configuration[54] (C_s point group), which is the geometry of the ideal barrier to be traversed in the TR mechanism of isomerization. The direction, but not the magnitude, of the deviations from the ideal TBP found in the actual $x°$-TR can be surmised from the TR mechanism. The value of $x°$ in $x°$-TR is estimated from the dihedral angle between planes 6 and 7 in Table VI, namely 17°. The ligand "pair" of the TR mechanism is H_2O(3), O(60), and the angle H_2O(3)–Mg(2)–O(60) is quite small, 79.2°. Ligands O(11), O(50), and O(41) constitute the TR "trio".[54]

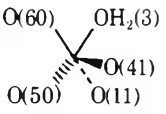
CN6 is commonly found[28,30–35,41,43–48,55–59] in Mg compounds, however CN4 Mg is not rare.[27,42,60–63] CN5 Mg has also been encountered, either as the only type in the formula unit,[64–66] or in combination with other CN types, e.g., 6,[34,41] or 4 and 6.[31] Formula units containing Mg atoms in CN6 and 7,[67] or even 8,[68,69] have been described. In most cases, the less common mixed coordination states are represented in structures where there is sharing between corners or edges of the respective polyhedra. *It should be noted that such sharing is not required to stabilize the aquo-MDP structures* (**6**).



ideal trigonal bipyramid (TBP)

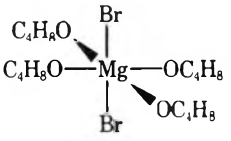


ideal tetragonal pyramid (TP)

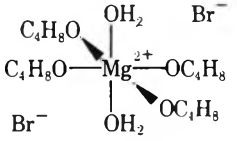


$x°$ turnstile rotation (TR)

The structures mentioned above include anhydrous as well as fully and partially hydrated complexes; in some of them, the crystal is polymeric, but in others, the crystal contains discrete molecules. A series of Mg complexes have been described[36,55,57,59] in which the same counteranion (bromide) and the same donor (tetrahydrofuran) generate an anhydrous

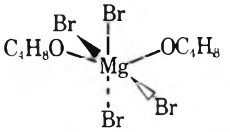


tetragonal



triclinic

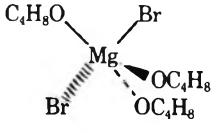
complex (tetragonal)[55,57] or a partially hydrated complex (triclinic),[59] both as molecular crystals, depending on experimental conditions. In addition, a related anhydrous complex (orthorhombic)[59] can also be obtained as a polymeric crystal. A fourth member of the series, namely the reagent 4 utilized in the present work, has been isolated only as microcrystalline



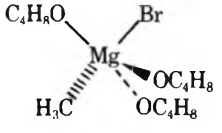
orthorhombic (polymeric)

powder. From the work of Vallino[65,70] on the related compound, monoclinic $CH_3MgBr(C_4H_8O)_3$, it is possible that $MgBr_2(C_4H_8O)_3$ represents another complex with CN5 Mg.

The lower coordination states of magnesium may simply result from steric interference in the attainment of the pre-



microcrystalline



monoclinic

Table IV. Solubility [M] of Magnesium Diphenyl Phosphate (5) and Pentaaquohexa(diphenyl phosphato)trimagnesium(II) (6) in Aprotic Organic Solvents at 25 °C

Solvent	5	6
Dichloromethane	0.02	0.2
Carbon tetrachloride	i[a]	i
Tetrahydrofuran	0.07	0.14
Diethyl ether	i	i
Benzene	0.002	0.003
Cyclohexane	i	i

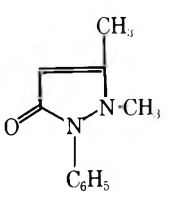
[a] i = <0.001 M.

ferred 6-coordination. For example, CN4 is observed in $C_2H_5MgBr[O(C_2H_5)_2]_2$[61] and $C_6H_5MgBr[O(C_2H_5)_2]_2$,[60] while a reduction of the size of the halogen and of the steric hindrance due to the ether, as in $[(C_2H_5)Mg_2Cl_3(C_4H_8O)_3]_2$,[40] leads to a structure with one CN5 and one CN6 Mg atom in the formula unit.[40] A smaller alkyl group and ether donor, but a large halogen, as in $CH_3MgBr(C_4H_8O)_3$,[65] leads to CN5 Mg. The diethyl ether complex $MgBr_2[O(C_2H_5)_2]_2$[62] has CN4 Mg, but the tetrahydrofuran analogue $MgBr_2(C_4H_8O)_2$[59] has CN6 Mg. The steric control of magnesium coordination may play an important role in the structure and conformation, and hence in the biochemical properties of hydrated nucleotide–magnesium complexes.

A comparison between the magnesium phosphodiester salt (6) and the calcium phosphomonoester salt prepared by Li and Caughlan[2] discloses that in both cases two formula units, $[(ArO)_2P(O)O]_6Mg_3(H_2O)_5$ vs. $[(ArO)(HO)P(O)O]_2Ca(H_2O)_3$, compose the unit cell (one formula per asymmetric unit in space group $P\bar{1}$). The degree of hydration per metal ion is higher in the calcium salt, which contains three water molecules in the pentagonal bipyramidal heptacoordinate sphere, as compared to the two and one water molecules coordinated to the two types of Mg atoms in 6. In both structures, the coordination sphere of the metal is completed by four oxygen atoms from four different phosphoryl groups. The Ca–O(water) and Ca–O(phosphoryl) distances are about 12% longer than the corresponding Mg–O distances.

Some Properties of MDP (5) and Aquo-MDP (6). The solubility of MDP and of aquo-MDP in aprotic organic solvents of relatively low polarity is given in Table IV. The hydrated complex is significantly more soluble than the anhydrous salt in both dichloromethane and tetrahydrofuran, suggesting weaker intermolecular forces in the triclinic crystals (6) than in the powder (5). Both solids are more soluble in benzene than in diethyl ether.

Anhydrous MDP exhibits very little tendency to form stable complexes with ethers, unlike other magnesium salts. This phenomenon is perhaps related to the strong tendency of phosphoryl oxygens to coordinate with Mg atoms. This is manifested not only in the organic and the inorganic phosphates, but also in tris(octamethylpyrophosphoramide)-magnesium(II),[58] which is not a salt, and in which both phosphoryl oxygens of the same phosphoramide molecule contribute to the 6-coordination sphere of the metal. Carbonyl oxygen also shows a strong tendency to coordinate with Mg ions, which is manifested in the structure of magnesium hexaantipyrine perchlorate,[56] where six molecules of the



heterocycle are octahedrally coordinated to the metal with oxygens as the ligands. This phenomenon is particularly important in some nucleotide salts.[12]

The ^{31}P NMR signal of MDP appears at significantly higher magnetic field in deuteriochloroform (+18.6 ppm) than in D_2O (+9.1 ppm, both from $H_3PO_4 = 0$), which reflects a more effective shielding of the phosphorus nucleus by electrons for the salt in the organic solvent relative to water.

Conclusions

The data presented in this paper, in conjunction with those contained in the cited references, reveal that magnesium possesses a combination of properties which undoubtedly contributes to the special role that this metal plays in the chemistry and biochemistry of phosphates. Among these properties are: (1) the tendency to form strong electrostatic and coordinative bonds with phosphoryl oxygens; (2) the tendency to form relatively stable complexes in all its coordination states (CN4, 5, 6, 7, and 8); (3) the particular relationship that exists between the Mg–O(phosphoryl) and Mg–O(water) bond distances, which relates to the ability of the hydrated magnesium phosphates to form hydrogen bridges connecting the metal ion with the phosphate oxygens; and (4) the acid-enhancing tendency of Mg ions, as in $Mg{-}O^+{-}H_2 \leftrightarrow Mg{-}O{-}H\ H^+$, which may also relate to the strength of its hydrogen bonds.

The present findings that the magnesium ion can achieve stable 5- and 6-coordinate states in an organic phosphate crystal which does not involve the sharing of corners or edges of the polyhedra, and that the difference in coordination number results exclusively from differences in the number of water molecules in the coordination spheres, are new and significant. Previous examples of variable metal coordination in magnesium phosphates had been observed among inorganic crystals, i.e., $Mg_3(PO_4)_2$[31] and α-$Mg_2P_2O_7$,[34] where polyhedron sharing contributes to the stability of the crystals.

Differences in CN are associated with differences in geometry, and it is evident that the conformation of a simple phosphodiester molecule, $(R^1O)(R^2O)P(O)OH$, can be altered significantly depending on the state of hydration of the magnesium ion with which the diester forms the electrostatic (salt) and the coordinative oxygen–metal bonds. The differences in geometry between a more or less regular octahedron on one hand, and a highly distorted TBP or TP (i.e., the $x°$-TR geometry) on the other hand, are quite significant; this point must be considered in any attempt to derive possible conformations for a polymeric crystal made up of phosphodiester units and magnesium ions. The state of hydration of the magnesium ion, and hence the resulting CN and geometry about the metal, is probably dependent on the availability of sufficient space near the metal to accommodate the water. Hence, steric effects associated with the R^1 and R^2 groups of the phosphodiester may contribute to the overall geometry of the salt through the operation of this effect.

Finally, we speculate that some of the features present in the aquo-MDP crystals may apply also to the structure and conformation of a more complex hydrated magnesium dinucleotide salt, $[(\text{nucleoside-3}')(\text{nucleoside-5}')P(O)O]_2Mg\cdot(H_2O)_x$. Since the latter is derived from the polyfunctional nucleoside molecule, it is obvious that the possible competition between the additional nitrogen- and oxygen-containing functions of the nucleosides[9-18,20-23,71-77] on one hand, and the two phosphoryl oxygens of the phosphate group and the water molecules on the other hand, for the available magnesium coordination sites, must be taken into consideration. However, models of a formula unit analogous to that present in the aquo-MDP salt (6, cf. 6′) can be built in which each pair of ArO groups attached to a phosphate can be replaced by a pair of nucleosides connected by the usual 3′ → 5′-internu-

cleotide bonds to give rise to a polynucleotide chain. An assessment of the possible biochemical significance of this model requires further studies on actual hydrated magnesium dinucleotides and small polynucleotides, none of which are available at present.

The phosphate groups in aquo-MDP occupy two different types of positions in the metal coordination polyhedra: *distal* and *vicinal* positions. The distal positions correspond to the collinear arrangement in an ideal octahedron, or to the trans-basal arrangement in an ideal tetragonal pyramid. The vicinal positions correspond to the orthogonal arrangement in an ideal octahedron, or to the cis-basal and basal-flagpole arrangements in the ideal tetragonal pyramid. These two types of phosphate–metal coordination geometries are reflected in significantly different O (phosphoryl)···O (phosphoryl) distances, e.g., O(10)···O(20) = 4.084 Å and O(21)···O(61) = 4.078 Å, which correspond to CN6 Mg distal configuration, and O(11)···O(60) = 3.933 Å, which corresponds to CN5 Mg distal configuration, on one hand, and O(10)···O(30) = 2.913 Å etc. and O(11)···O(41) = 3.019 Å etc., which correspond to CN6 and CN5 Mg vicinal configurations, respectively.

The above data concerning the observed O···O interatomic distances between phosphate groups in our simple hydrated magnesium phosphodiester complex may be compared with the recent crystallographic study of metal binding to yeast phenylalanine tRNA by Jack et al.[78] These authors found three *strong* binding sites for magnesium, and inferred the metal coordination from the refined atomic coordinates of the macromolecule. They concluded that the magnesium ions in two of the sites link "close phosphate groups"; it is possible that these O···O distances correspond to our vicinal inner sphere coordination O···O distances. Jack et al. characterized the magnesium in the third binding site as having "a rather special environment linking single-stranded regions of the dihydrouridine and the T-ψ-C loops". They speculated that: "this site is probably involved in the first stage of melting of the tRNA molecule, and may be critical for stabilizing the tertiary structure". The only acceptable binding at magnesium site no. 3 (ref 78, Table 2) is that of the phosphoryl oxygen G19-OR. On the other hand, *distal* type coordinations are actually found at samarium sites no. 3 and 5 (ref 78, Table 1). *Vicinal* type coordinations are found at samarium sites no. 1 and 2, just as they are at magnesium sites no. 1 and 2, as pointed out by Jack et al.

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Registry No.—**4**, 63866-80-8; **5**, 19015-72-6; **6**, 63865-88-3; diphenyl methyl phosphate, 115-89-9.

Supplementary Material Available: Table V, positional and thermal parameters; Table VI, some least-squares planes and dihedral angles between planes; and Figure 3, computer-generated stereo drawing of one formula unit of compound **6** (5 pages). Ordering information is given on any current masthead page. (The structure factors, 40 pages, can be obtained by writing to the senior author.)

References and Notes

(1) (a) Institute for Cancer Research, Philadelphia, Pa. Research supported by U.S. Public Health Services Grants GM21589, CA06427, and RR05539 from the National Institutes of Health and an appropriation from the Commonwealth of Pennsylvania. (b) State University of New York at Stony Brook. Research supported by Grant CHE7616785 from the National Science Foundation and Grant GM20672 from the National Institute of General Medical Sciences.
(2) C. T. Li and C. N. Caughlan, *Acta Crystallogr.*, **19**, 637 (1965).
(3) M. U. Haque and C. N. Caughlan, *J. Am. Chem. Soc.*, **88**, 4124 (1966).
(4) G. D. Smith, A. Fitzgerald, C. N. Caughlan, K. A. Kerr, and J. P. Asmore. *Acta Crystallogr., Sect. B*, **30**, 1760 (1974).
(5) C. N. Caughlan and M. U. Haque, *Inorg. Chem.*, **6**, 1998 (1967).
(6) J. M. A. Hoeflake, *Recl. Trav. Chim. Pays-Bas*, **36**, 24 (1916).
(7) Y. Kyogoku and Y. Iitaka. *Acta Crystallogr.*, **21**, 49 (1966).
(8) J. Hazel and R. L. Collin, *Acta Crystallogr., Sect. B*, **28**, 2951 (1972).
(9) K. N. Trueblood, P. Horn, and V. Luzzati, *Acta Crystallogr.*, **14**, 965 (1961).
(10) H. Sternglanz, E. Subramanian, J. C. Lancey, Jr., and C. E. Bugg, *Biochemistry*, **15**, 4797 (1976).
(11) G. R. Clark and J. D. Orbell, *J. Chem. Soc., Chem. Commun.*, 697 (1975).
(12) K. Aoki, *J. Chem. Soc., Chem. Commun.*, 748 (1976).
(13) N. C. Seeman, J. M. Rosenberg, F. L. Suddath, J. J. P. Kim, and A. Rich, *J. Mol. Biol.*, **104**, 109 (1976).
(14) B. Hingerty, E. Subramanian, S. D. Stellman, S. B. Boyde, T. Sato, and R. Langridge, *Biopolymers*, **14**, 227 (1975).
(15) J. M. Rosenberg, N. C. Seeman, R. O. Day, and A. Rich, *J. Mol. Biol.*, **104**, 145 (1976).
(16) A. Chwang and M. Sundaralingam, *Acta Crystallogr., Sect. B*, **30**, 1233 (1974).
(17) W. Saenger, D. Suck, and F. Eckstein, *Eur. J. Biochem.*, **46**, 559 (1974).
(18) W. Saenger and F. Eckstein, *J. Am, Chem. Soc.*, **92**, 4712 (1970).
(19) M. K. Wood, M. Sax, and J. Pletcher, *Acta Crystallogr., Sect. B*, **31**, 76 (1975).
(20) O. Kennard, N. W. Isaacs, W. D. S. Mutherwell, J. C. Coppola, D. L. Wampler, A. C. Larson, and D. G. Watson, *Proc. R. Soc. London, Ser. A*, **325**, 401–436 (1971).
(21) G. A. Jeffrey and M. Sundaralingam, *Adv. Carbohydr. Chem.*, **30**, 445 (1974).
(22) (a) M. A. Viswamitra, T. P. Seshadri, M. L. Post, and O. Kennard, *Nature (London)*, **258**, 497 (1975); (b) M. A. Viswamitra, M. V. Hosur, Z. Shakked, and O. Kennard, *ibid.*, **262**, 234 (1976).
(23) D. Suck, P. C. Manor, and W. Saenger, *Acta Crystallogr., Sect. B*, **32**, 1727 (1976).
(24) S. Abrahamson and I. Pascher, *Acta Crystallogr.*, **21**, 79 (1966).
(25) M. Sundaralingam and L. H. Jensen, *Science*, 1035 (1965).
(26) P. B. Hitchcock, P. Mason, K. M. Thomas, and G. G. Shipley, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 3036 (1974).
(27) F. S. Ezra and R. L. Collin, *Acta Crystallogr., Sect. B*, **29**, 1398 (1973).
(28) C. H. Schwalbe, R. Goody, and W. Saenger, *Acta Crystallogr., Sect. B*, **29**, 2264 (1973).
(29) The following abbreviations are used: CN = coordination number; MDP = magnesium diphenyl phosphate; aquo-MDP = pentaaquohexa(diphenyl phosphato)trimagnesium(II); TBP = trigonal bipyramid(al); TP = tetragonal pyramid(al); TR = turnstile rotation.
(30) D. J. Sutor, *Acta Crystlallogr.*, **23**, 418 (1967).
(31) A. G. Nord and P. Kierkegaard, *Acta Chem. Scand.*, **22**, 1466 (1968).
(32) A. A. Khan and W. H. Baur, *Acta Crystaliogr., Sect. B*, **28**, 683 (1972).
(33) J. R. Rea and E. Kostiner, *Acta Crystallogr., Sect. B*, **28**, 3461 (1972).
(34) C. Calvo, *Acta Crystallogr.*, **23**, 289 (1967).
(35) A. G. Nord and K. B. Lindberg, *Acta Chem. Scand., Ser. A*, **29**, 1 (1975).
(36) F. Ramirez, R. Sarma, Y.-F. Chaw, T. McCaffrey, J. F. Marecek, B. McKeever, and D. Nierman, *J. Am. Chem. Soc.*, **99**, 5285 (1977).
(37) R. J. W. Cremlin, G. W. Kenner, J. Mather, and A. Todd, *J. Chem. Soc.*, 528 (1958).
(38) "International Tables for X-Ray Crystallography", 2nd ed, Vol. 3, Kynoch Press, Bermingham, 1968, p 202.
(39) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).
(40) The structure $[C_2H_5Mg_2Cl_3(C_4H_8O)_3]_2$ of Toney and Stucky[41] can be viewed as the association of two $C_2H_5MgCl(C_4H_8O)$ and two $MgCl_2(C_4H_8O)_2$ moieties. The formula unit contains five four-membered bridging units consisting of Mg and Cl atoms, two of the latter having CN3 and four have CN2. The geometry about CN6 Mg is a distorted octahedron, while that about CN5 Mg is neither regular TBP nor regular TP. There are, in fact, striking similarities between this structure[41] and the aquo-MDP (**6**).
(41) J. Toney and G. D. Stucky, *J. Organomet. Chem.*, **28**, 5 (1971).
(42) J. Toney and G. D. Stucky, *Chem. Commun.*, 1168 (1967).
(43) K. R. Andress and J. Gunderman, *Z. Kristallogr., Kristallogeom., Kristallphys., Kristallchem., Abt. A*, **87**, 345 (1934).
(44) W. H. Baur and J. L. Rolin, *Acta Crystallogr., Sect. B*, **28**, 1448 (1972).
(45) C. W. Stephan, C. H. MacGillavry, and B. Koch, *Acta Crystallogr., Sect. B*, **28**, 1029 (1972b).
(46) G. DeWith, S. Harakema, and G. J. van Hummell, *Acta Crystallogr., Sect. B*, **32**, 1980 (1976).
(47) J. P. Deloume, H. Loiseleur and G. Thomas, *Acta Crystallogr., Sect. B*, **29**, 668 (1973).
(48) B. Morosin, *Acta Crystallogr.*, **22**, 315 (1967).
(49) W. H. Baur, *Acta Crystallogr., Sect. B*, **30**, 1195 (1974).
(50) R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960).
(51) R. Sarma, F. Ramirez, and J. F. Marecek, *J. Org. Chem.*, **41**, 473 (1976).
(52) P. Narayanan, H. M. Berman, F. Ramirez, J. F. Marecek, Y.-F. Chaw, and V. A. V. Prasad, *J. Am. Chem. Soc.*, **99**, 3376 (1977).
(53) For a different treatment of this problem see: (a) R. R. Holmes, *Acc. Chem. Res.*, **5**, 296 (1972); (b) *J. Am. Chem. Soc.*, **97**, 5359 (1975).
(54) (a) P. Gillespie, P. Hoffmann, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsolis, and I. Ugi, *Angew. Chem., Int. Ed., Engl.*, **10**, 687 (1971); (b) I. Ugi and F. Ramirez, *Chem. Br.*, **8**, 198 (1972).
(55) F. Schröder and H. Spandau, *Naturwissenschaften*, **53**, 360 (1966).
(56) M. Vijayan and M. A. Viswamitra, *Acta Crystallogr.*, **23**, 1000 (1967).
(57) M. C. Pérucaud and M. T. LeBihan, *Acta Crystallogr., Sect. B*, **24**, 1502

(1968).
(58) M. D. Joesten, M. S. Hussain, and D. G. Lenhart, *Inorg. Chem.*, **9**, 151 (1970).
(59) R. Sarma, F. Ramirez, B. McKeever, Y.-F. Chaw, J. F. Marecek, D. Nierman, and T. McCaffrey, *J. Am. Chem. Soc.*, **99**, 5289 (1977).
(60) G. Stucky and R. E. Rundle, *J. Am. Chem. Soc.*, **86**, 4825 (1964).
(61) (a) L. G. Guggenberger and R. E. Rundle, *J. Am. Chem. Soc.*, **86**, 5344 (1964); (b) *ibid.*, **90**, 5375 (1968).
(62) H. Schibilla and M. T. LeBihan, *Acta Crystallogr.*, **23**, 332 (1967).
(63) P. T. Moseley and H. M. M. Shearer, *Chem. Commun.*, 279 (1968).
(64) G. D. Stucky and R. E. Rundle, *J. Am. Chem. Soc.*, **86**, 4821 (1964).
(65) M. Vallino, *J. Organomet. Chem.*, **20**, 1 (1969).
(66) K. Manning, E. A. Petch, H. M. M. Shearer, and K. Wale, *J. Chem. Soc., Chem. Commun.*, 107 (1976).
(67) A. I. Pozhidaev, T. N. Polinova, and M. A. Poraikoshits, *Acta Crystallogr., Sect. A*, **28**, 576 (1972).
(68) A. Zeman and J. Zeman, *Acta Crystallogr.*, **14**, 835 (1961).
(69) G. V. Gibbs and J. V. Smith, *Am. Mineral.*, **50**, 2023 (1965).
(70) Although the geometry about the magnesium in this structure was said to be TBP,[65] the angles given and the fact that the methyl and bromines are disordered do not permit a definitive assignment of configuration. Hence, the structure is drawn as an x^{o}-TR configuration, in which the value of x is undetermined.
(71) The following papers contain data on *nucleoside*–metal ion interactions (i.e., in the absence of phosphate groups): (a) P. DeMeester, D. M. L. Goodgame, T. J. Jones, and A. C. Skapskis, *Biochem. J.*, **139**, 791 (1974); (b) P. DeMeester, D. M. L. Goodgame, A. C. Skapskis and B. T. Smith, *Biochim. Biophys. Acta*, **340**, 113 (1974); (c) E. Stetten, *Acta Crystallogr., Sect. B*, **30**, 1961 (1974); (d) E. Stetten and B. Thorstensen, *ibid.*, **30**, 2438 (1974); (e) D. J. Szalda, L. G. Marzilli, and T. J. Kistenmacher, *Inorg. Chem.*, **14**, 2078 (1975); (f) D. J. Szalda, T. J. Kistenmacher, and L. G. Marzilli, *ibid.*, **15**, 2783 (1976); (g) T. J. Kistenmacher, L. G. Marzilli, and D. J. Szalda, *Acta Crystallogr., Sect. B*, **32**, 186 (1976).
(72) A. S. Mildvan, *The Enzymes, 3rd Ed.*, **2**, Chapter 9 (1970).
(73) S. K. Dhar, "Metal Ions in Biological Systems", Plenum Press, New York, N.Y., 1973.
(74) G. L. Eichhorn, "Inorganic Biochemistry", Elsevier, Amsterdam, 1973, Chapter 33.
(75) R. M. Clement, J. Sturm, and M. P. Daune, *Biopolymers*, **12**, 405 (1973).
(76) H. Sigel, Ed., "Metal Ions in Biological Systems", Vol. 1–6, Marcel Dekker, New York, N.Y., 1974–1976.
(77) I. Sissoeff, J. Grisvard, and E. Guille, *Prog. Biophys. Mol. Biol.*, **31**, 165 (1976).
(78) A. Jack, J. E. Ladner, D. Rhodes, R. S. Brown, and A. Klug, *J. Mol. Biol.*, **111**, 315 (1977).

Specificity in the Micellar Catalysis of a Hofmann Elimination[1,2]

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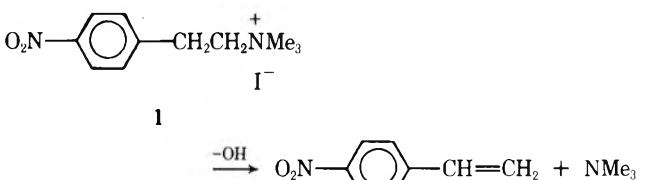
The E2 elimination of trimethylamine from *p*-nitrophenethyltrimethylammonium iodide in 0.1 M NaOH is inhibited by anionic micelles of sodium dodecyl sulfate. Cationic micelles of hexadecyltrimethylammonium bromide and zwitterionic micelles of *N*,*N*-dimethyl-*N*-dodecylglycine have little effect on the reaction rate. However, micelles of *N*,*N*-dimethyl-*N*-hexadecyl-*N*-(2-hydroxethyl)ammonium bromide and *N*,*N*-dimethyl-*N*-hexadecyl-*N*-(3-hydroxypropyl)ammonium bromide are catalytic at high alkali concentrations (pH >12.0), where the surfactants are converted into proteophilic zwitterions which participate as bases in the elimination. This is a significant exception to the general observation that all surfactants of the same charge type cause the same type of reactivity change.

Surfactants affect the reactivity of molecules hydrophobic enough to be taken into micelles and, in the last few years, considerable attention has been directed to the catalysis observed in many cases.[3-5] We recently reported that cationic micelles of hexadecyltrimethylammonium bromide (CTABr) markedly increase the acidity of carbon acids.[6] We have since examined the catalytic effectiveness of CTABr and other surfactants toward the hydroxide-catalyzed elimination reaction of 4-nitrophenethyltrimethylammonium iodide (1).



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This reaction received some attention by Hughes and Ingold[7] and more recently by Hodnett[8] but this is the first reported examination of the rate of 4-nitrostyrene formation as a function of pH, temperature, and surfactant concentration. This is the first reported study of the effect of micelles on the synthetically important Hofmann elimination reaction.

Experimental Section

Materials. Sodium dodecyl sulfate (Aldrich) and CTABr (Matheson) were purified by the methods of Grunwald.[9] *N*,*N*-Dimethyl-*N*-hexadecyl-*N*-(2-hydroxethyl)ammonium bromide (2) was prepared by quaternizing *N*,*N*-dimethylethanolamine (Aldrich) with 1-bromohexadecane (Eastman) in refluxing 2-propanol and was purified by recrystallization from EtOH: mp 194–204 °C (lit.[10] 208–210 °C); NMR (D_2O) δ 3.10 (s, NCH_3), 1.26 [s, $C(CH_2)_n$], 0.86 (t, CCH_3). *N*,*N*-Dimethyl-*N*-dodecylglycine[11] (3) was prepared by quaternizing *N*,*N*-dimethylglycine with 1-bromododecane (Aldrich) in 2-propanol and was purified by recrystallization from EtOH–Et_2O: mp 200–205 °C (lit.[11] 183 °C); NMR (D_2O) δ 3.29 (s, NCH_3), 1.31 1s, $C(CH_2)_n$], 0.85 (t, CCH_3). The *N*,*N*-dimethylglycine was prepared by reductive methylation[12] and was purified by recrystallization from EtOH–Et_2O. *N*,*N*-Dimethyl-*N*-hexadecyl-*N*-(3-hydroxypropyl)ammonium bromide (4) was prepared by quaternizing *N*,*N*-dimethylpropylamine (Aldrich) with 1-bromohexadecane (Eastman) in refluxing 2-propanol and was purified by recrystallization from EtOH: mp 84–89 °C; NMR (D_2O) δ 3.12 (s, NCH_3), 1.32 [s, $C(CH_2)_n$], 0.89 (t, CCH_3). *n*-Octylamine was distilled under reduced pressure and stored over NaOH.

4-Nitrophenethyltrimethylammonium Iodide (1). Phenethylamine (22 g, 0.13 mol) was slowly added to 100 mL of rapidly stirred red fuming nitric acid at 5 °C. After 3 h the reaction mixture was poured onto ice and made alkaline with NaOH solution. The product was extracted with ether; the extract was dried (Na_2SO_4) and evaporated to dryness. The crude 4-nitrophenethylamine (22 g, 0.13 mol) was combined with 100 mL of 2-propanol, 16 g of K_2CO_3, and 137 g (60 mL, 0.91 mol) of iodomethane and heated at reflux for 60 h. When cool the reaction mixture solidified. Part of the solid was soluble in hot EtOH, and this solution yielded yellow crystals of product which were recrystallized twice: mp 195–196 °C (lit.[7] 199 °C); NMR (Me_2SO-d_6) δ 3.40 (s, NCH_3), 3.53 (s, NCH_2), 3.84 (m, $ArCH_2$), 8.00 and 8.55 (AA′BB′ pattern, ArH). Anal. Calcd for $C_{11}H_{17}N_2O_2I$: C, 39.30; H, 5.10; N, 8.33; I, 37.75. Found: C, 39.27; H, 5.17; N, 8.49; I, 37.82.

Kinetics. The reactions were followed spectrophotometrically at 320 nm using a Beckman Model DB spectrophotometer with a water-jacketed cell compartment. The temperature was maintained within 0.1 °C by a Lauda K2/R constant temperature water circulator. All surfactant solutions were prepared on the day of use from carbonate-free NaOH solution and stored in tightly stoppered flasks. The NaOH stock solutions were prepared from freshly boiled, N_2 satu-

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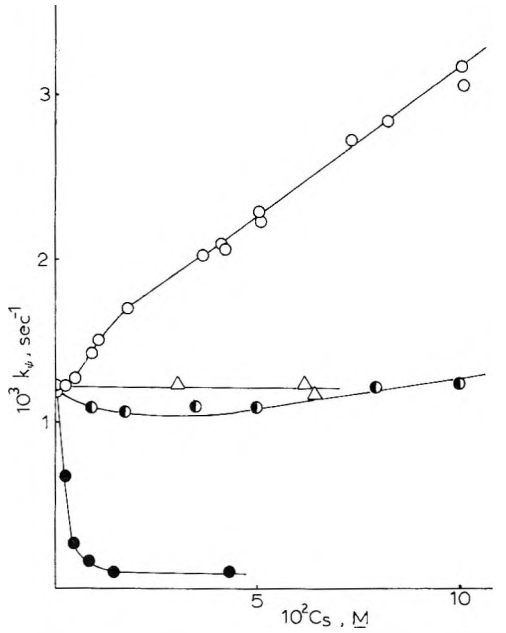

Figure 1. The observed first-order rate constant k_ψ for 4-nitrostyrene formation from 1 in 0.1 M NaOH at 39 °C as a function of surfactant concentration. The surfactants are (○) 2, (△) 3, (◐) CTABr, and (●) NaLS.

rated, glass-distilled water and standardized by titration with potassium acid phthalate (phenolphthalein). The pH of the 0.10 M NaOH stock solutions was always found to be 12.93 ± 0.06 whenever aliquots were removed (vs. pH 12.0 standard buffer). All kinetic runs were initiated by injecting 50 μL of an aqueous substrate stock solution into a cuvette of the appropriate buffer or NaOH solution in the spectrophotometer cell compartment. The first-order rate constants, k_ψ, were evaluated from plots of log $(A_\infty - A_t)$ vs. time (seconds) where A_t and A_∞ are the absorbances at time t and after 10 half-lives, respectively. The A_∞ values were stable except in the presence of *n*-octylamine, at low pH (<12) or with higher concentrations of 2 than described here. The rate constants for *n*-octylamine runs were evaluated by the method of Guggenheim. All rate constants used to evaluate activation parameters were taken from lines with least-squares correlation coefficients greater than 0.998. The second-order rate constants, k_{II}, were calculated using the stoichiometric NaOH concentrations.

Results and Discussion

In the absence of surfactant the values of $10^4 k_\psi$, the first-order rate constant, are 12.2, 9.8, 6.4, 3.0, and 1.1 s^{-1} for 0.10, 0.08, 0.05, 0.02, and 0.01 M NaOH, respectively, at 39 °C. The ionic strength was maintained at 0.10 M with NaCl. A plot of k_ψ vs. hydroxide ion concentration is linear indicating an E2 mechanism. The second-order rate constant is 1.16×10^{-2} M^{-1} s^{-1} at 39 °C. The observed $10^4 k$ values for the reaction in 0.10 M NaOH at 25.0, 35.0, 39.0, 45.0, and 49.7 °C are 4.0, 8.9, 12.0, 22, and 30, respectively, corresponding to $\Delta H^\ddagger$ and $\Delta S^\ddagger$ values of 15.2 kcal/mol and −23 eu. The large negative entropy is consistent with a bimolecular (E2) process. The solvent-isotope effect is also consistent with an E2 mechanism. The first-order rate constant in 0.0135 M NaOD–D_2O at 39 °C is 2.97×10^{-4} s^{-1}. This corresponds to a solvent-isotope effect, k_{HO^-}/k_{DO^-}, of 0.53 which compares very favorably with the values of 0.56 and 0.58 reported by Thornton[13] for $PhCH_2CH_2N^+Me_3Br^-$ and *p*-$ClPhCH_2CH_2N^+Me_3Br^-$, respectively, at 80.5 °C.

The reaction is inhibited by NaCl and $Me_3N^+CH_2CH_2O$-HI^- in 0.10 M NaOH. The values of $10^4 k_\psi$ are 6.08, 4.6, and 3.3 s^{-1} for 0.488, 1.29, and 3.41 M NaCl, respectively, and 7.24 and 6.8 s^{-1} for 0.313 and 1.87 M $Me_3N^+CH_2CH_2OHI^-$ at 39 °C. Inhibition by added electrolytes is the expected situation for the reaction of an anion with a cation.[14]

Surfactant Effects. The effect of sodium dodecyl sulfate (NaLS), CTABr, 2, and 3 on k_ψ for 0.10 M NaOH at 39 °C is given in Figure 1; in this figure C_s represents the concentration of surfactant. The effect of higher CTABr concentrations and the effect of added solutes at high CTABr concentrations are given in Table I.

Table I. Effect of CTABr and Additional Solutes

C_{CTABr}, M	Solute	C_{solute}, M	$10^3 k_\psi$,[a] s^{-1}
			1.16
0.106			1.39
0.178			1.4
0.205			1.52
0.006	Igepal[b]	0.023	1.08
0.027	Igepal[b]	0.023	1.30
0.149	Igepal[b]	0.023	1.44
0.100	*n*-Octylamine	0.062	1.5
0.100	*n*-Octylamine	0.103	1.5

[a] First-order rate constant at 39 °C. [b] Igepal CO-630: nonylphenoxypoly(ethyleneoxy)ethanol (General Aniline and Film Corp.).

Anionic micelles of NaLS retard the elimination by incorporating substrate, protecting it from hydroxide ions. Ester saponification is inhibited by anionic micelles for the same reason.[15] Anionic micelles may also retard elimination because the stabilizing interactions between the anionic micelle and cationic substrate are reduced upon transition state formation. Low concentrations (<0.1 M) of CTABr are not catalytic probably because little or no substrate is taken into the cationic micelle. The limited incorporation of cationic substrate into cationic micelles is consistent with our finding that the aromatic ^1H NMR signals of 1 in D_2O do not shift upfield upon the addition of enough CTABr to produce a 0.1 M solution. Upfield shifts are observed when aromatic solubilisates are incorporated into CTABr micelles.[16] Concentrations of CTABr high enough to incorporate substrate cause only a slight rate increase because the number of hydroxide ions per micelle is small at such CTABr concentrations. Mixtures of CTABr and the nonionic surfactant Igepal CO-630[17] are inhibitory at low CTABr/Igepal ratios and no more catalytic than CTABr alone at high ratios. Added *n*-octylamine does not appreciably increase the catalytic effectiveness of CTABr. There is a slow decline in the final absorbance reading (A_∞) in the presence of amines, probably because of the amine attack on the styrene. Micelles of the zwitterionic surfactant 3 are not catalytic.

Micelles of 2 are catalytic and, as Table II indicates, the extent of catalysis varies with the concentration of 2 in a complicated manner depending on the concentration of NaOH. The rate constant increases most steeply with the concentration of 2 when the hydroxide ion concentration is around 0.186 M. At hydroxide ion concentrations well above and below this value, the rate constant increases less steeply. We believe that a significant portion of the surfactant molecules is converted into the alkoxide (zwitterion) form at these NaOH concentrations and that 2 is catalytic because the proteophilic zwitterion acts as a base in the elimination. Another explanation is that the alkoxy form of the surfactant can act as an indirect general base which abstracts a proton from water, forming a hydroxide ion which then reacts with substrate. Such a reaction is kinetically indistinguishable from direct proton abstraction from the substrate by the alkoxide form of the surfactant.

$$HO^- + RN^+Me_2CH_2CH_2OH \rightleftharpoons H_2O + RN^+Me_2CH_2CH_2O^-$$

The catalysis is not just due to an electrostatic effect because the nonnucleophilic zwitterion 3 is not a catalyst.

Table II. Catalysis by 2 in NaOH Solution[a]

C_{NaOH}, M	10^2C_s,[b] M	10^3k_ψ,[c] s^{-1}	$k_{\psi cat}$[d]/$k_{\psi 0}$
0.010[e]		1.1	
0.010[e]	2.6	1.90	1.7
0.010[e]	8.3	3.25	3.0
0.010[e]	12.4	3.40	3.1
0.10		1.16	
0.10	0.50	1.29	1.11
0.10	0.91	1.43	1.23
0.10	1.05	1.52	1.31
0.10	1.81	1.72	1.48
0.10	3.63	2.04	1.76
0.10	4.10	2.11	1.82
0.10	4.20	2.06	1.78
0.10	4.78	2.06	1.78
0.10	5.03	2.24	1.93
0.10	7.26	2.74	2.36
0.10	8.20	2.85	2.45
0.10	10.6	3.21	2.77
0.186		2.26	
0.186	2.6	4.02	1.78
0.186	4.9	4.78	2.12
0.186	7.5	5.89	2.61
0.186	9.9	6.86	3.04
0.504		5.07	
0.504	1.5	6.53	1.29
0.504	2.9	8.69	1.71
0.504	6.2	11.4	2.25

[a] Rate constants measured at 39 °C. [b] Concentration of *N*,*N*-dimethyl-*N*-hexadecyl-*N*-(2-hydroxyethyl)ammonium bromide. [c] Observed first-order rate constant. [d] Ratio of the observed first-order rate constant to that observed at the same NaOH concentration without added surfactant. [e] Ionic strength maintained at 0.1 with 0.09 M NaCl.

Moreover, we have found that nonmicellar electrolytes retard the reaction.

The presence of an ionizable OH group is essential for catalysis. We found that micelles of **4** are catalytic and the extent of catalysis depends upon the NaOH concentration. The data in Table III indicate that $k_{\psi cat}/k_{\psi 0}$ (the ratio of rate constants in the presence and absence of **4**) increases more steeply with surfactant concentration in 0.624 M NaOH than in 0.0154 M NaOH. The surfactant **4** does not form as much zwitterion at the lower NaOH concentration.

Bunton and co-workers[18] have recently shown that micelles of **2** are catalytic bases in the transformation of the 3-bromo-3-phenylpropionate ion to the *trans*-cinnamate ion in dilute alkali. They estimated[10,18] a pK_a of 12.4 for **2** but found, as we did, that the extent of catalysis is not directly proportional to the base concentration. The fraction of surfactants converted into zwitterions is not directly proportional to the NaOH concentration because, unlike a monomeric species, a micellar acid does not have a constant K_a but one that depends on the net charge of the micelle[19] which reflects the extent of ionization and counterion binding. Moreover, the catalytic effectiveness of zwitterions may be higher when few are formed because the cationic substrate initial state would be destabilized relative to the transition state by the largely cationic micelle. Catalysis by **2** is inhibited by added NaCl; the 10^3k_ψ values (s^{-1}, 39 °C) observed for 0.10 M NaOH with 0.050 M **2** decreased from 2.24 to 1.44 and 1.38 with 0.88 and 1.16 M NaCl, respectively. Added NaCl increases the viscosity of alkaline solutions of **2**; a 0.050 M solution of **2** in 0.10 M NaOH with 3.5 M NaCl is opalescent and almost too viscous to pour. We were not able to examine the catalytic effectiveness of concentrations of **2** greater than 0.10 M in 0.10 M NaOH because these solutions were too viscous for uniform mixing. Also we could not directly verify the lack of catalysis by **2** at pH values significantly below the pK_a of **2** because product decomposition precluded stable infinities over such long reaction times.

Table III. Catalysis by 4 in NaOH Solution[a]

C_{NaOH}, M	10^2C_s,[b] M	10^4k_ψ,[c] s^{-1}	$k_{\psi cat}$[d]/$k_{\psi 0}$
0.0154		2.43	
0.0154	1.6	2.60	1.07
0.0154	8.1	3.55	1.44
0.0154	13.1	4.40	1.81
0.0964		11.2	
0.0964	2.1	15.7	1.40
0.0964	4.5	19.5	1.74
0.0964	7.5	25.7	2.29
0.0964	14.2	33.1	2.96
0.0624		56.1	
0.624	2.0	79.7	1.42
0.624	4.5	106	1.88
0.624	11.7	168	2.99

[a] Rate constants measured at 39 °C. [b] Concentration of *N*,*N*-dimethyl-*N*-hexadecyl-*N*-(3-hydroxypropyl)ammonium bromide. [c] Observed first-order rate constant. [d] Ratio of the observed first-order rate constant to that observed at the same NaOH concentration without added surfactant.

We have found a significant exception to the general observation that all surfactants of the same charge type cause the same type of reactivity change and we are currently investigating the catalytic effectiveness of other β-hydroxy quaternary ammonium surfactants on the Hofmann elimination reactions of chiral compounds.

Registry No.—**1**, 7101-10-2; **2**, 20317-32-2; **3**, 683-10-3; **4**, 63989-29-7; *N*,*N*-dimethylethanolamine, 108-01-0; 1-bromohexadecane, 112-82-3; *N*,*N*-dimethylglycine, 1118-68-9; 1-bromododecane, 143-15-7; *N*,*N*-dimethylpropylamine, 926-63-6; phenethylamine, 64-04-0; 4-nitrophenethylamine, 24954-67-4; iodomethane, 74-88-4; CTABr, 57-09-0.

References and Notes

(1) Support of this work by the Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.
(2) Presented in preliminary form at the 11th Western Regional Meeting of the American Chemical Society, North Hollywood, Calif., Oct 30, 1975.
(3) E. H. Cordes and R. B. Dunlap, *Acc. Chem. Res.*, **2**, 329 (1969); E. H. Cordes and C. Gitler, *Prog. Bioorg. Chem.*, **2**, 1 (1973).
(4) E. J. Fendler and J. H. Fendler, *Adv. Phys. Org. Chem.*, **8**, 271 (1970).
(5) C. A. Bunton, *Prog. Solid State Chem.*, **8**, 239 (1973).
(6) M. J. Minch, M. Giaccio, and R. Wolff, *J. Am. Chem. Soc.*, **97**, 3766 (1975).
(7) E. D. Hughes and C. K. Ingold, *J. Chem. soc.*, 523 (1933); E. D. Hughes, C. K. Ingold, and C. S. Patel, *ibid.*, 526 (1933).
(8) E. M. Hodnett and J. J. Flynn, Jr., *J. Am. Chem. Soc.*, **79**, 2300 (1957); E. M. Hodnett and W. J. Dunn, *J. Org. Chem.*, **32**, 4116 (1967).
(9) E. F. J. Duynstee and E. Grunwald, *J. Am. Chem. Soc.*, **81**, 4540 (1959).
(10) C. A. Bunton and L. G. Ionescu, *J. Am. Chem. Soc.*, **95**, 2912 (1973).
(11) A. H. Beckett and R. J. Woodward, *J. Pharm. Pharmacol.*, **15**, 422 (1963).
(12) R. E. Bowman and H. H. Straud, *J. Chem. Soc.*, 342 (1950).
(13) L. F. Steffa and E. R. Thornton, *J. Am. Chem. Soc.*, **89**, 6149 (1967).
(14) M. R. Wright *J. Chem. Soc. B*, 545–547 (1968).
(15) F. M. Menger and C. E. Portnoy, *J. Am. Chem. Soc.*, **89**, 4698 (1967).
(16) C. A. Bunton, M. J. Minch, J. Hidalgo, and L. Sepulveda, *J. Am. Chem. Soc.*, **95**, 3262 (1973).
(17) Nonylphenoxypoly(ethyleneoxy)ethanol was generously provided by GAF Corp.
(18) C. A. Bunton, A. A. Kamego, and P. Ng, *J. Org. Chem.*, **39**, 3469 (1974).
(19) S. H. Yalkowsky and G. Zografi, *J. Pharm. Sci.*, **59**, 798 (1970).

Fragmentation of a Pyrazolenine Epoxide to an Unstable Oxabicyclobutane

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4,5-Epoxy-3,5-diphenyl-3-methyl-1-pyrazolenine (**1b**) pyrolyzes to a 2.8:1 mixture of (*E*)-dypnone **6a** and (*Z*)-2,3-diphenyl-2-butenal (**7a**). The latter product is most likely formed from an oxabicyclobutane intermediate. Photolysis of the epoxypyrazolenine (**1b**) does not extrude N_2, but rearranges to a mixture of two azine aldehydes **10a,b.**

The 2-oxabicyclobutane molecule is a close relative of several well-known isomeric systems which include cyclopropanones, epoxyallenes, and oxetenes. No one has yet prepared any member of the oxabicyclobutane family. The best evidence for oxabicyclobutanes as an intermediate is from kinetic studies of the peracid oxidation of cyclopropenes.[3,4] These studies were primarily aimed, however, at mechanistic questions. In this paper, we present our attempts to prepare oxabicyclobutanes by extrusion of nitrogen from bicyclic azo epoxides. This route is successful for the preparation of certain substituted bicyclobutanes, for example,[5]

Results

In an earlier report,[6] we studied the reactions of pyrazolenine epoxide **1a.** Although thermal extrusion of nitrogen gave mesityl oxide, sensitized and direct irradiation gave only

1a, $R_1 = R_2 = R_3 = Me$

azine aldehydes. Instead of C–N bond cleavage, irradiation initiated a vinylagous epoxide–carbonyl rearrangement that did not lead to loss of nitrogen.

In an attempt to eliminate the photolytic rearrangement, we have studied the chemistry of epoxide **1b.** The phenyl substituents in **1b** might stabilize the transition state for C–N bond cleavage and successfully lead to an oxabicyclobutane.

The synthesis of **1b** is shown below. Treatment of known[7] pyrazolenine **2** with acetyl hypobromite gave a 5:1 mixture of two bromo acetates, **3a** and **3b.** On treatment with methoxide, the mixture gave a small yield of the desired epoxide **1b** (from **3b**).

The major product from the methoxide treatment of **3a,b** was bromo alcohol **4a.** Acetylation of the alcohol **4a** regenerated acetate **3a.** The stereochemistry of the **3a–4a** pair is unknown, although the *lack* of epoxide formation from **3a** suggests that **3a** is a *cis*-bromoacetate.[8]

The stereochemistry of epoxide **1b** at position C-3 can be tentatively assigned from the ^{13}C NMR spectrum. The methyl carbon on C-3 resonates at δ 17.73 and is a *clean* quartet (J = 130 Hz). The quartet is due to geminal coupling with the methyl hydrogens. The absence of further splitting (≤1 Hz)

5

suggests that the dihedral angle between the C-3 methyl and C-4 hydrogen is near 90°. Vicinal coupling constants between ^{13}C and H follow the familiar Karplus relationship where small dihedral angles produce larger coupling constants than angles near 90°.[9]

In order to show that a stereochemical dependence of vicinal coupling constants exists, we have obtained the complete ^{13}C NMR spectrum of epoxide **1a.** This epoxide has methyl C's

1a

at position 3 that are cis and trans to the epoxide H. Dreiding models show an 85° dihedral angle between the *trans*-methyl C and the epoxide H. The angle between the *cis*-methyl C and the epoxide H is only ~25°. If the sterochemical assignment of structure **5** is correct, one of the methyl carbon nuclei on C_3 in compound **1a** will show no coupling to the epoxide H, while

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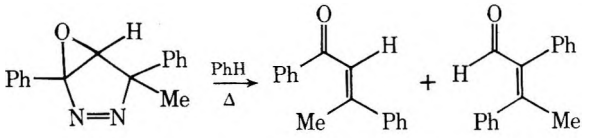
the other methyl carbon will show a finite coupling to the epoxide H.

The ^{13}C NMR of epoxide **1a** shows a remarkable set of coupling relationships. One methyl C at δ 13.4 is a clean quartet (J = 129 Hz) due to geminal ^{13}C–H coupling. Another methyl C at δ 19.1 is a quartet of quartets (J = 4, 129 Hz). The third methyl C at δ 22.1 is a doublet of quartets of quartets (J = 2, 5, 129 Hz). The latter two C's are the geminal methyl C's. Both show large geminal coupling with their respective H's (q, J = 129 Hz). Both also show mutual coupling with each other's three protons (q, J = 4–5 Hz), but, significantly, only the C at δ 22.1 also shows a finite coupling to the epoxide H (d, J = 2 Hz). This shows that the two geminal methyl C's do couple differently to the epoxide hydrogen. We don't have experimental proof which ^{13}C-methyl has no observable coupling with the epoxide hydrogen. Theoretically, however, it is the *trans*-methyl carbon in both structures **5** and **1a** which fails to show an observable coupling to the epoxide hydrogen.

The epoxide methyl ^{13}C at δ 13.4 also doesn't couple with the epoxide H. This result is not surprising, since vicinal coupling constants between two epoxide hydrogen nuclei are smaller (~2–4 Hz)[10] than might be anticipated.

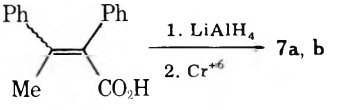
The pyrolysis of epoxide **1b** gave a 90% conversion to two major products, **6a** and **7a**, in a ratio of ~2.8:1. Both products



1b **6a** **7a**

were identified by comparison with authentic samples. Furthermore, a control experiment showed that (*Z*)-dypnone **6b** and (*E*)-2,3-diphenyl-2-butenal **7b** were not formed but were stable to the reaction conditions.

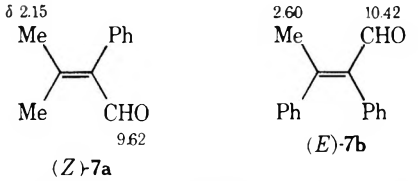
The two geometric isomers **7a,b** have not been previously distinguished. One of the two isomers had been prepared before by both Breslow[11] and Padwa.[12] We have prepared both aldehyde isomers **7a,b** from acids **8a,b.**[13] There is a large



8a, b

amount of indirect NMR chemical-shift data which might be used to distinguish isomers **7a,b.** We feel, however, that the best evidence for distinguishing **7a** from **7b** is the fact that **7b** isomerizes to **7a** in acidic methanol. Aldehyde **7a** is therefore probably the *Z* isomer in accord with the well-known thermodynamic stabilities of the two isomers of stilbene[14a] and α,α'-dimethylstilbene.[14b]

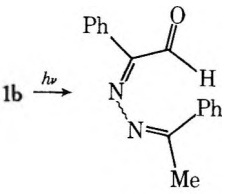
Additional evidence for assigning stereochemistry to **7a,b** is that the chemical shifts for the aldehyde and methyl protons



(*Z*)-**7a** (*E*)-**7b**

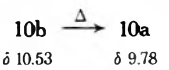
are higher field in **7a.** Such shifts are found in stilbene derivatives when the phenyl groups are cis to vicinal substituents.[15a] Furthermore, the methyl signal of (*Z*)-2-butenal is further downfield than in (*E*)-2-butenal.[15b]

Epoxide **1b** was irradiated through Pyrex in both PhH and CH_3CN solvents. Two products, **10a,b,** were formed at both short and long conversions. The yield of the two products was ~90%. The two aldehydes show ^1H NMR singlets at δ 9.78 and



10a, b

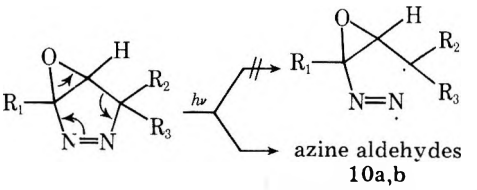
10.53. Heating of the product mixture at 85 °C caused conversion of **10b** into **10a.** This evidence, plus other spectral evidence (see Experimental Section), and a $C_{16}H_{14}ON_2$ empirical formula show that the irradiation caused a vinylogous epoxide–carbonyl rearrangement to produce two isomeric



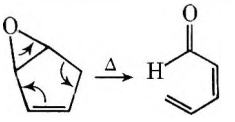
azine aldehydes **10a,b.** Further work to characterize these photoproducts was not done, since the result completely parallels the result found for the irradiation of epoxide **1a.**[6]

Discussion

Our hope was that the phenyl substituents of epoxide **1b** might stabilize the transition state for C–N bond cleavage and thereby reduce the photochemical epoxide rearrangement. The long-wavelength UV (λ_{max} 365), however, suggests that the π^* system of the azo group overlaps substantially with the strained epoxide σ bond. The pyrazolenine **2,** where such π-type conjugation is maximum, has λ_{max} 366 nm. As a result of the extensive conjugation of the epoxide group with the azo π^* system, the n,π^* excitation energy initiates a vinylogous epoxide–carbonyl rearrangement instead of C–N bond cleavage.



This rearrangement reaction has been observed previously with epoxide **1a.**[6] Another precedent is the known conversion of cyclopentadiene monoepoxide to pentadienal.[16] This re-

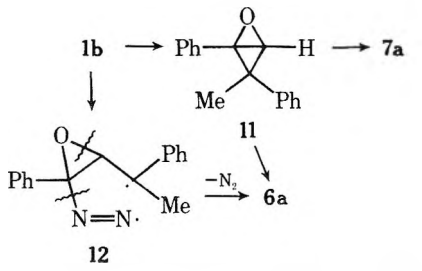


action, however, occurs in the ground-state manifold. In the ground state, epoxides **1a,b** do not undergo the vinylogous epoxide–carbonyl rearrangement. Rather, the weak C–N bonds fragment with the extrusion of N_2.

These results fit into a coherent scheme. The kinetically weakest bonds (most reactive) in the excited states of epoxides **1a,b** are not the C–N bonds, but rather the strained, π^*-conjugated σ bonds of the epoxide moiety. In the ground electronic state, the C–N bonds are the weakest bonds which do fragment with the extrusion of N_2. When the C–N bonds are replaced with the stronger C–C bonds in cyclopentadiene monoepoxide, then the weakest, most reactive bonds are once again the strained epoxide σ bonds.

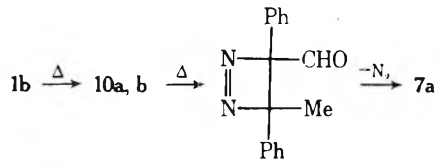
The most significant result of this work was the finding that aldehyde **7a** was a product in the pyrolysis of epoxide **1b.** No aldehydes were found in the previous study with epoxide **1a.**[6]

There are several possible routes for the formation of aldehyde **7a.** The only likely one is via oxabicyclobutane **11.** Such a mandatory intervention of an oxabicyclobutane is unprecedented.[3,4] Dypnone **6a** can also be formed from oxa-

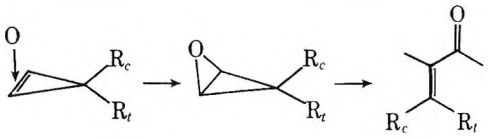


bicyclobutane **11**, although **6a** may be formed directly from diradical **12**.

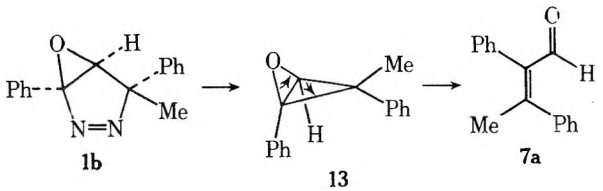
Another route to aldehyde **7a** might be the pyrolysis of azine aldehydes **10a,b**. We have observed no aldehydes, however, when an equilibrating mixture of azines **10a,b** was heated at 85 °C for 1 h.



A final question is whether the formation of the particular geometric isomer **7a** is *consistent* with an oxabicyclobutane intermediate. In part, the answer to this question is obscured by not having absolute proof for the stereochemistry of epoxide **1b**, but if one assumes that the stereochemistry of structure **5** (epoxide **1b**) is correct then a decision can be made. Our other studies on cyclopropane epoxidations show that the substituent trans to the entering oxygen is found predominantly cis to the carbonyl in the unsaturated enone product.[17]



The reaction shows an orbital symmetry control that is similar to the cycloreversion of bicyclobutanes. If epoxide **1b** (structure **5**) generates oxabicyclobutane **13** with retention of stereochemistry, then enal **7a** should be the major geometric isomer. This was observed.



Conclusion

Irradiation of epoxypyrazoline **1b** did not lead to loss of N_2. Rather, a rearrangement occurred to an azine aldehyde. Thermolysis of the epoxypyrazoline produces a reactive oxabicyclobutane which fragments to unsaturated carbonyl products. This is the first time this route to oxabicyclobutanes has been successful.

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. UV spectra were obtained on a Cary 118 spectrophotometer. Infrared spectra were obtained on Perkin-Elmer 137 or 467 spectrometers. NMR spectra were obtained on a JEOLCO C-60 HL, MH-100, or PFT-100 spectrometer. Mass spectra were obtained on a Hitachi RMU-6E or DuPont 21-490B spectrometer. All solvent evaporations were done on a rotary evaporator. Elemental analyses were done by Chemalytics, Inc., Tempe, Arizona.

(*E*)- and (*Z*)-1,3-Diphenyl-2-buten-1-one [Dypnone (6a,b)]. The $AlCl_3$-catalyzed condensation of acetophenone was performed following the procedure of Calloway.[18] Distillation gave a 60% yield of (*E*)-dypnone **6a**: bp 150 °C (0.7 mm) [lit.[18] 160–165 (1 mm)]; IR (neat) 1660 cm^{-1}; ^1H NMR (CCl_4) δ 2.65 (d, J = 2 Hz, 3), 7.27 (br s, 1), 7.5–7.8 (m, 10), 8.1–8.2 (m, 2).

Irradiation of (*E*)-dypnone in ethanol by a sunlamp following the procedure of Lutz and Slade[19] gave a 1:2 mixture of (*E*)- and (*Z*)-dypnone. The ^1H NMR (CCl_4) absorptions of (*Z*)-dypnone **6b** were δ 2.25 (d, J = 2 Hz, 3), 6.41 (narrow triplet, 1), 6.9–7.9 (m, 10).

***syn*- and *anti*-(*E*)-1,3-Diphenyl-2-buten-1-one Tosylhydrazone.** The condensation of dypnone **6a** and tosylhydrazide was carried out by the procedure of Sato.[7] The product precipitated in 67% yield as a mixture of syn and anti isomers (stereochemistry unknown): mp 146–148 °C [lit.[7] 149–150 °C]; IR ($CHCl_3$) 3260, 1625, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) (I) δ 1.83 (s, 3), 2.38 (s, 3), 6.18 (s, 1), 6.9–8.0 (m, 15); (II) 2.32 (s, 3), 2.38 (s, 3), 5.88 (s, 1), 6.9–8.0 (m, 15).

3,5-Diphenyl-3-methylpyrazolenine (2). The NaH-induced decomposition of the tosylhydrazone was carried out by the procedure of Sato.[7] The collected crystalline precipitate was formed in 70% yield: mp 85–86 °C [lit.[7] 83–84 °C]; UV (hexane) 366 (ε 200), 283 (4000), 232 nm (18 800); IR ($CHCl_3$) 1650, 1600, 1495, 1450, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76 (s, 3), 7.1–7.5 (m, 9, looks like the vinyl H may be a singlet at 7.17), 7.8–8.2 (m, 2).

5-Bromo-4-acetoxy-3,5-diphenyl-3-methyl-1-pyrazoline (3a,b). A solution of 1.0 mL (19 mmol) of bromine (Mallinkrodt) in 20 mL of CCl_4 was added dropwise to a solution of 4.0 g (24 mmol) of silver acetate (Baker analyzed reagent) in 160 mL of CCl_4 at 0 °C (30 min). The mixture was stirred at 0 °C until the orange color turned to yellow (~30 min). The mixture was filtered, and 3.00 g (12.5 mmol) of 3,5-diphenyl-3-methylpyrazolenine (**2**) was added to the filtrate. The mixture was kept in the refrigerator overnight. A 50-mL portion of 50% (w/v) Na_2SO_3 and 5% (w/v) $NaHCO_3$ solution was added to decompose any unreacted acetyl hypobromite. The CCl_4 solution was washed with 50 mL of water and dried over sodium sulfate. The solvent was removed and gave 4 g (100%) of residue. Silica gel chromatography (Baker analyzed reagent, 40–140 mesh) with 1:1 hexane–$CHCl_3$ solution as eluent gave a 2-g (50%) mixture of impure bromoacetates, **3a,b**, in an approximate 5:1 ratio: IR ($CHCl_3$) 1750 cm^{-1}; ^1H NMR (CCl_4) of the major isomer **3a** 1.76 (s, 3), 2.22 (s, 3), 5.67 (s, 1), 7.0–7.5 (m, 10). The minor isomer has a 6.03 singlet for 1 H. The two isomers have not been isolated in pure forms.

4,5-Epoxy-3,5-diphenyl-3-methyl-1-pyrazoline (1b). A modified procedure of Ellington, Hey, and Meakins[20] was used. A 15.1-g portion (28.5 mmol) of the two isomers of 5-bromo-4-acetoxy-3,5-diphenyl-3-methyl-1-pyrazoline (**3**) in a 5:1 ratio (~70% pure) was dissolved in 150 mL of methanol and chilled to 0 °C. A 2.5-g portion (46 mmol) of sodium methoxide was added. The mixture was kept in the refrigerator for 2 h. The mixture was added to 200 mL of 1:1 CCl_4–hexane solution and washed with 200 mL of water. The organic layer was dried over sodium sulfate and concentrated to one-third of its original volume. The solution was stored in the refrigerator overnight to give 2.05 g (30%) of impure 5-bromo-4-hydroxy-3,5-diphenyl-3-methyl-1-pyrazoline (**4a**): mp 118 °C (dec); UV (MeOH) 346 nm (ε 100); IR ($CHCl_3$) 3540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (s, 3), 2.65 (d, J = 10 Hz, 1), 4.21 (d, J = 10 Hz, 1), 7.2–7.6 (m, 8), 7.7–7.9 (m, 2). The two doublets were often singlets in other spectra, showing that the coupling involves a hydroxyl proton. Anal. Calcd for $C_{16}H_{15}N_2BrO$: C, 58.02; H, 4.57; N, 8.45; Br, 24.13. Found: C, 57.90; H, 4.42; N, 7.50, Br, 26.33.

The solvent was evaporated from the filtrate. The residue was dissolved in 30 mL of CCl_4 and 120 mL of hexane. The solution was kept in the freezer for 2 weeks which resulted in 0.7 g of crude crystalline 4,5-epoxy-3,5-diphenyl-3-methyl-1-pyrazoline (**1b**). The crude product was recrystallized from CCl_4–hexane solution and yielded 0.3 g of epoxide **1b**: mp 102–103 °C; UV (hexane) 365 nm (ε 240); IR (CCl_4) 3000, 1495, 1450, 1410, 1220, 970, 695 cm^{-1}; ^1H NMR (CCl_4) δ 1.83 (s, 3), 3.79 (s, 1), 7.1–7.8 (m, 10); ^{13}C NMR ($CDCl_3$) δ 17.73 (q, J = 130 Hz), 68.96 (d of closely spaced multiplets, J = 200 Hz), 91.23 (s) 93.72 (s), 122–137 (m, 7 peaks are visible in the H-decoupled spectrum); MS (20 eV) *m/e* 250 (p, 1), 223 (6), 222 (41), 221 (100), 207 (12), 145 (21), 131 (12), 119 (53), 105 (41), 104 (47), 77 (29). Anal. Calcd for $C_{16}H_{14}ON_2$: C, 76.80; H, 5.60; N, 11.20. Found: C, 76.74; H, 5.85; N, 11.79; and C, 75.77; H, 5.66; N, 10.80.

5-Bromo-4-acetoxy-3,5-diphenyl-3-methyl-1-pyrazoline (3a). A 1.50-g portion (19.2 mmol) of freshly distilled acetyl chloride (Eastman Chemicals) was added dropwise to a stirring solution of 3.3 g (10 mmol) of bromohydrin **4a** in 80 mL of 1:1 pyridine–ether solution. The mixture was kept at 40 °C for 3 h and stirred overnight. The solution was filtered, and a 100-mL portion of ether was added to the filtrate. The resulting solution was washed with 160-mL of 6 M HCl solution and 100 mL of 5% (w/v) $NaHCO_3$ solution. The ether extract was dried over Na_2SO_4 and the solvent was evaporated. ^1H NMR of the residue showed a 1 to 1 mixture of the bromohydrin **4a** and the

bromoacetate **3a**. The mixture was dissolved in 50 mL of 1:1 CCl_4–hexane solution and refrigerated overnight and filtered. The solvent was evaporated from the filtrate to give 1.3 g (70%) of 80% pure 5-bromo-4-acetoxy-3,5-diphenyl-3-methyl-1-pyrazoline (**3a**): IR (neat) 3450, 1750, 1450, 1375, 1225 cm^{-1}; ^1H NMR ($CDCl_3$) same as before; see above.

This material, when hydrolyzed as above with NaOMe in MeOH, gave a 70% yield of 5-bromo-4-hydroxy-3,5-diphenyl-3-methyl-1-pyrazoline (**4a**). This compound was identified by ^1H NMR and IR.

3,3,5-Trimethyl-4,5-epoxy-1-pyrazoline (1a). The material was prepared as described by Friedrich, de Vera, Hoss, and Warren:[6] ^{13}C NMR ($CDCl_3$) δ 13.35 (q, J = 129 Hz), 19.05 (q of q, J = 4, 129 Hz), 22.14 (d of q of q, J = 2, 5, 129 Hz), 65.28 (m of d, J = 191, each multiplet has ca. seven peaks spaced ~3 Hz apart), 85.36 (m, ca. seven peaks spaced ~4 Hz apart), 90.34 (m, ca. four peaks spaced ~5 Hz apart).

Pyrolysis of 4,5-Epoxy-3,5-diphenyl-3-methyl-1-pyrazoline (1b). A 40-mg portion (0.16 mmol) of epoxide **1b** was dissolved in 250 μL of benzene-d_6 and placed in an NMR tube. A 2-μL portion of cyclohexane was added as an internal standard. The NMR tube was sealed in vacuo and heated at 85 °C. The disappearance of epoxide **1b** was first order with a half-life of ~2 h. As epoxide gradually disappeared, two new CH_3 signals appeared at 0.44- and 1.13-ppm downfield from cyclohexane in a ratio 1:2.8 with >90% proton balance. Another signal that is one-third as intense as the upfield CH_3 signal appeared 8.40-ppm downfield from cyclohexane. Comparison with authentic spectra in PhH-d_6 solution showed the two products to be (**Z**)-2,3-diphenylbut-2-en-1-al (**7a**) and (*E*)-dypnone (**6a**), respectively. Samples of (*Z*)-dypnone **6b** and (*E*)-aldehyde **7b** which have CH_3 signals downfield from cyclohexane by 0.54 and 0.76 ppm, respectively, were stable to the reaction conditions (in the presence of decomposing epoxide) but were not found.

The reaction mixture was thick-layer chromatographed on silica gel. Elution with CCl_4 produced two bands which were identified by ^1H NMR and IR as (*Z*)-aldehyde **7a** and (*E*)-dypnone **6a**.

1,2-Diphenylpropan-2-ol. The procedure of Hell[21] was used which condenses benzylmagnesium chloride and acetophenone. A 95% yield of crude alcohol was obtained: ^1H NMR (CCl_4) δ 1.45 (s, 3), 1.78 (s, 1), 2.90 (d, J = 12 Hz, 1), 3.00 (d, J = 12, 1 Hz), 6.8–7.3 (m, 10).

(*E*)-1,2-Diphenylpropene. The procedure of Koelsch[13] was used to dehydrate 1,2-diphenylpropan-2-ol with HOAc–H_2SO_4: yield 67%; mp 81–82 °C [lit.[13] 79–82 °C]; ^1H NMR (CCl_4) δ 2.22 (d, J = 1.5 Hz, 3), 6.70 (br s, 1), 7.0–7.5 (m, 10). The ^1H NMR agrees with the literature.[22]

1,2-Diphenyl-1,2-dibromopropane. A 40-mL (0.75 mol) portion of bromine (Mallinckrodt) was added to 145 g (0.750 mol) of (*E*)-1,2-diphenyl-1-propene in 800 mL of CCl_4 over a period of 20 min. The mixture was stirred for another 5 min. The excess bromine was removed by adding 150 mL of a 10% (w/v) sodium sulfite solution and stirring until the orange color disappeared (10 min). The product was recrystallized from the CCl_4 solution: yield 185.5 g (70%) of a 3:5 mixture of relatively pure diasteriomeric 1,2-diphenyl-1,2-dibromopropanes; mp 122–129 °C (dec); IR (CCl_4) 1500, 1455, 1450, 1380, 1220, 1040 cm^{-1}; ^1H NMR (CCl_4) (I) δ 2.42 (s, 3), 5.50 (s, 1), 6.8–7.6 (m, 10); (II) δ 2.34 (s, 3), 5.53 (s, 1), 7.0–7.6 (m, 10); MS (70 eV) *m/e* 356 (p + 4, 3), 354 (p + 2,7), 352 (p, 3), 273 (66), 194 (100), 179 (47), 105 (43), 91 (18). Anal. Calcd for $C_{15}H_{14}Br_2$: C, 50.88; H, 3.99; Br, 45.13. Found: C, 50.32; H, 3.82; Br, 46.52.

(*E*)- and (*Z*)-1-Bromo-1,2-diphenyl-1-propene. A modified procedure of Cram[23] was used. An alcoholic potash solution was prepared by adding 50 g (0.68 mol) of potassium hydroxide pellets (Fisher) to 720 mL of absolute ethanol. A 113-g (0.320 mol) portion of 1,2-diphenyl-1,2-dibromopropane was added. The resulting mixture was refluxed for 7 h and stirred overnight at room temperature. The mixture was filtered. The precipitate was washed with 600 mL of hexane. The alcoholic solution was concentrated and the hexane wash was added. The organic solution was washed with 2 × 400 mL of water and dried over sodium sulfate. Crystallization yielded 70 g (80%) of a 1:4 mixture of (*Z*)- and (*E*)-1-bromo-1,2-diphenyl-1-propene (stereochemistry unassigned). The crystals were dissolved in 200 mL of hexane and cooled. Crystals were formed: mp 155–159 °C; UV (hexane) 260 nm (ϵ 6450); IR (CCl_4) 1600, 1495, 1450, 880, 710 cm^{-1}; ^1H NMR (CCl_4) δ 1.98 (s, 3), 7.1–7.4 (m, 10). Anal. Calcd for for $C_{15}H_{13}Br$: C, 65.95; H, 4.80; Br, 28.98. Found: C, 66.14; H, 5.02; Br, 28.92. The filtrate was chilled in an acetone–dry ice bath. Light-orange impure crystals were collected: mp 40–42 °C; UV (hexane) 274 (ϵ 7100), 224 nm (18 600); IR (CCl_4) 1600, 1495, 1450, 1380, 920, 885, 710 cm^{-1}; ^1H NMR (CCl_4) δ 2.35 (s, 3), 6.95 (m, 10). Anal. Calcd for $C_{15}H_{13}Br$: C, 65.95; H, 4.80; Br, 28.98. Found: C, 65.36, H. 4.65; Br, 29.02.

The literature sample may have been a low-melting mixture, bp 153–156 °C (0.001 mm).[13]

(*E*)- and (*Z*)-2,3-Diphenyl-2-butenoic Acids (8a,b). A solution of 70 g (0.26 mol) of (*E*)- and (*Z*)-1-bromo-1,2-diphenyl-1-propene (1:4) in 720 mL of ether cooled to 0 °C and 18.5 g (0.780 mol) of magnesium turnings (Mallinckrodt) was added. The mixture was stirred under a nitrogen atmosphere for 4 h. The yellowish suspension was poured over 4 lb of dry ice and allowed to stand overnight. The magnesium salt was hydrated by the addition of 250 g of ice into the reaction vessel. A 20% (v/v) acetic acid solution was added until the aqueous layer was acidic to litmus paper. The ether phase was separated, and the aqueous layer was extracted with 250 mL of ether. The combined ether solutions were concentrated and extracted several times with saturated sodium bicarbonate solution until the aqueous layer was basic. The combined aqueous extracts were acidified with glacial acetic acid. The white precipitate was collected and washed with 400 mL of water. The precipitate was air dried overnight and yielded 30 g (50%), mp 126–143 °C, of mixed acids in a 1 to 3 ratio (stereochemistry unassigned): ^1H NMR ($CDCl_3$) (I) δ 2.38 (s, 3), 6.7–7.3 (m, 10), 10.00 (br s 1); (II) δ 1.98 (s, 3), 7.1–7.5 (m, 10), 10.0 (br s, 1). The precipitate was recrystallized from a 1:3 $CHCl_3$–hexane solution. The filtrate was kept in the refrigerator overnight. The crystals that were formed were identified as isomer I: mp 162–164 °C; UV (MeOH) 256 nm (ϵ 12 300); IR ($CDCl_3$) 3000 (br), 1690, 1495, 1445 cm^{-1}: MS (70 eV) *m/e* 238 (p, 60), 220 (32), 166 (41), 118 (32), 96 (35), 91 (100), 82 (42). Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.55; H, 5.77. Isomer II was always contaminated with isomer I. The literature sample melted at 124–126 °C.[13]

(*E*)- and (*Z*)-2,3-Diphenyl-2-buten-1-ol. A 22-g portion (0.092 mol) of (*E*)- and (*Z*)-2,3-diphenyl-2-butenoic acids (1:3) was added over a period of 10 min to 7.0 g (0.18 mmol) of lithium aluminum hydride (Ventron) in 400 mL of anhydrous ether. The mixture was stirred for 1.5 h under a nitrogen atmosphere. The grayish slurry was cautiously and slowly added to 200 g of ice and stirred until the mixture turned white. The white suspension was acidified with concentrated HCl. The ether layer was separated, and the aqueous layer was extracted with 100 mL of ether. The combined ether solutions were evaporated to one-half of their original volume and washed with several portions of saturated sodium bicarbonate solution until the washing was basic. The ether solution was dried over sodium sulfate, and the solvent was evaporated. The residue yielded 18 g (87%) of a 2:1 ratio of (*Z*)- and (*E*)-2,3-diphenyl-2-buten-1-ol (stereochemistry undetermined): bp 123 °C (0.25 nm); ^1H NMR (CCl_4) (I) δ 1.72 (s, 1, OH), 2.08 (s, 3), 4.27 (s, 2), 7.10 (m, 10); (II) δ 1.72 (s, 1, OH), 1.75 (s, 3), 3.93 (s, 2), 6.82 (m, 10). Chromatography on silica gel with benzene as eluent yielded isomer I pure: mp 95–96 °C; UV (MeOH) 239 nm (ϵ 10 200); IR ($CHCl_3$) 3580, 1490, 1440, 1380, 990 cm^{-1}; MS (70 eV) *m/e* 224 (p, 72), 209 (30), 191 (23), 178 (20), 115 (32), 91 (67), 77 (30). Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.84; H, 7.27.

Preparation of (*Z*)- and (*E*)-2,3-Diphenyl-2-butenal (7a,b). A 13-g portion (58 mmol) of (*E*)- and (*Z*)-2,3-diphenyl-2-buten-1-ol was dissolved in 300 mL of dried acetone and 45 g (0.25 mol) of CrO_3–pyridine complex was added. The mixture was kept at room temperature for 58 h. A 600-mL portion of ether was added and filtered. The filtrate was washed with 2 × 200 mL of water, 100 mL of 15% aqueous HCl, and 200 mL of 5% (w/v) $NaHCO_3$ solution. The ether solution was dried over Na_2SO_4 and the solvent was evaporated to give 8.1 g (60%) of the mixed aldehydes in a ratio 2:1 (Z:E). The solid was recrystallized from a 1:1 $CHCl_3$–hexane solution to give the yellow (*Z*)-2,3-diphenyl-2-butenal (**7a**): mp 131–133 °C (lit. 128–129,[12] 127–128[11]); IR ($CHCl_3$) 2750 (weak), 1668, 1395, 1380 cm^{-1}; UV (MeOH) 275 nm (ϵ 9500); ^1H NMR ($CDCl_3$) δ 2.15 (s, 3), 6.9–7.5 (m, 10), 9.62 (s, 1); MS (70 eV) *m/e* 222 (p, 100), 207 (20), 193 (19), 179 (35), 178 (40), 115 (63), 91 (43). Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.30; H, 6.51.

Further evaporation of the solvent produced crystals which when recrystallized from 1:3 $CHCl_3$–hexane gave (*E*)-2,3-diphenyl-2-butenal (**7b**): mp 105–106 °C; UV (MeOH) 292 nm (ϵ 13 300); IR ($CDCl_3$) 2750 (weak), 1670, 1377, 1330 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60 (s, 3), 6.7–7.4 (m, 10), 10.42 (s, 1); MS (70 eV) *m/e* 222 (p, 100), 207 (15), 193 (15), 179 (20), 178 (20), 115 (35), 91 (15). Anal. Calcd for $C_{16}H_{14}O$: C, 86.45, H, 6.35. Found: C, 87.08; H, 6.49 and C, 85.97; H, 6.46.

Isomerization of (*E*)-2,3-Diphenyl-2-butenal (7b). A 24.3-mg portion (0.11 mmol) of (*E*)-2,3-diphenyl-2-butenal (**7b**) was dissolved in 5 mL of methanol containing 120 μL of concentrated HCl. The mixture was stirred for 40 min at room temperature. A 40-mL portion of ether was added, and the mixture was washed with 20 mL of 5% (w/v) $NaHCO_3$ solution. The ether extract was dried over Na_2SO_4.

The solvent was evaporated to yield (*Z*)-2,3-diphenyl-1-butenal (**7a**) (^{1}H NMR). No *E* isomer **7b** was found. A quantitative experiment performed in CH_3OD in the ^{1}H NMR spectrometer showed an 80% conversion to the *Z* isomer.

Photolysis of 4,5-Epoxy-3,5-diphenyl-3-methyl-1-pyrazoline (1b) in PhH. A 132.3-mg portion of (0.529 mmol) of epoxide **1b** was dissolved in 2 mL of benzene. Six 300-μL portions were placed in individual NMR tubes. One of the tubes was kept in the refrigerator while the other five tubes were photolyzed at 5 °C using a sunlamp. One tube was removed every hour and kept in the refrigerator. ^{1}H NMR analysis of each tube showed two products appearing in a 2:1 ratio. In ppm downfield from the epoxide CH_3 (which occurs 0.30-ppm downfield from cyclohexane), the two products appeared at 0.37 (3 H), 8.83 (1 H), and 0.20 (3 H), 8.23 (1 H), respectively. The contents of each tube were evaporated, dissolved in CCl_4, and analyzed by ^{1}H NMR. In ppm downfield from the epoxide CH_3 (δ 1.83 ppm), the two products appear at 0.60 (3 H), 8.70 (1 H), and 0.46 (3 H), 7.95 (1 H), respectively. The integrals showed a 90% conversion to these two products.

The tubes were combined and the solution was heated at 85 °C for 1 h. ^{1}H NMR showed a small amount of the thermolysis products (see above). In addition, about half of the major photolysis product had disappeared with a corresponding increase in the minor photoproduct.

The PhH was evaporated, the residue was dissolved in 5:1 hexane–CCl_4, and the solution was put in the freezer. A yellow impure precipitate was formed: mp 95–96 °C; UV (hexane) 268 nm (ε 16 600); IR (CCl_4) 2820, 1710, 1650, 1450, 1370, 1250, 870 cm^{-1}: ^{1}H NMR (CCl_4) δ 2.30 (s, 3), 7.2–7.5 (m, 9), 7.6–7.8 (m, 2), 9.80 (s, 1); MS (70 eV) *m/e* 250 (p, 2), 221 (4), 119 (100), 104 (100), 77 (100), 51 (47). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.63; N, 11.20. Found: C, 77.42; H, 5.85; N, 10.74.

Irradiations in CD_3CN showed similar results with formation of the same two photoproducts. In all cases, comparison of the ^{1}H NMR's of the irradiated solutions with ^{1}H NMR's of aldehydes **6a,b** and dypnones **7a,b** showed the latter four compounds were not present (<10%). Control experiments showed that both the aldehydes and dypnones were stable to the reaction conditions.

Registry No.—**1a**, 54541-36-5; **1b**, 63904-61-0; **2**, 22675-60-1; **3**, 63904-62-1; **4a**, 63904-63-2; **6a**, 22573-24-6; **6a** *anti*-hydrazine, 63904-64-3; **6a** *syn*-hydrazone, 63904-65-4; **6b**, 54435-79-9; **7a**, 63904-66-5; **7b**, 63904-67-6; **8a**, 60728-10-1; **8b**, 60728-09-8; **10a**, 63904-68-7; **10b**, 63904-69-8; acetophenone, 98-86-2; tosylhydrazide, 1576-35-8; 1,2-diphenylpropan-2-ol, 5342-87-0; (*E*)-1,2-diphenylpropene, 833-81-8; (*R,*R**)-1,2-diphenyl-1,2-dibromopropane, 63904-70-1; (*R*S*)-1,2-diphenyl-1,2-dibromopropane, 63904-71-2; bromine, 7726-95-6; (*E*)-1-bromo-1,2-diphenyl-1-propene, 63904-72-3; (*Z*)-1-bromo-1,2-diphenyl-1-propene, 63904-73-4; (*E*)-2,3-diphenyl-2-buten-1-ol, 63904-74-5; (*Z*)-2,3-diphenyl-2-buten-1-ol, 22641-64-1.

References and Notes

(1) Taken primarily from the Ph.D. Thesis of N. L. de Vera, University of Rochester, 1976.
(2) Y.-S. P. Lam, along with N. L. de Vera, made critical contributions in the obtainment and analysis of the ^{13}C NMR spectra.
(3) L. E. Friedrich and R. A. Fiato, *J. Org. Chem.*, **39**, 2267 (1974), and references therein.
(4) L. E. Friedrich and R. A. Fiato, *J. Am. Chem. Soc.*, **96**, 5783 (1974), and references therein.
(5) P. G. Gassman and W. T. Greenlie, *J. Am. Chem. Soc.*, **95**, 980 (1973).
(6) L. E. Friedrich, N. L. de Vera, W. P. Hoss, and J. T. Warren, *Tetrahedron Lett.*, 3139 (1974).
(7) T. Sato and S. Watanabe, *Bull. Chem. Soc. Jpn.*, **41**, 3017 (1968).
(8) (a) P. D. Bartlett and R. H. Rosenwald, *J. Am. Chem. Soc.*, **56**, 1990 (1934); (b) C. M. Suter and G. A. Lutz, *J. Am. Chem. Soc.*, **60**, 1360 (1938).
(9) L. T. J. Delbaere, M. N. G. James, and R. U. Leumieux, *J. Am. Chem. Soc.*, **95**, 7866 (1973).
(10) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, *29*, 1136 (1964).
(11) R. Breslow, J. Lockhart, and A. Small, *J. Am. Chem. Soc.*, **84**, 2793 (1962).
(12) A. Padwa, *Tetrahedron Lett.*, 1049 (1965).
(13) C. F. Koelsch and R. V. White, *J. Org. Chem.*, **6**, 602 (1941).
(14) (a) J. Coops and G. J. Hoijtink, *Recl. Trav. Chim. Pays-Bas*, **69**, 358 (1950). (b) Y. Nagai, O. Simanura, and L. Ehara, *Bull. Chem. Soc. Jpn.*, **35**, 244 (1962).
(15) (a) N. Inamoto, S. Masuda, Y. Nagai, and O. Simamura, *J. Chem. Soc.*, 1433 (1963); (b) D. E. McGreer and B. D. Page, *Can. J. Chem.*, **47**, 866 (1969). See also J. M. F. Gagan, A. G. Lane, and D. Lloyd, *J. Chem. Soc. C*, 2484 (1970).
(16) P. Schiess and H. L. Chia, *Helv. Chim. Acta*, **53**, 485 (1970).
(17) L. E. Friedrich and R. A. Cormier, *Tetrahedron Lett.*, 4761 (1971).
(18) N. D. Calloway and L. D. Greene, *J. Am. Chem. Soc.*, **59**, 809 (1937).
(19) R. E. Lutz and L. T. Slade, *J. Org. Chem.*, **26**, 4888 (1961).
(20) P. S. Ellinger, D. G. Hey, and G. D. Meakins, *J. Chem. Soc. C*, 1329 (1966).
(21) C. Hell, *Chem. Ber.*, **37**, 453 (1904).
(22) A. F. Casy, A. Parulkar, and P. Pocha, *Tetrahedron*, **24**, 3031 (1968).
(23) D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5851 (1952).

Phenylacetone Dianion: Alkylation with Iodomethane[1]

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The alkylation products of the phenylacetone dianion have been examined. It has been shown that the alkylation is nonregioselective, carbon–carbon bond formation taking place at either the α or α′ position. Both the ease of formation of the dianion and the monoalkylation product ratio are affected by the metal ions present. Methylation at the terminal position does not predominate in any case examined.

In recent years carbon–carbon bond formation by means of dianion alkylation has become an increasingly important synthetic tool.[3] Although such reactions have most frequently involved β-dicarbonyl compounds,[3a] carboxylic acids,[3b] β-keto sulfones[3c] and imides[3d] have also proven useful. With each of these precursors the dianion alkylation is normally regioselective, carbon–carbon bond formation taking place at the position from which the second proton has been removed. This observation has been succinctly summarized in the generalization that "the more basic (and less stable) enolates usually react more readily with alkylating agents".[4] Versatility is thus available, since regioselective alkylation can be accomplished in a predictable fashion using either monoanion or dianion alkylation procedures; the position of alkylation is normally well defined and different with each method.

Of course it is well known that many factors contribute to the relative rates and regioselectivity of alkylation of enolate anions. Among these considerations are charge densities,[5] steric interactions in the transition state, solvent, metal ion effects,[6] and the principle of least motion.[7] All of these contribute to the relative nucleophilicity observed for separate enolate anions or for differing positions on the same dianion. Despite these other factors, however, dianion alkylation regioselectivity has generally been successfully predicted simply on the basis of relative pK_a values.

In 1967 Hauser reported[8] that the combination of a phenyl

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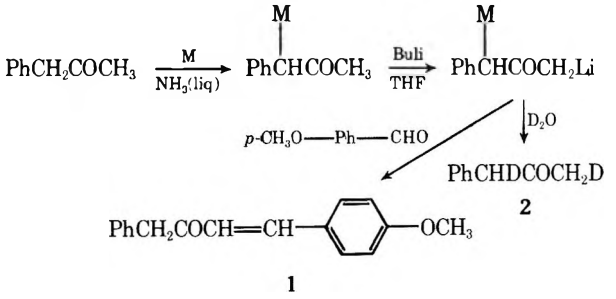
Table I. Product Distribution for the Reaction:[a]

$$C_6H_5CH_2COCH_3 \xrightarrow[\text{3. MeI}]{\text{1. Base A, 2. Base B}} \xrightarrow{\text{4. } H_3O^+}$$

Rxn	Reactants: Base A	Base B	MeI, equiv	Yield, %[b]	Product Distribution, %: Phenylacetone	3-phenyl-2-butanone (8)	1-phenyl-2-butanone (9)	2-phenyl-3-pentanone (10)
1	NaH	BuLi	1	80	22	40	31	7
2	NaH	LDIPA	1	84	92	3	4	
3	NaH	LDIPA + BuLi	1	70	45	25	27	
4	KH	BuLi	Excess	91		3	4	93
5	KH	BuLi	1	91	1	43	56	1

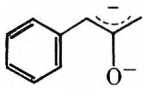
[a] All reactions utilized anhydrous THF as solvent. [b] The cited yield includes all products and recovered starting material ($PhCH_2COCH_3$ + 8 + 9 + 10).

Scheme I



group and a ketone provides sufficient activation for dianion formation, the specific example being phenylacetone (Scheme I). Evidence cited for the intermediacy of the dianion was the condensation reaction with anisaldehyde to give the linearly conjugated unsaturated ketone 1 and deuteration with D_2O to give the 1,3-dideuteriophenylacetone (2). This report came to our attention since, in connection with another synthetic problem, it became necessary to make compounds which are derived, in principle, by alkylation at the terminal positions of phenylacetone and its derivatives.

The difference in acidity for protons at the two positions flanking the carbonyl in phenylacetone has recently been reported to be 7.2 pK units.[9] Based on this rather substantial difference, it would seem reasonable to predict regioselective alkylation at the more basic terminal position, analogous to the dianions derived from β-dicarbonyls. On the other hand, to the extent that the dianion can be formulated as **3**, it might



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be more appropriate to take the kinetically controlled protonation of the cinnamyl anion as the analogy,[10] in which case a nonregioselective alkylation would be predicted.

The work reported by Hauser (Scheme I) does not shed light on the problem, suffering from three major criticisms. First, the condensation product 1 is identical to that obtained from the equilibrium-controlled condensations of the enolate.[11] In contrast, the kinetically controlled alkylation of the enolate occurs almost exclusively at the methylene position.[12] Although it has been shown that enolate condensation occurs exclusively and steroselectively at the methylene position under conditions in which the kinetically controlled product is trapped by zinc ion,[13] condensation product 1 would probably be formed from the enolate under the reported reaction conditions and therefore its isolation does not unambiguously demonstrate the intermediacy of the dianion, nor does it speak unequivocally to the question of dianion reaction regioselectivity.

The second criticism involves the irreproducability of the deuteration experiment in our hands. Instead of the regioselective incorporation of two deuteriums to give **2**, we routinely observe polydeuteration. This proton exchange is not surprising in light of the reported alkylation of phenylacetone in the presence of aqueous base.[12c]

Finally, Hauser reports that the dianion derived from the sodium enolate (M = Na in Scheme I) is bright red, while that derived from the lithium enolate is yellow. Although, as we shall demonstrate, the counterion greatly affects the ease of dianion formation and its reactivity, it is surprising that the absorbance maximum is so dramatically shifted. Although this may appear to be a trival point, we believe it to indicate, based upon our results, that the dilithio dianion was not formed as reported. This observation makes the condensation and deuteration results all the more ambiguous.

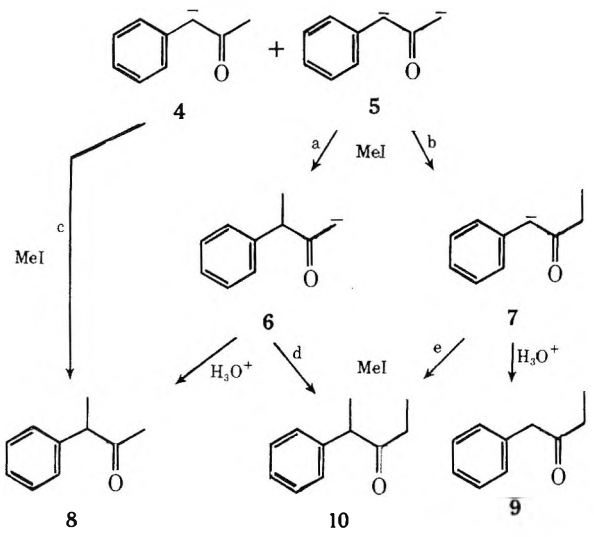
For all of these reasons, we have embarked on a study of the phenylacetone dianion. We have initially chosen to examine the alkylation reaction of the dianion, both because this was ultimately our synthetic goal and because alkylation is not an equilibrium-controlled process, thus avoiding the ambiguities described above.

Results and Discussion

The principle results of this study are summarized in Table I. We have chosen to form the enolates in anhydrous THF rather than in liquid ammonia as previously described (Scheme I). These enolates have then been deprotonated in THF using a slight excess of n-butyllithium. Iodomethane (MeI) has been used as the alkylating agent in all cases. Product analysis has involved a combination of two gas chromatographic systems[14] and NMR spectral analysis of both crude reaction mixtures and preparatively purified products.

Treatment of the sodium enolate of phenylacetone—formed by reaction of the ketone with excess sodium hydride—with a slight excess of n-butyllithium gives the bright, rust-red solution reported by Hauser. Upon alkylation with 1 equiv of MeI, followed by protonation of the resulting enolates, the mixture of products shown as reaction 1 in Table I is obtained. Although 71% of the volatile product mixture is

Scheme II



monoalkylated, both dialkylated [2-phenyl-3-pentanone (**10**)] (7%) and unalkylated (22%) material are present. Furthermore, there are two monoalkylated products, alkylation having occurred at either the methylene position of the original phenylacetone to give 3-phenyl-2-butanone (**8**) (40%) or at the methyl position to give 1-phenyl-2-butanone (**9**) (31%).

These observations can be interpreted in several ways, as illustrated in Scheme II. The fact that starting material is recovered from the reaction leads us to believe that the conversion from enolate **4** to dianion **5** is not complete; that is, that there is enolate present in the dianionic solution. Intuitively one would predict that the dianion **5** would be more reactive than the enolate **4** toward methyl iodide, an expectation which is experimentally demonstrable, as we shall discuss presently. Thus, it would be anticipated that, upon addition of 1 equiv of MeI, the dianion would react regioselectively by pathway a or b, or nonregioselectively by pathways a and b to initially give monoanions **6** and/or **7**. Competition between these enolates (**4**, **6**, and/or **7**) for the residual MeI leads directly to monoalkylated product **8** and dialkylated product **10**. Since there is not sufficient MeI present in the reaction mixture, alkylation will not be complete and protonation of the mixture with water will give rise to monoalkylated products **8** and **9** (from **6** and **7**, respectively) and the recovery of starting material (by protonation of **4**). The relative amounts of the various products will, of course, reflect the relative rates of the alkylation processes. Clearly, because of the assumptions required for the interpretation of the data, this experiment does not elucidate the chemistry of the phenylacetone dianion.

Clarification of the situation requires either that a method be found for distinguishing between reactions of the mono- and dianion, or, alternatively, that a technique be found for assuring total conversion of the enolate to the dianion. Reactions 2–5 (Table I) demonstrate solutions involving both of these alternatives.

The recovery of starting material from reaction 2, in which lithium diisopropylamide (LDIPA) was used as the second base, demonstrates two points crucial to the following discussion: (1) that LDIPA is not a sufficiently strong base to deprotonate the sodium enolate of phenylacetone to give the dianion, and (2) that LDIPA is a much better nucleophile than the sodium enolate, effectively scavenging the alkylating agent. The first point is not surprising since House has routinely used excess LDIPA for the stereoselective formation of the *cis*-enolate of phenylacetone.[15] In no instance has he reported reactions which suggest a dianion intermediate. The second point is confirmed by the presence of methyldiisopropylamine in an acid extract of the reaction mixture.[16] Thus, an order of relative nucleophilicities has been established which potentially allows the masking of enolate reactions in the presence of LDIPA. The technique is illustrated in the following experiment.

In reaction 3 (Table I) the sodium enolate is deprotonated by *n*-butyllithium in the presence of LDIPA. Upon alkylation with MeI, the LDIPA effectively scavenges excess alkylating agent thereby eliminating the ambiguities introduced by enolate competition in reaction 1 (pathways c, d, and e of Scheme I). The result is a simplified product mixture in which there is no dialkylated phenylacetone (**10**) and both monoalkylated products **8** and **9** must be derived from the dianion.

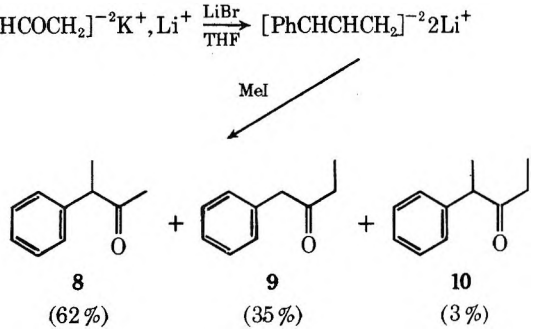
The product mixture demonstrates that the alkylation is totally nonregioselective, giving rise to equal amounts of α and α' alkylation (**8** and **9**, respectively). We have examined this reaction many times under a variety of conditions. Although the ratio of nonalkylated to alkylated products may vary depending upon the reaction conditions, the ratio of the two monoalkylated products is always 1:1. It is, in fact, possible to simply titrate the solution of the dianion with MeI, using as an indicator the disappearance of the red color; even in this crude experiment a 1:1 ratio of monalkylated products (**8**:**9**) is observed. No products have been isolated from any of our experiments which suggest ring alkylation. Furthermore, when starting from the sodium enolate, we have never observed alkylation to exceed 65–70%, at least 30% of the product mixture constituting recovered starting material. Our conclusions are that the sodium enolate is not totally deprotonated by *n*-butyllithium and that the dianion, when formed, is equally reactive at both positions flanking the carbonyl.

The situation is somewhat different in the case of the potassium enolate, formed by reaction of the ketone with potassium hydride. As illustrated in reactions 4 and 5 (Table I), the enolate is rapidly, and apparently completely, converted to the dianion by *n*-butyllithium even at 0 °C. Upon treatment with excess MeI (reaction 4) this dianion is alkylated at both the terminal and the methylene positions to give **10** in high yield. With 1 equiv of MeI, the reaction is again nonregioselective (reaction 5), although there is a slight, reproducible preference for terminal alkylation (1.3:1).

Clearly, when the dianion is formed by alkyllithium deprotonation of either the sodium or potassium enolate, there are two different associated counterions. It has been well established[17] that the counterion is an important factor, affecting both the reactivity and regioselectivity of enolate alkylations. This has been attributed to the degree of association of the ion pair; whereas lithium associates relatively tightly, particularly with the oxygen of the enolate, the potassium–enolate ion-pair association is relatively weak. These considerations lead to some uncertainty in the interpretation of our results, since it is not clear how the two different counterions are associated with the dianion. This could be resolved if the dianion were formed under conditions such that the two counterions were identical.

To date, all efforts to achieve the direct formation of the dilithio dianion of phenylacetone have failed. These attempts have included: (1) reaction of the ketone with 2–3 equiv of LDIPA, (2) *n*-butyllithium deprotonation of the lithium enolate, formed by reaction of the ketone with LDIPA, and (3) *n*-butyllithium or *tert*-butyllithium deprotonation of the lithium enolate, formed by methyllithium displacement of the trimethylsilyl enol ether.[15] In all cases, the expected deep-red color was faint or absent, and upon alkylation with limited MeI only phenylacetone was recovered. Apparently, in each case the dianion was not formed and the residual strong base effectively scavenged the alkylating reagent. These observations contradict the results reported by Hauser (Scheme I) and

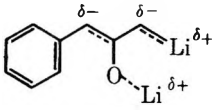
Scheme III



it is our belief that he did not form the dilithio dianion from the lithium enolate. Condensation product **1** probably arises from the enolate rather than from the dianion in that system.

Since the direct route to the dilithio dianion seemed fruitless, we have taken an indirect approach. This is outlined in Scheme III and is based upon the observation[18] that potassium enolates are rapidly and quantitatively transmetalated to give lithium enolates in the presence of anhydrous lithium bromide in THF. Thus, the potassiolithio dianion, formed as described in reactions 4 and 5 (Table I), was treated with 2–10 equiv of anhydrous lithium bromide prior to addition of the alkylating agent. This resulted in rapid formation of a precipitate, presumably potassium bromide. Upon alkylation, the ratio of monoalkylated products was dramatically affected, preference being shown for alkylation at the methylene position (**8**:**9** = 1.5–1.8:1).

This result can be rationalized by considering the dianion to be tightly associated with its counterions, perhaps as in **11**.



11

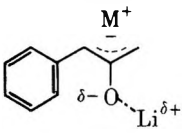
This species would be expected to alkylate preferentially at the methylene position, on the basis of analogy with the lithium enolates.[17] However, it is not clear that the transmetallation has gone to completion; the presence of residual potassiolithio dianion in the mixture will skew the results in favor of terminal alkylation. It does seem reasonable to say, on the basis of these observations, that the alkylation preference is at the methylene position for the dilithio dianion.

Conclusions

In contrast to the dianions derived from β-dicarbonyls, the phenylacetone dianion is not alkylated regioselectively. This observation is also counter to predictions based solely upon pK_a considerations, demonstrating once again that the generalized relationship between pK_a and nucleophilicity, sometimes promolgated to and amongst our students, is highly imperfect. We are presently in the process of investigating the steric and electronic effects on this system and those results will be reported at a later date.

We are also in the process of investigating the rather puzzling order of enolate reactivity toward *n*-butyllithium deprotonation. We have shown that, whereas the lithium enolate is unreactive, the potassium enolate is rapidly and completely deprotonated at 0 °C to form the dianion. The sodium enolate exhibits intermediate reactivity, being deprotonated sluggishly and negligibly at 0 °C, but to the extent of about 65% in 15 min at room temperature.[19] One possible rationale for these observations is based on the report that *n*-butyllithium is transmetalated by sodium or potassium *tert*-butoxide to form lithium *tert*-butoxide and *n*-butylsodium or *n*-butylpotassium.[20] In our system the enolate salt may serve as the transmetalating agent, producing the lithium enolate and the strongly basic metal alkyl. These bases are apparently sufficiently strong to deprotonate the highly coordinated lithium enolate, though the deprotonation does not go to completion in the sodium system as evidenced by the alkylation results. On the other hand, with the lithium enolate, no transmetalation can take place to give a stronger base, and apparently *n*-butyllithium itself does not deprotonate the monoanion. Although this is an attractive rationalization for the observed phenomena, experimental substantiation is presently unavailable.

It is clear that the counterions have a significant effect on the alkylation process. If one pictures the dianion as shown in **12**, these observations can be rationalized in terms of the



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degree of association of the dianion with its counterions. Based upon a mechanism of formation involving the previously postulated transmetalation, we have proposed that the lithium ion is coordinated with the oxygen. The other counterion may then be associated with the second negative charge which is delocalized in the carbon side chain. When this counterion is potassium, that portion of the molecule is most "naked", in agreement with the recently reported ^{13}C NMR analysis of the enolates.[21] In this relatively bare state, there is a slight preference for alkylation at the terminal position. On the other hand, when the second counterion is lithium, the ion pair is expected to be highly associated, perhaps as shown in **11**. This leads to alkylation preference at the methylene. The intermediate associative capacity of the sodium ion is reflected in the totally nonregioselective alkylation of the sodiolithio dianion.

Experimental Section

All syringes and reaction vessels were carefully washed and oven dried prior to use. Reaction flasks were equipped with rubber septums and cooled under a nitrogen atmosphere which was maintained throughout the course of the reaction. The solvent used in each reaction was THF which had been freshly distilled from $LiAlH_4$ under a nitrogen atmosphere. Unless otherwise specified, all solvent and reagent additions and solution transfers were performed by means of syringes. Alkyllithium reagents (*n*-butyllithium in hexane, ca. 2.25 M; methyllithium in ether, ca. 1.8 M; and *tert*-butyllithium in pentane, ca. 1.8 M) were obtained from Alpha Inorganics and were standardized by titration[22] prior to use. Phenylacetone and 1-phenyl-2-butanone (**9**) were obtained from Aldrich Chemical Co. Authentic samples of the alkylated products **8** and **10** were prepared by iodomethane alkylation of the sodium enolates of phenylacetone and **9**, respectively.[12b,23]

Product analyses were carried out using NMR spectra and GLC. We have found it necessary to utilize two GLC systems.[14] Both columns have been calibrated with standard mixtures of dodecane (internal standard) and ketones. For the DC-710 column, which was used for overall yield determinations, the detector response ratio was found to be 1.2 (dodecane/ketone). The data from both columns were used to determine product distributions. For example, whereas the dialkylated product **10** is not separable from the monoalkylated product **9** on the DC-710 silicone oil column, it is cleanly separated on the Carbowax column. On the other hand, **10** and phenylacetone have the same retention time on the Carbowax column.[24] It has therefore been necessary to examine retention times and relative peak areas for all product mixtures on both chromatographic systems and to analyze the preparatively purified products on both columns as well as spectrally (NMR). In all cases product structural assignments have been confirmed both by GLC retention times and by the characteristic NMR spectra. For some relatively simple, two or three component mixtures, it has been possible to assign product distributions on the basis of NMR spectra and GLC analysis of the mixture. In representative cases these assignments have been completely confirmed by preparative separation.

Following are the NMR spectral data for each of the four major reaction products: phenylacetone ($CDCl_3$) δ 2.09 (s, 3), 3.64 (s, 2), 7.28 (s, 5); 3-phenyl-2-butanone (8) ($CDCl_3$) δ 1.39 (d, 3), 2.01 (s, 3), 3.74 (q, 1), 7.29 (s, 5); 1-phenyl-2-butanone (**9**) ($CDCl_3$) δ 1.00 (t, 3), 2.44 (q, 2), 3.65 (s, 2), 7.26 (s, 5); 2-phenyl-3-pentanone (**10**) ($CDCl_3$) δ 0.95 (t, 3), 1.38 (d, 3), 2.35 (q, 2), 3.75 (q, 1), 7.27 (s, 5).

The Potassiolithio Dianion. (A) Monoalkylation. A large excess of KH (5 g, 18 mM) as a 22% dispersion in oil was weighed into a 50-mL three-necked flask. The KH was washed three times with pentane to remove the mineral oil. It was then suspended by stirring in 10 mL of anhydrous THF, and a mixture of 2.008 g of phenylacetone (15.0 mM) and 1.0100 g of dodecane (internal GLC standard) in 5 mL of THF was slowly added from a pressure-equalized addition funnel. When hydrogen evolution had ceased (20–30 min) the mixture was allowed to stand until the excess KH had settled, and the resulting enolate solution was transferred to a 100-mL three-necked flask. The residual KH was washed with two 5-mL portions of THF and these washes were combined with the enolate solution. Standardized *n*-butyllithium solution in hexane (16.9 mM) (7.5 mL) was added at room temperature and the resulting rust-red dianion solution was allowed to stir for 15 min.

The mixture was cooled in an ice bath and 0.95 mL of MeI (15.3 mM) in 10 mL of THF was added from a pressure-equalized addition funnel with vigorous stirring. After 5–10 min, the resulting yellow mixture was acidified with dilute acid and diluted with ether. The ether phase was extracted with two portions of dilute acid and the resulting aqueous phase was back-extracted with two portions of ether. The combined organic extract was dried (Na_2SO_4) and the solvent removed in vacuo at 25 °C. The residue was dissolved in 10.0 mL of $CHCl_3$ for gas chromatographic analysis.

Based on dodecane as the internal standard a 91% yield was obtained (phenylacetone + alkylated products). The product distribution was: phenylacetone (<1%), 1-phenyl-2-butanone (**9**) (56%), and 3-phenyl-2-butanone (8) (43%). (See reaction 5, Table I.)

(B) Dialkylation. The cooled rust-red solution of the dianion, prepared as described above, was transferred to a cooled flask containing 5 mL of MeI (81 mM) in 15 mL of THF. After 5–10 min, the resulting solution was diluted with water and ether. The ether phase was washed twice with dilute acid, the combined aqueous extracts were back-extracted with two portions of ether, and the combined organic phase was dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was dissolved in 10.0 mL of $CHCl_3$ for gas chromatographic analysis.

The product yield was 91% (phenylacetone + alkylated products). The mixture contained: 2-phenyl-3-pentanone (**10**) (93%), 3-phenyl-2-butanone (8) (3%), and 1-phenyl-2-butanone (**9**) (4%). (See reaction 4, Table I.)

The Sodiolithio Dianion. (A) Unmasked Reaction. An excess of NaH (2.0 g, 42 mM) as a 50% dispersion in oil was weighed into a 100-mL three-necked flask. The NaH was washed two times with pentane to remove the mineral oil and was then suspended in 5 mL of THF. To this suspension was slowly added 5.001 g of phenylacetone (37.3 mM) and 1.510 g of dodecane (GLC internal standard) in 15 mL of THF from a pressure-equalized addition funnel. In order to maintain reasonable hydrogen evolution, the addition was carried out slowly and the reaction was cooled in an ice bath. When addition was complete, the reaction mixture was stirred at room temperature for 15 min or until hydrogen evolution had ceased. It was then allowed to stand at room temperature until the excess NaH had settled; this usually required 1–2 h, although it was sometimes left overnight. The resulting enolate solution was transferred to a clean dry flask and the NaH washed with two portions of THF.

To the yellow enolate solution was added 38 mM (16.8 mL) *n*-butyllithium solution in hexane. This mixture was allowed to stir for 15 min after which it was cooled in an ice bath and 2.3 mL (37 mM) of MeI in 10 mL of THF was added with vigorous stirring. After 5–10 min, the reaction was acidified and extracted as previously described for the potassiolithio system.

Based on dodecane, the yield was 80%. The following product distribution was obtained: phenylacetone (22%), 3-phenyl-2-butanone (8) (40%), 1-phenyl-2-butanone (**9**) (31%), and 2-phenyl-3-pentanone (**10**) (7%). (See reaction I, Table I.)

(B) Masking of the Enolate with LDIPA. The sodium enolate was prepared as described above using 5.016 g of phenylacetone (37.4 mM), 2.016 g of dodecane, and 2.0 g of NaH (42 mM). Prior to separation of the enolate solution from residual NaH, 6.0 mL (42.6 mM) of diisopropylamine (DIPA) was added. When the NaH had settled this solution was transferred to another flask and the NaH washed with two portions of THF. To this enolate solution was added 40 mM (17.8 mL) *n*-butyllithium in hexane; the mixture was allowed to stir for 15 min at room temperature, and was then cooled in an ice bath. Iodomethane (2.3 mL, 37 mM) in 10 mL of THF was added to the vigorously stirred solution. After 5–10 min, the reaction was acidified, extracted, and analyzed as previously described.

Based on internal standard, the yield was 84%, with the following product distribution: phenylacetone (92%), 3-phenyl-2-butanone (8) (3%), and 1-phenyl-2-butanone (**9**) (4%). (See reaction 2, Table I.)

The acidic aqueous phase from the extractions of this reaction was made basic with sodium hydroxide and extracted three times with ether. After drying (Na_2SO_4), the organic solvent was partially removed and the residue subjected to GLC analysis and preparative separation.[16] The predominant product was methyldiisopropylamine,[25] present as 60–70% of the acid-soluble material. The structure assignment is based on the characteristic NMR spectrum and upon comparison of the GLC retention time (4 min) with that of an authentic sample, synthesized by methylation of DIPA with MeI: NMR ($CDCl_3$) δ 1.01 (d, 12), 2.13 (s, 3), 2.91 (septet, 2).

(C) Masking of the Enolate with LDIPA in the Presence of Dianion. The enolate was formed as described above using 5.0220 g of phenylacetone (37.5 mM), 1.0130 g of dodecane, and 2.1 g of NaH (44 mM). After hydrogen evolution had ceased, 5.3 mL (37.5 mM) of DIPA was added and the mixture was allowed to stand at room temperature until the residual NaH had settled. After transfer of the enolate–DIPA solution to a clean flask with the usual washing of the residual NaH, 78 mM (34.7 mL) *n*-butyllithium in hexane was added at room temperature. After stirring for 15 min, the mixture was cooled in an ice bath and 2.4 mL of MeI (38.6 mM) in 10 mL of THF was added with vigorous stirring. This was followed after 5 to 10 min by acidification and extraction in the usual fashion.

Based on dodecane, a product yield of 60% was realized. The following products were present: phenylacetone (45%), 2-phenyl-3-butanone (8) (25%), 1-phenyl-2-butanone (**9**) (27%), and unidentified products (3%). (See reaction 3, Table I.)

Dilithio Dianion. (A) Direct Method. Into a clean, dry 100-mL three-necked flask was placed 3.009 g (14.6 mM) of the *trans*-trimethylsilyl enol ether of phenylacetone,[15] 1.020 g of dodecane (internal GLC standard), and a few milligrams of bipyridyl which serves as an alkyllithium indicator. To this solution was added 15 mM (8.4 mL) methyllithium in ether. The resulting mixture was allowed to stir at room temperature for 15 min, and additional methyllithium was added as necessary to maintain an excess, as judged by the purple color of the indicator. To this solution was added 16 mM (7.2 mL) *n*-butyllithium and the mixture was stirred for an additional 15 min at room temperature. It was then cooled in an ice bath and 0.91 mL (14.7 mM) of MeI was added in 5.0 mL of THF with vigorous stirring. After 5–10 min, the resulting reaction mixture was acidified and extracted in the previously described manner. GLC analysis showed only one volatile product, phenylacetone, isolated in 93% yield.

Identical results were obtained using *tert*-butyllithium as the second base, or with 2 equiv of LDIPA. In none of these instances was alkylation of the phenylacetone observed.

(B) Indirect Method. The potassiolithio dianion was formed as previously described using 4.1 g of KH (22.5 mM), 2.047 g of phenylacetone (15.3 mM), 1.012 g of dodecane (internal GLC standard), and 15.75 mM (7 mL) *n*-butyllithium. To this solution was added 2.5 g (29 mM) of anhydrous LiBr (Alpha Inorganics) in 15 mL of THF. (The LiBr solution had been previously treated with *n*-butyllithium using bipyridyl as indicator to assure that no water was present.) Immediately a precipitate formed. The mixture was stirred for 15 min at room temperature and then cooled in an ice bath. To the cold, vigorously stirred solution was added 0.95 mL of MeI (15.2 mM) (1 equiv). A portion (15 mL) of the resulting reaction mixture was transferred to 3 mL of MeI (48 mM) in 15 mL of THF. After 5–10 min, both reactions were acidified and extracted as previously described.

For the portion of the reaction treated with excess MeI, analysis of the mixture demonstrated the following product distribution (80% yield): 3-phenyl-2-butanone (8) (4%), 1-phenyl-2-butanone (**9**) (11%), and 2-phenyl-3-pentanone (**10**) (85%).

For that portion of the reaction treated with only 1 equiv of MeI, the product analysis was as follows (70% yield): 2-phenyl-3-butanone (**10**) (3%), 3-phenyl-2-butanone (8) (62%), 1-phenyl-2-butanone (**9**) (35%).

For a reaction utilizing 10 equiv of lithium bromide, the product analysis was essentially the same, with the ratio of 8:**9** decreasing from 1.8:1 to 1.5:1.

Registry No.—Iodomethane, 74-88-4; potassiolithio phenylacetone, 63866-06-8; sodiolithio phenylacetone, 63866-07-9; sodium phenylacetone enolate, 61674-95-1; dilithio phenylacetone, 63866-04-6.

Reference and Notes

(1) (a) This research has been supported by Grant GM20368 from the National Institutes of Health. (b) This work was presented in preliminary form at the 173rd National Meeting of the American Chemical Society in New Orleans, March 22, 1977.
(2) Present address: Department of Chemistry and Physics, St. Mary's College, Notre Dame, Indiana 46556.
(3) (a) T. M. Harris and C. M. Harris, *Org. React.*, **17**, 155–211 (1969); (b) P. L. Creger, *Org. Synth.*, **50**, 58 (1970); P. L. Creger, *J. Am. Chem. Soc.*, **89**, 2500 (1967); **92**, 1396, 1397 (1970); (c) N. M. Carroll and W. I. O'Sullivan, *J. Org. Chem.*, **30**, 2830 (1965); (d) S. D. Work, D. R. Bryant and C. R. Hauser, *J. Org. Chem.*, **29**, 722 (1964); *J. Am. Chem. Soc.*, **86**, 872 (1964); J. F. Wolfe and T. G. Rogers, *J. Org. Chem.*, **35**, 3600 (1970).
(4) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 554
(5) H. Zimmerman, in "Molecular Rearrangements", P. DeMayo, Ed., Wiley-Interscience, New York, N.Y., 1963, p 345 ff.
(6) M. Szwarc, *Acc. Chem. Res.*, **2**, 87 (1969).
(7) J. Hine, *J. Org. Chem.*, **31**, 1236 (1966); J. Jullian and Ngyuen-Thoi-Lai, *Bull. Soc. Chim. Fr.*, 3948 (1970).
(8) C. Mao, C. R. Hauser, and M. L. Miles, *J. Am. Chem. Soc.*, **89**, 5303 (1967).
(9) F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. J. McCollum, M. Van Der Puy, N. R. Vanier, and W. S. Matthews, *J. Org. Chem.*, **42**, 321 (1977).
(10) H. F. Herbrandson and D. S. Mooney, *J. Am. Chem. Soc.*, **79**, 5809 (1957); A. Streitweiser, "Molecular Orbital Theory", Wiley, New York, N.Y., 1961.
(11) S. A. Fine and P. D. Pulaski, *J. Org. Chem.*, **38**, 1747–1749 (1973); H. Midorikawa, *Bull. Chem. Soc. Jpn.*, **27**, 210 (1954); R. Dickinson, *J. Chem. Soc.*, 2234–2241 (1926).
(12) (a) C. M. Suter and A. W. Weston, *J. Am. Chem. Soc.*, **64**, 533–536 (1942); (b) H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963); (c) A. Jonczyk, B. Serafin, and M. Makosza, *Rocz. Chem.*, **45**, 1027 (1971); *Chem. Abstr.*, **75**, 109997e.
(13) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).
(14) 8% Carbowax on Chromosorb W (7 ft) at 140 °C with a low helium flow, and 10% DC-710 silicone oil on Chromosorb W (10 ft) at 140 °C with a high helium flow. All preparative separations were performed on the silicone oil column.
(15) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(16) The amine was detected and separated at 60 °C on the DC-710 column using a low helium flow.[14] The NMR spectrum of the isolated amine was consistent with the assigned structure. The GLC retention time agreed with that of an authentic sample.
(17) H. O. House, "Modern Synthetic Reactions, 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, and references cited therein.
(18) C. A. Brown, *J. Org. Chem.*, **39**, 1324, 3913 (1974).
(19) Prolonged reaction periods in this very basic environment lead to decomposition of both solvent and reactants.
(20) M. Schlosser, *J. Organomet. Chem.*, **8**, 9 (1967); M. Schlosser and J. Hartmann, *Angew. Chem., Int. Ed. Engl.*, **12**, 508 (1973); L. Lochmann, J. Pospisil, and D. Lim, *Tetrahedron Lett.*, 257 (1966).
(21) H. O. House, A. V. Prabhu, and W. V. Phillips, *J. Org. Chem.*, **41**, 1209 (1976).
(22) S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).
(23) J. Levy, *Bull. Soc. Chim., Fr.*, **45**, 941 (1929).
(24) The following typical retention times have been observed at column temperatures of 140 °C. DC-710: $C_{12}H_{12}$ = 3.6 min, phenylacetone 6.5 min, **8** = 7.1 min, **9** and **10** = 10.4 min. Carbowax: **8** = 2.6 min, phenylacetone and **10** = 3.3 min, **9** = 4.3 min. ($C_{12}H_{12}$ has too short a retention time to be a useful standard on the Carbowax column.)
(25) L. Spialter and J. A. Pappalardo, *J. Org. Chem.*, **22**, 840 (1957).

Perfluoroacetylenic Ethers[1]

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The first examples of perfluoroacetylenic ethers, $CF_3C{\equiv}COCF_3$ and $CF_3C{\equiv}COCF_2CF_2CF_3$, were synthesized via several routes starting with $CF_3CCl{=}CCl_2$. They homopolymerize at room temperature and have been copolymerized with other perfluoro monomers.

In the course of our work on fluorocarbon polymers the need arose to investigate perfluoroalkoxyacetylenes, a hitherto unknown class of compounds. As a starting point for their synthesis we chose $CF_3CCl{=}CCl_2$, a commercially available material,[2] which can be readily converted to $CF_3C{\equiv}CZnCl$ by zinc dust in dimethylacetamide.[3] Halogenation of this species[4] yielded $CF_3C{\equiv}CCl$ (**1**) and $CF_3C{\equiv}CBr$ (**2**), respectively, which have been made before less conveniently or in lower yields[5–7] by other routes. The IR and Raman spectra of both **1** and **2** have been reported,[8,9] as has the microwave spectrum of **1**.[10]

$$F_3CCCl{=}CCl_2 \xrightarrow[DMAC]{Zn} F_3CC{\equiv}CZnCl \xrightarrow{X_2} F_3CC{\equiv}CX$$

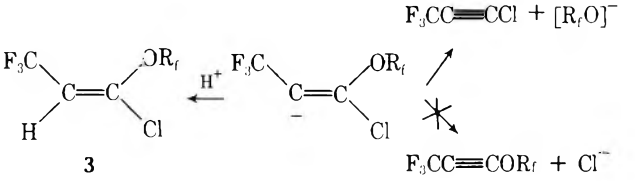
1, X = Cl

2, X = Br

Despite the reported high-yield replacement of Cl^- in **1** by $(F_3C)_3C^-$,[11] the direct halide replacement by R_fO^- in **1** or **2** did not appear very promising because of the known poor nucleophilicity of R_fO^- and the equilibrium[12]

$$R_fCF_2O^- \rightleftharpoons R_fCFO + F^-$$

Furthermore, in view of the established mode of trans addition to acetylenes[13,14] and, hence, also of trans elimination, the intermediate vinylic carbanion would be expected to eliminate R_fO^- rather than Cl^-. On the other hand, conducting the reaction in the presence of a proton source should trap the carbanion and give rise to the perfluoroalkoxy vinyl ether (**3**).



Indeed, when I was treated with "$AgOCF_3$", made in situ from AgF, COF_2, and HF in adiponitrile, compound **3**, bp 49–50 °C, was obtained in about 45% yield. There was no evidence for CF_3O^- addition to the 2 position. Compound **3** was a single isomer, identified as trans (H, OCF_3) by NMR spectroscopy. Treatment with strong base under drastic conditions converted it only to **1** (Scheme I). Irradiation in the presence of a trace of bromine converted **3** to a 50:50 cis/trans mixture. This mixture, upon being passed through soda lime at 210 °C, yielded both **1** and $CF_3C{\equiv}COCF_3$ (**4**), although in low yields and conversions thus confirming the trans elimination mechanism, though not providing a convenient synthetic path to **4**.

Compound **3** was readily converted to the dibromo derivative **5**, which evolved bromine during distillation at atmospheric pressure, but which could be distilled undecomposed in vacuo. Triethylamine converted **5** cleanly to a cis/trans mixture of **6**. No dehydrochlorination was observed.

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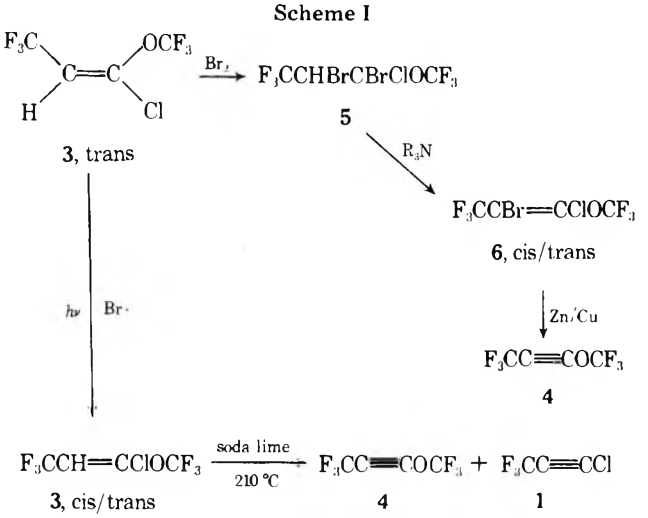
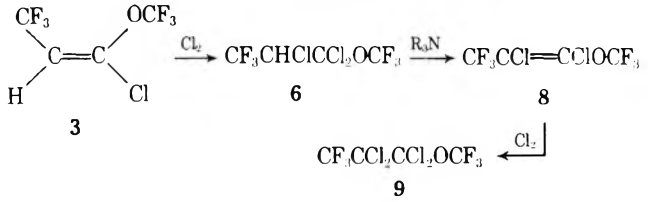
Scheme I

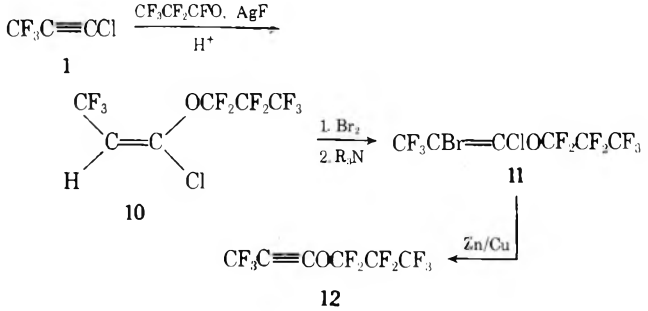


When **6** was treated with zinc–copper couple[15] in diglyme, the desired perfluoroalkoxyacetylene (**4**) was formed and distilled out of the reaction vessel, along with small amounts of **1**. In addition, $CF_3C{\equiv}CZnCl$ was formed, as evidenced by the appearance of the characteristic 2150 cm^{-1} infrared band in the solution, and the formation of $CF_3C{\equiv}CH$ (identified by IR) upon adding water. Yields of crude **4** averaged 45–50%. It appears that only one isomer of **6** is converted to the desired product.

By contrast, under identical dehalogenation conditions neither **8** (obtained as a cis/trans mixture from **3** via chlorination to **6** and dehydrochlorination) nor **9** produced any **4**.



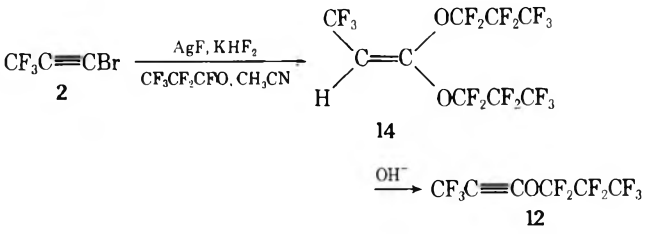
Because the boiling points of **4** and **1** were too close for their convenient separation (0 and 3 °C, respectively) we decided to replace OCF_3 by a larger perfluoroalkoxy group. Replacing CF_2O by CF_3CF_2CFO in the original synthetic scheme, the analogous series of compounds, **10**, **11**, and **12**, was obtained. The 1-perfluoropropoxy-3,3,3-trifluoropropyne (**12**) boiled around 50 °C and was easily separated from **1**, although some yield losses occurred during redistillation because it polymerized in the pot.



As yields of **12** averaged about 46%, again probably arising from just one of the **11** isomers, a synthesis was sought which would overcome this drawback.

The readily prepared $CF_3C{\equiv}CBr$ (**2**) behaved differently toward R_fO^- than **1**: while **13**, the bromo analogue of **10**, was formed in very small yield, the major product was the ketene acetal **14**, bp 118 °C.

Formation of **14** probably proceeds via addition of R_fO^- to **13**, yielding a carbanion capable of rotating around the single bond, and hence of eliminating Br^-.



Reaction of **14** with molten KOH was clean, affording a 30:70 mixture of **12** and starting material per pass, which could be easily separated by distillation for recycling of **14**. This approach constitutes the most convenient synthesis of **12**.

The perfluorinated acetylenic ethers **4** and **12** are colorless liquids (bp 0 and 50 °C, respectively) characterized by a strong C≡C band at 2315 and 2299 cm^{-1}, respectively. They can be stored unchanged at −80 °C, but they homopolymerize slowly at room temperature to polymers which are transparent, probably due to plasticization by lower oligomers. Drying in vacuo produces white powders of high chemical and thermal stability.

This facile homopolymerization of **4** and **12** is in contrast to the homopolymerization of hexafluoro-2-butyne (HFB), where catalysis (γ irradiation,[16] triphenylphosphine,[17] fluoride ion,[18,19] transition metal complexes,[20] or nitrosyl hexafluorophosphate[21]) and generally harsher conditions are necessary.

Compared to $(HFB)_n$,[20] the homopolymers of **4** and **12** exhibit somewhat lower thermal stability (10% weight loss at 470 and 420 °C, respectively, vs. 540 °C for $(HFB)_n$).

The copolymerization of **12** with various fluoromonomers was also investigated. It would be expected that this monomer would be more amenable toward polymerization than HFB, because the $-OC_3F_7$ group is known to offer less resistance to polymerization than the $-CF_3$ group. This study focused on polymerization at high pressures (500–4000 atm) using perfluoropropionyl peroxide (3P) initiator at 25 °C. In order to carry out these polymerizations on a small scale, the monomers and 3P were charged into a platinum tube, sealed, and inserted into a vessel which could be pressurized with nitrogen. Since the platinum tubing readily collapsed, the 500–4000-atm pressure was transferred to the contents of the tube.

Copolymers of **12** containing 50 and 67% HFB were prepared at 4000 atm in quantitative conversion to clear transparent materials. However, these polymers proved to be similar to $(HFB)_n$ and $(12)_n$ in that they were very thermally stable (1% weight loss at 400 °C N_2 atmosphere) and showed no signs of flow in attempts to compression mold samples at temperatures up to 400 °C.

Attempts to copolymerize **12** with tetrafluoroethylene, hexafluoropropene, and $CF_2{=}CFOR_f$ ($R_f = CF_3, C_3F_7$) have been moderately successful and represent the first time that tetrafluoroethylene and the fluorovinyl ethers have been copolymerized with any perfluoroacetylene. Copolymers of tetrafluoroethylene have been prepared which contain 20, 50, and 60% of **12**. They are more transparent and stiffer than Teflon; moreover, these materials flow well under compression molding conditions at 300 °C, in contrast to all other polymers prepared from perfluoroacetylenes.

Thermal analysis results indicated these materials to be genuine copolymers. TGA showed very similar stability for all copolymer samples. Degradation began at ~350 °C compared to 460 °C for polytetrafluoroethylene in a N_2 atmosphere. DTA/DSC at high sensitivities detected transition temperatures or melting of small amounts of crystallites. The copolymer containing 2% **12** shows a melting peak (318–324 °C) a few degrees below that of Teflon, as expected for copolymer. All copolymers of **12** with tetrafluoroethylene decomposed at temperatures >500 °C.

Inherent viscosities have been determined in fluorocarbon oil, Freon E2, which was a solvent for these polymers. The copolymers of **12** with tetrafluoroethylene had inherent viscosities as high as 1.2. The viscosity data suggest that the molecular weight of these copolymers is independent of polymerization pressure and dependent on 3P concentration. Higher conversion of monomers is observed at increased pressure (4000 atm).

Copolymers of **12** containing 50% hexafluoropropene CF_2=$CFOCF_3$ and CF_2=$CFOC_3F_7$ have been prepared. All of these copolymers were much less stable than those based on tetrafluoroethylene. The CF_2=$CFOC_3F_7$ copolymer began to show weight loss at about 200 °C in a N_2 atmosphere with distinct phase transitions in the 60–70 °C region. The other two copolymers were somewhat more thermally stable with a 1% weight loss at about 250 °C and phase transitions in the 75–120 °C region. None of these copolymers showed melting points and they were completely decomposed at temperatures in excess of 500 °C. In contrast to the copolymerization with tetrafluoroethylene, the molecular weights and conversions of copolymers based on the other perfluoromonomers showed a dependence on polymerization pressure.

While structural studies on copolymers containing **12** are not conclusive, it is probable that the polymer chain is linear and contains double bonds. In support of this, infrared and Raman spectra of all copolymers showed the presence of carbon–carbon double bonds in the 1600–1725-cm^{-1} region.

Experimental Section

The following chemicals were purchased and used as received: perfluoropropionyl fluoride from PCR Inc., CF_3CCl=CCl_2 from Columbia Organic Chemicals Co., Inc., and AgF from Ozark-Mahoning Co.

NMR spectra are referred to internal $CFCl_3$.

1-Chlorotrifluoropropyne (1). To a slurry of CF_3C≡$CZnCl$ made from 1 mol of CF_3CCl=CCl_2 by the literature method[3] and stirred in a flask equipped with a −80 °C reflux condenser was added chlorine (44 mL at −80 °C, 1 mol) by passing it over the surface. Chlorine was absorbed exothermally and the flask had to be externally cooled to maintain the temperature at 10–30 °C. When all chlorine had reacted, the −80 °C condenser was replaced by a water-cooled condenser. The mixture was heated to 90–100 °C, and the volatiles were passed through the water condenser to a −80 °C trap. Redistillation on a cold still gave **1**, bp ~3–4 °C in 40–50% yields. Its vapor IR spectrum was in accord with literature data.[8]

Trifluoro-1-bromopropyne (2). To a slurry of CF_3C≡$CZnCl$ made from 1 mol of CF_3CCl=CCl_2 was added dropwise, at 10–20 °C, 1 mol of bromine. After completion of the addition the flask was connected to a vacuum source through a −80 °C trap and the product was distilled over while the flask was warmed slowly to 50 °c. The crude product obtained in ~60% yields was purified by redistillation on a spinning band column. It boils at 24–25 °C and polymerizes slowly at room temperature, but keeps well at −80 °C. The IR spectrum agreed with literature data.[8]

***(E)*-1-Trifluoromethoxy-1-chloro-3,3,3-trifluoropropene (3).** A mixture of 120 mL of adiponitrile (acetonitrile was equally good, but it codistilled with the product), 40 g of silver oxide, 2.0 mL of water, 40 mL (at −80 °C) of CF_3C≡CCl, and 150 g of carbonyl fluoride was loaded into a 320-mL autoclave and shaken for 2 h at 75 °C. After venting off low boilers, the reaction mixture was distilled, and material having bp 40–60 °C was collected. This liquid was stirred overnight with a saturated sodium bicarbonate solution (to remove acyl fluoride impurities characterized by an IR band at 1850 cm^{-1}). The organic layer was separated, run through a short column of alumina, and finally fractionated on an efficient spinning band column. Yields of the cut, bp 49–50 °C, d_{25} = 1.467 g/mL, averaged 40 g (45%).

Similar results were also obtained using Cu_2O instead of Ag_2O in the above procedure.

Anal. Calcd for C_4HClF_6O: C, 22.4; H, 0.47; Cl, 16.6; F, 53.1; mol wt, 214. Found: C, 22.4; H, 0.52; Cl, 16.6; F, 52.9; mol wt (parent mass spectrum peak), 214.

^1H NMR: quartet (J = 6.8 Hz) at 4.70 ppm. ^{19}F NMR: quartet (J = 1.8 Hz) at 57.8 ppm and a doublet of quartets (J = 6.8, 1.8 Hz) at −60.0 ppm in 1:1 ratio assigned to the OCF_3 and CF_3 groups, respectively. IR (in CCl_4): 3077 (w), 1710 (w), 1670 (vs), 1400 (vs), 1300–1100 (vs), 1080 (m), 910 (m), 855 (s), 720 (w) cm^{-1}.

3 (cis/trans). Irradiation of the pure *E* isomer CF_3CH=$CClOCF_3$, to which a few drops of bromine was added, with a sunlamp gave within 2 h a roughly 50:50 mixture of cis/trans isomers as evidenced by: (a) GC showing the appearance of a lower boiling component at 84 mm, the starting material being at 91 mm; (b) boiling point of the mixture dropping to 46–49 °C; and (c) the ^{19}F NMR spectrum showing, in addition to the starting material, two new peaks in a 1:1 ratio, a singlet at −59.0 ppm and a doublet (J = 6.5 Hz) at −60.4 ppm.

Fractional distillation of this mixture gave a lower boiling cut somewhat enriched in the cis isomer (60:40).

***(E)*-1-Perfluoro-*n*-propoxy-1-chloro-3,3,3-trifluoropropene (10).** A mixture of 26 g of silver fluoride, 14 g of sodium bifluoride, 120 mL of adiponitrile, 35 mL (at −80 °C) of CF_3C≡CCl, and 170 g of perfluoropropionyl fluoride was shaken in a 330-mL autoclave for 2 h at 90 °C. Distillation gave 7 mL (20%) of unreacted CF_3C≡CCl, along with 63 g of liquid, bp 80–90 °C, corresponding to a conversion of 80% and a yield of 72%. The liquid was stirred overnight in aqueous sodium acetate and then separated, run through a short alumina-packed column, and redistilled. The main cut has bp 88–90 °C, d_{25} = 1.583 g/mL. It was a single isomer, as shown by GC and NMR data.

Anal. Calcd of $C_6HClF_{10}O$: C, 22.9; H, 0.32; Cl, 11.3; F, 60.4. Found: C, 23.0; H, 0.55; Cl, 11.3; F, 60.5.

^{19}F NMR has peaks at −62.0 (3 F), −83.4 (3 F), −86.4 (2 F), and −131.3 ppm (2 F) (J_{f-H} = 7.5 Hz), consistent with structure **10**. IR (in CCl_4): 3125 (w), 1670 (vs), 1330 (vs), 1300–1100 (vs), 1060 (vs), 1040 (vs), 980 (vs), 970 (s), 855 (s, br), 806–730 (vs), 697 (s, br) cm^{-1}.

1,1-Bis(perfluoro-*n*-propoxy)-3,3,3-trifluoropropene (14). A 330-mL shaker tube was charged with 50.8 g (0.4 mol) of AgF, 15.6 g (0.2 mol) of KHF_2, and 100 mL of acetonitrile. After cooling and evacuation, 34 g (0.2 mol) of CF_3C≡CBr and 133 g (0.8 mol) of perfluoropropionyl fluoride were distilled in. After reaction at 100 °C for 2 h, excess perfluoropropionyl flouride was vented into a trap and saved for later recycle. The residue was filtered to remove solids. This crude product consisted of two layers, an upper layer consisting primarily of acetonitrile and a lower layer which was nearly pure CF_3CH=$C(OC_3F_7)_2$. The lower layer was washed with aqueous sodium acetate, dried in an alumina column, and distilled on a spinning band column (bp 118 °C). Typical yields were 45%, but the system was not optimized.

^{19}F NMR CF_3^aCH=$C(OCF_2^cCF_2^eCF_2^b)(OCF_2^cCF_2^eCF_3^b)$: a, −59.6 (3 F); b, −81.8 (6 F); c, −84.0 (2 F); d, −86.3 (2 F); e, −130.0 ppm (4 F). ^1H NMR: unresolved four-line pattern at 5.1 ppm. IR (gas): 3100 (vw), 1720 (m), 1340 (m), 1250 (s), 1150 (s), 1100 (m), 1030 (w), 1010 (w), 990 (m), 750 (w) cm^{-1}. Mass spectrum: parent peak at m/e 464, plus other peaks consistent with CF_3CH=$C(OC_3F_7)_2$.

2,3,3-Trichloro-3-trifluoromethoxy-1,1,1-trifluoropropane (7). To 21.4 g (0.1 mol) of CF_3CH=$CClOCF_3$ stirred under a −80 °C condenser and irradiated with a sunlamp was added 6 mL of chlorine (at −80 °C, an excess). Uptake of chlorine was rapid, as evidenced by the dissappearance of the C=C band in the IR. After a few hours, the solution was distilled, and the main cut, bp 105–110 °C, was obtained in 23.4 g (82.1%) yield. Redistillation afforded a pure product boiling at 109–110 °C.

Anal. Calcd for $C_4HCl_3F_6O$: C, 16.8; H, 0.35; Cl, 37.2; F, 40.0. Found: C, 16.8; H, 0.39; Cl, 37.3; F, 39.7.

^1H NMR: quartet (J = 7.7 Hz) at 5.50 ppm. ^{19}F NMR: singlet at −56.2 ppm and doublet (J = 7.7 Hz) at −68.8 ppm assigned to OCF_3 and CF_3, respectively.

2,3-Dichloro-1-trifluoromethoxy-3,3,3-trifluoropropene (8). To a solution of 28.5 g (0.1 mol) of $CF_3CHClCCl_2OCF_3$ in 40 mL of *o*-dichlorobenzene was added 14 g (excess) of diisopropylethylamine (triethylamine is equally good). The solution was heated and volatiles were distilled out on a spinning band column. The cut bp 60–72 °C was collected and obtained in 24.2 g (97%) yield. Pure product boils at 72–73 °C, d_{25} = 1.581 g/mL. GC shows the presence of two isomers in about 55:45 ratio.

Anal. Calcd for $C_4Cl_2F_6O$: C, 19.3; H, 0.00; Cl, 28.5; F, 45.8. Found: C, 19.6; H, 0.00; Cl, 28.4; F, 45.9.

^{19}F NMR showed two isomers present: *trans*-dichloro, singlets at −60.1 and −65.2 ppm; *cis*-dichloro, quartets (J = 2 Hz) at −61.0 and −65.2 ppm. IR (in CCl_4): 1630 (vs), 1300–1100 (vs), 1005, 990 (s), 893–885 (s), 844 (s), and 702 (vs) cm^{-1}.

1,1,2,2-Tetrachloro-1-trifluoromethoxy-3,3,3-trifluoropropane (9). A mixture of 12.5 g (0.05 mol) of CF_3CCl=$CClOCF_3$ and 2.8 mL (at −80 °C) of chlorine was stirred under a −80 °C condenser and irradiated with a sunlamp for 2 h, at which time the yellow color

had faded and no C=C band was present in the IR. Distillation gave a little unreacted starting material, then the product, bp 130 °C, d_{25} = 1.739 g/mL, obtained in 13 g (82%) yield.

Anal. Calcd for $C_4Cl_4F_6O$: C, 15.0; H, 0.00; Cl, 44.4; F, 35.6. Found: C, 15.0; H, 0.10; Cl, 44.0; F, 35.8.

IR (in CCl_4): 1300–1200 (vs, br), 1100 (vs), 1020 (s), 935 (m), 910 (w, br), 855 (s, vs), 813 (s, br sh to 730), 702 (s) cm^{-1}.

1-Chloro-1,2-dibromo-1-trifluoromethoxy-3,3,3-trifluoropropane (5). A mixture of 10.7 g (0.05 mol) of $CF_3CH{=}CClOCF_3$ and 8 g (0.05 mol) of bromine was stirred and irradiated with a sunlamp until the red color disappeared. The product boiled around 140 °C (atm) with evolution of bromine, but could be distilled undecomposed at 59–60 °C (35–36 mm), yield 15 g (82%), d_{25} = 2.100 g/mL.

Anal. Calcd for $C_4HBr_2ClF_6O$: C, 12.8; H, 0.27; Cl, 9.47; Br, 42.7. Found: C, 13.0; H, 0.39; Cl, 9.99; Br, 42.3.

1-Chloro-2-bromo-1-trifluoromethoxy-3,3,3-trifluoropropene (6). A mixture of 90 mL (0.6 mol) of $CF_3CH{=}CClOCF_3$ and 34 mL (excess) of bromine was stirred and irradiated with a sunlamp for 3 h (a test of a small sample showed at this time disappearance of the C=C band in the IR and a shift of the C–H band from 3125 to 2985 cm^{-1}). The whole solution was then slowly added to a stirred mixture of 30 mL of o-dichlorobenzene, 500 mL of water, and 100 mL of triethylamine. After the exothermic reaction subsided, the two-phase mixture was stirred for 2 h; then the organic layer was separated and washed twice with dilute hydrochloric acid. It was then run through a bed of alumina and was finally fractionated on a spinning band column. After recovery of 10 g of starting material, the main cut boiled at 86–87 °C. The overall yield was 149 g (83.5%), d_{25} = 1.833 g/mL.

Anal. Calcd for C_4BrClF_6O: C, 16.3; H, 0.00, Br, 27.2; Cl, 12.1. Found: C, 16.4; H, 0.09, Br, 26.5; Cl, 12.1.

IR (in CCl_4): 1620 (vs), 1300–1100 (vs), 968 (vs), 876 (vs), 830 (s), 820–706 (br), 696 (s) cm^{-1}.

1-Chloro-2-bromo-1-perfluoro-*n*-propoxy-3,3,3-trifluoropropene (11). A mixture of 174 g (0.55 mol) of $CF_3CH{=}CClOCF_2CF_2CF_3$ and 29 mL (excess) of bromine was irradiated with a sunlamp for 2 h. The crude mixture was then diluted with 200 mL of o-dichlorobenzene, placed along with 400 mL of water into a 1 L flask, and 88 mL (excess) of triethylamine was added dropwise to the stirred solution. After stirring overnight, the organic phase was washed twice with dilute HCl; then it was run through a short alumina column. Fractionation on a spinning band column gave 17.5 g of recovered starting material, bp 85–80 °C; the remainder boiled at 121–125 °C, d_{25} = 1.844 g/mL, and was obtained in 185 g (94%) overall yield at a conversion of 90%.

Anal. Calcd for $C_6BrClF_{10}O$: C, 18.4; H, 0.00; Br, 20.7; Cl, 9.02; F, 48.3. Found: C, 18.4; H, 0.28; Br, 22.0; Cl, 8.79; F, 48.1.

IR (in CCl_4): 1620 (vs), 1330 (vs), 1300–1120 (vs), 1100 (vs), 1030 (w), 990 (vs), 948 (w), 935 (m), 851 (m), 830 (m), 806–719 (m, br), 697 (s) cm^{-1}.

Trifluoromethoxy-3,3,3-trifluoropropyne (4). To a suspension of 75 g of zinc–copper couple[12] in 250 mL of dry diglyme, stirred at 120 °C, was added dropwise 50 mL of $CF_3CBr{=}CClOCF_3$. After a short induction period, the reaction commenced and proceeded exothermally, so that the temperature stayed at ~140 °C without external heat application. Volatiles were trapped in a −80 °C trap and purified by fractionation. The main product, bp −1 to 0 °C, was obtained in 18 mL (~50%) yield.

Its IR spectrum has very strong bands at 2326, 1300, 1250, 1160, and 1110 cm^{-1}, with weaker bands at 1366, 1028, and 935 cm^{-1}. The C≡C band is clearly distinguishable from that of $CF_3C{\equiv}CCl$ at 2257 cm^{-1}, which was also present along with $CF_3CBr{=}CClOCF_3$ and $CF_3CH{=}CClOCF_3$, as a minor component in the crude first distillate.

The residual reaction mixture had a strong band at 2150 cm^{-1}, ascribed to $CF_3C{\equiv}CZnX$, since addition of water resulted in the evolution of gas identified as $CF_3C{\equiv}CH$ (by IR).

1-Perfluoro-*n*-propoxy-3,3,3-trifluoropropyne (12). (A) To 20 g of zinc–copper couple stirred along with 0.2 g of anhydrous $ZnCl_2$ in 100 mL of dry diglyme at 150 °C was added dropwise 20 mL (37 g, 0.094 mol) of $CF_3CBr{=}CClOC_3F_7$. Heating was maintained at such a rate that steady distillation took place and material having bp 40–55 °C was collected. The distillate was combined with about 2 mL of liquid collected in the −80 °C trap behind the receiver. The combined liquids were washed with 150 mL of cold aqueous sodium acetate solution and, after a further water wash, were passed through a short alumina column. The product was obtained in 12 g (46%) yield. Careful fractionation on a spinning band column gave a heart cut, bp 49–50 °C, which was 99% pure by GC. In the course of distillation about half of the product polymerized in the pot.

^{19}F NMR spectrum was consistent with the structure, $F_3{}^aCC{\equiv}COCF_2{}^bCF_2{}^cCF_3{}^d$: a, −52.8 (3 F); b, −131.2 (J = 1 Hz, 2 F); c, −88.7 (J = 15.1, Hz, 2 F); d, −84.3 (J = 15.5 Hz, 3 F) ppm.

(B) A 500-mL flask was fitted with an N_2 inlet, mechanical stirrer, syringe port, and an outlet to a 50 mL dry ice cooled receiver. The system was purged with nitrogen and charged with 300 g of KOH pellets. After heating to 220–240 °C (molten KOH), the nitrogen flow was turned off and 30 mL of $CF_3CH{=}C(OC_3F_7)_2$ was added dropwise via syringe. After 15 min a slow nitrogen flow was used to drive over all fluorocarbons into the receiver. The product was a 30:70 mixture of $CF_3C{\equiv}COC_3F_7$ and unconverted $CF_3CH{=}C(OC_3F_7)_2$; yields were around 95%.

After repeating the above step several times, the combined products were dried by passage through a short alumina column into a distillation flask. A simple still was used to collect the $CF_3C{\equiv}COC_3F_7$ boiling at 50–52 °C and the $CF_3CH{=}C(OC_3F_7)_2$ boiling at 116–118 °C.

Since normal fractional distillation of $CF_3C{\equiv}COC_3F_7$ results in extensive polymerization, the product was redistilled on a spinning band column as a 30–50% solution in Rimar 101, a fluorocarbon solvent of bp 100 °C which is primarily c-$(CF_2CF_2CF_2CF(C_4F_9)O)$. Pure product boils at 51.5–52 °C.

IR (in CCl_4): 2300 (vs), 1360 (m), 1330 (vs, br), 1260–1060 (vs), 980 (vs), 948 (vs), 893 (w), 873 (vw), 806–714 (s, br) cm^{-1}.

Poly(trifluoromethoxy-3,3,3-trifluoropropyne) $(4)_n$. Freshly redistilled $CF_3C{\equiv}COCF_3$ (about 13 mL) was sealed in a heavy-walled ampule. On standing at room temperature over the weekend, the contents solidified. The ampule was cooled to −80 °C and opened, and the volatiles were distilled out. About 2 mL of liquid was collected, the IR of which showed, apart from unreacted $CF_3C{\equiv}COCF_3$, the presence of $CF_3CH{=}CClOCF_3$ and of carbonyl-containing impurities (1820, 1720 cm^{-1}).

The polymer, obtained in 16 g yield, does not melt on a block up to 320 °C. It sublimes without melting in a Bunsen flame when the spatula reaches red heat. The polymer is amorphous under the microscope and has a C=C absorption at 1670–1640 cm^{-1} in the IR.

Poly(perfluoropropoxy-1-perfluoropropyne) $(12)_n$. Pure samples of $CF_3C{\equiv}COCF_2CF_2CF_3$ polymerized on standing for 24 h at room temperature to transparent, slightly reddish solids. Drying in vacuo at 230 °C gave a colorless solid.

Anal. Calcd for $C_6F_{10}O$: F, 68.4. Found: F, 68.4.

No glass transition was noted between −120 and 380 °C; 10% weight loss occurs at 420 °C under N_2 and at 380 °C in air.

General Procedure for High-Pressure Polymerization. Small-scale polymerizations at 500–4000 atm were carried out in platinum tubes. Platinum tubing of 13-mm diameter was cut to the desired length (20 cm) and sealed at one end. The tube was flamed out while attached to a vacuum line, cooled to 25 °C, and filled with nitrogen. After further cooling in wet ice/acetone, the required amount of perfluoropropionyl peroxide solution in F-113 was syringed into the chilled tube. After freezing the 3P/F-113 solution in liquid nitrogen, the tube was evacuated and the appropriate monomers were distilled in via the vacuum line system. The top was then pinched off with a C clamp and melt sealed.

The cold platinum tube was then transferred to a shaker tube, pressurized with nitrogen to the desired pressure, and allowed to stand at 25 °C for 24 h. Since the platinum tube readily collapsed, the pressure was transferred to the contents within the tube.

After removal from the shaker tube, the platinum tubes were refrozen in liquid nitrogen, opened, and attached to a vacuum line. The tube was allowed to warm up under vacuum and any volatiles were condensed in a trap for analysis. Finally, the tube was cut open to remove any polymer. The results are summarized (see Table I in supplementary material).

Volatiles were analyzed by IR, checking for the presence of –C≡C– and –C=C– absorptions in the region of 2440–2220 and 1640–1590 cm^{-1}, respectively.

All viscosity measurements were carried out at 30 °C in Freon E2. In all cases very dilute solutions (~0.015 g/L) were employed.

Supplementary Material Available: TGA curves for $(4)_n$ and $(12)_n$ and a table of the copolymers prepared (Table I) (2 pages). Ordering information is given on any current masthead page.

Registry No.—1, 673-93-8; **2**, 819-01-2; *trans*-**3**, 63904-26-7; *cis*-**3**, 63904-27-8; **4**, 63904-24-5; $(4)_n$, 63904-25-6; **5**, 63904-28-9; *cis*-**6**, 63904-29-0; *trans*-**6**, 63904-30-3; **7**, 63904-31-4; *cis*-**8**, 63904-32-5; *trans*-**8**, 63904-33-6; **9**, 63904-34-7; **10**, 63904-35-8; *cis*-**11**, 63904-36-9; *trans*-**11**, 63904-37-0; **12**, 63904-22-3; $(12)_n$, 63904-23-4; 14, 63904-38-1; $CF_3C{\equiv}CZnCl$, 63904-39-2; chlorine, 7782-50-5; carbonyl flouride, 353-50-4; perfluoropropionyl fluoride, 422-61-7.

References and Notes

(1) Presented in part at the 2nd Joint CIC/ACS Conference Montreal, Canada, May 29–June 2, 1977.
(2) Available from Columbia Organic Chemical Co., Inc., P.O. Box 9696, Columbia, S.C. 29290.
(3) W. G. Finnegan and W. P. Norris, *J. Org. Chem.*, **28**, 1139 (1963).
(4) This reaction was first demonstrated by Dr. F. D. Marsh.
(5) W. P. Norris and W. G. Finnegan, *J. Org. Chem.*, **31**, 3293 (1966), made $CF_3C{\equiv}CCl$ in trace amounts by the reaction of cupric chloride with the zinc derivative.
(6) A. M. Shchekotikhin, V. S. Blagoveshchenskii, U. V. Sidorenko, and O. K. Denisov, *Zh. Vses. Khim. Ova.*, **7**, 580 (1962); also USSR Patent 169 522 (March 17, 1965) [*Chem. Abstr.*, **63**, 2897 (1965)], synthesized both $CF_3C{\equiv}CCl$ and $CF_3C{\equiv}CBr$ by gas-phase dehydrohalogenation of $CF_3CCl{=}CHCl$ and $CF_3CBr{=}CHBr$, respectively, with NaOH at 210–290 °C in 19–27% yields.
(7) $CF_3C{\equiv}CX$ compounds (X = Cl, Br, I) have also been prepared by the halogenation of $CF_3C{\equiv}CLi$: Dr. E. Kloster Jensen, the University of Oslo, personal communication.
(8) E. Augdahl, E. Kloster-Jensen, V. Devarajan, and S. J. Cyvin, *Spectrochim. Acta, Part A*, **29**, 1329 (1973).
(9) E. Augdahl, E. Kloster-Jensen, V. Devarajan, and S. J. Cyvin, *Aust. J. Chem.*, **26**, 269 (1973).
(10) A. Bjørseth and K. M. Marstokk, *J. Mol. Struct.*, **13**, 191 (1972).
(11) N. I. Delyagina, B. L. Dyatkin, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **No. 7**, 1666 (1974).
(12) R. D. Chambers, "Fluorine in Organic Chemistry", Wiley, New York, N.Y., 1973, pp 223 ff.
(13) E. K. Raunio and T. G. Frey, *J. Org. Chem.*, **36**, 345 (1971).
(14) W. E. Truce and G. J. W. Tichenor, *J. Org. Chem.*, **37**, 2391 (1972).
(15) R. D. Smith and H. E. Simmons, *Org. Synth.*, **41**, 72 (1961).
(16) H. C. Brown and H. L. Gewandter, *J. Org. Chem.*, **25**, 2071 (1960).
(17) W. R. Cullen and D. S. Dauson, *Can. J. Chem.*, **45**, 2887 (1967).
(18) J. A. Jackson, *J. Polym. Sci.*, **10**, 2935 (1972).
(19) W. T. Flowers, R. N. Haszeldine, and P. G. Marshall, *Chem. Commun.*
(20) J. L. Boston, D. W. A. Sharp, and G. Wilkinson, *J. Chem. Soc.*, 3488 (1962).
(21) S. K. M. Ehrenstorfer, *J. Polym. Sci., Part A*, **7**, 969 (1969).

Effects of Bridgehead Substituents on the Mass Spectral Fragmentation Pathways for the 9-Methyl-9-azabicyclo[3.3.1]nonane Framework

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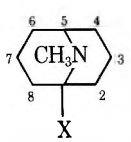
The mass spectral fragmentations of the 9-methyl-9-azabicyclo[3.3.1]nonane nucleus functionalized at a bridgehead position with H (**1**), OH (**2**), OCH_3 (**3**), $OCOCH_3$ (**4**), $NHCH_3$ (**5**), Cl (**6**), and CN (**7**) are reported. The productions of the base ions were found to be strongly dependent on the nature of the bridgehead substituent. For the parent amine **1** the base ion is formed by α cleavage of the 1,2 bond, loss of cyclopropane (carbons 2, 3, and 4), and loss of hydrogen from carbon 6. For the bridgehead hydroxy and methylamino derivatives the most abundant ions arise from α scission of the 1,2 bond, loss of ethylene (carbons 2 and 3), and loss of hydrogen from carbon 5. Bridgehead methyl ether **3** gives rise to its base peak via α cleavage of the 1,2 bond, loss of cyclopropane, and loss of the *O*-methyl group. Acetate **4** takes part in a Hofmann–Loeffler type abstraction of an acetyl hydrogen by the initially generated nitrogen radical cation (in concert with the expulsion of ketene), followed by α cleavage of the 1,2 bond and loss of cyclopropane in route to its base peak. The α-amino chloride merely expels chlorine to produce its base ion. The 1-cyano derivative **7** forms its base peak by cleavage of the 4,5 bond, formation of an iminium radical by attack of the carbon radical (produced from the previous α cleavage) on the cyano carbon, homolytic scission of the bond between carbon 1 and the iminium carbon, and finally cleavage of the 2,3 bond. Other less important fragmentation sequences are also discussed.

Investigations focused on the performance of bridgehead functionalized bridged bicyclic compounds have proven to be of tremendous value in the elucidation of the relationships between structure and reactivity.[2,3] During the last few years heterobicyclic materials (in which the heteroatom is adjacent to the bridgehead carbon atom which bears the bridgehead functionality) have been subjected to various theoretical and experimental tests, the results of which have provided some very interesting postulates pertaining to the relative degrees of stabilization (or destabilization) by resonance and/or induction via the heteroatom.[4–6] In this report, the substantial effects of a bridgehead substituent on the electron-impact-induced fragmentation patterns for the 9-methyl-9-azabicyclo[3.3.1]nonane (granatanine) system (**1–7**) are described.[7,8]



1, X = H
2, X = OH
3, X = OCH_3
4, X = $OCOCH_3$
5, X = $NHCH_3$
6, X = Cl
7, X = CN

Previous reports concerned with interpretations of the mass spectra of compounds in the granatanine system have dealt exclusively with substrates having functionality at the 3 position.[9] In all cases, homolytic cleavage of a carbon–carbon bond adjacent to the nitrogen was shown to be the primary fragmentation process leading ultimately to the production of the base ion.[10] In a recent report from this laboratory it was disclosed that, with certain 1-alkoxy-9-methyl-9-azabicyclo[3.3.1]nonanes, the Hofmann–Loeffler hydrogen-abstraction process can compete effectively with the usual α-cleavage mechanism.[11] For three of the compounds whose mass spectra have been examined in the present study, scission of the 1,2 bond does *not* ultimately result in the formation of the base ion. Furthermore, for the remaining four compounds, wherein cleavage of the 1,2 bond is the predominant initial fragmentation step, the nature of the bridgehead substituent exerts considerable influence on subsequent fragmentations, particularly those leading to the base ions.

Results and Discussion

Table I collects the relative intensity data for the important ions derived from electron impaction of the various bridgehead functionalized 9-methyl-9-azabicyclo[3.3.1]nonanes **1–7**.[12] Inspection of the data reveals that two fragmentation pathways are common to all of the compounds investigated; these sequences are outlined in Chart I. Following α cleavage to produce a′, cyclopropane (or its equivalent) is expelled to provide radical cation b, which in turn goes on to cation c by the loss of a hydrogen atom.[13] In support of the process involving the expulsion of cyclopropane (a′ → b), appropriate

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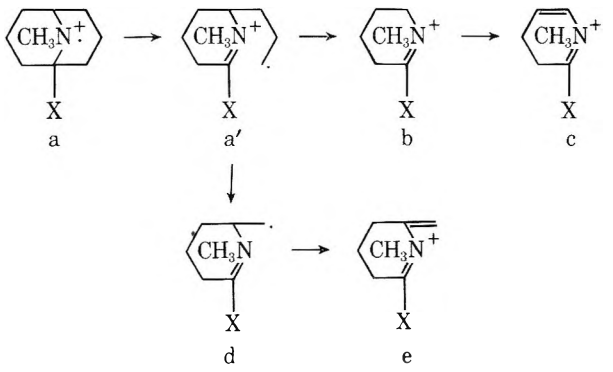
Table I. Relative Intensity Data for Bridgehead Substituted Amines

			m/e; ion; %			
1,[a] X = H	2,[a] X = OH	3[a] X = OCH_3	4,[a] X = $OCOCH_3$	5,[a] X = $NHCH_3$	6,[a] X = Cl	7,[a] X = CN
139; a; 27	155; a; 71	169; a; 52	197; a; 44	168; a; 63	173; a; 46	164; a; 26
138; m; 2	154; g; 5	154; g; 68	169; d; 5	153; g; 20	145; d; 9	136; d; 3
111; d; 5	138; m; 1	141; d; 22	168; e; 2	140; d; 20	144; e; 52	135; e; 19
110; e, n; 35	137; l; 4	140; e; 98	155; b, h; 92	139; e; 100	138; m; 100	122; b; 12
97; b; 25	127; d; 23	138; m; 1	154; c, g; 40	138; m; 3	137; l; 29	121; c; 41
96; c; 100	126; e; 100	127; b; 79	138; m; 21	137; l; 3	131; b; 88	110; n; 100
	113; b, f; 100	126; c; 94	137; l; 65	126; b; 78	130; c; 84	
	112; c; 95	112; f; 100	127; j; 22	125; c; 56	110; n; 77	
	110; n; 4	110; n; 19	126; k; 80	110; n; 16		
			113; i; 100			
			112; f; 76			
			110; n; 16			

[a] Registry no.: **1**, 491-25-8; **2**, 56258-84-5; **3**, 63989-30-0; **4**, 63989-31-1; **5**, 63989-32-2; **6**, 51209-45-1; **7**, 63989-33-3.

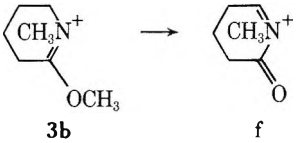
Chart I



metastable peaks were detected for alcohol **2** (*m/e**, 82.4), ether **3** (*m/e**, 95.5), and amine **5** (*m/e**, 94.5). Furthermore, for bridgehead alcohol **2** a mass-analyzed ion kinetic energy (MIKE) spectrum[14] positively confirmed the loss of cyclopropane from the *m/e* 155 ion (**2a′**) as the *only* pathway leading to the production of the *m/e* 113 ion (**2b**). Immonium ion **1c** is the base peak in the mass spectrum of granatanine itself.

In the other fragmentation scheme common to all of the granatanines of the present study, radical cation a′ expels ethylene (substantiated by the mass-analyzed ion kinetic energy spectrum for the amino alcohol **2**) to generate radical cation d, which then can lose a hydrogen from carbon 5 to give cation e. The a′ → d → e processes are responsible for the base peaks in the mass spectra of the bridgehead hydroxy and methylamino derivatives **2** and **5**, respectively.

For the α amino bridgehead methyl ether **3**, the base peak (f) is derived from radical cation **3b** by the loss of the methyl group bonded to oxygen (eq 1). The **3b** → f step is supported

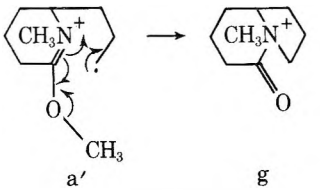


(1)

3b f

by a metastable peak at *m/e** 98.8 and is in complete agreement with the results previously reported for several other 1-alkoxy-9-methyl-9-azabicyclo[3.3.1]nonanes.[11]

Bridgehead methyl ether **3** also gives rise to an abundant ion (*m/e* 154) formed by the loss of methyl radical from the molecular ion. This process (a′ → g) is formulated as taking place as shown in eq 2. If the loss of methyl radical and the C(2)–N bond formation occur simultaneously with the α cleavage (a → a′), the process is essentially a Wagner–Meerwein type migration.[11,15] In addition to **3**, bridgehead acetate **4** and amine **5** exhibit the types of cleavages depicted in eq 1 and 2.



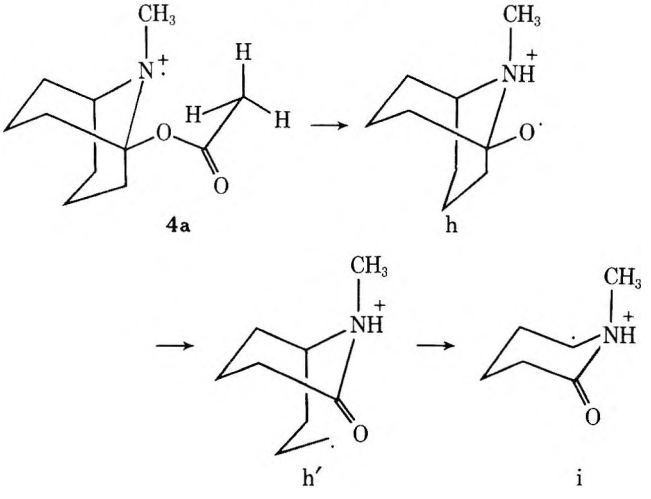
(2)

a′ g

The base peak (i) of amino acetate **4** is produced by yet another fragmentation sequence (Chart II). In a manner analogous to the hydrogen-transfer step of the condensed-phase Hofmann–Loeffler reaction, the molecular ion **4a** (an amininium ion) abstracts an acetyl hydrogen and simultaneously expels ketene to generate the ammonium alkoxy radical h, which undergoes α scission to give the isomeric species h′; loss of cyclopropane from h′ provides the most intense ion in the spectrum (i). The fragmentations outlined in Chart II have ample precedence in the mass spectra of various 1-substituted secondary and tertiary alkoxy granatanines.[11] The availability of activated (by the carbonyl group) hydrogens suitable for abstraction by nitrogen via an intramolecular six-membered transition state, and the fact that a small neutral molecule (ketene) can be eliminated in concert with the hydrogen transfer are responsible for the pathway illustrated in Chart II. Moreover, Green and co-workers have recently demonstrated conclusively that the Hofmann–Loeffler reaction can indeed take place in the mass spectrometer.[16]

Two other fragmentation sequences are also found in the mass spectrum of acetate **4**. Radical cation h′ can lose ethylene to provide j, which can go on to k by the loss of a hydrogen

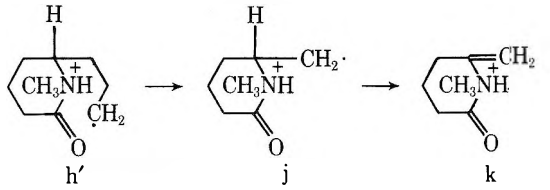
Chart II



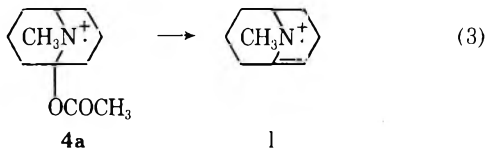
4a h

h′ i

Chart III



atom (Chart III). Finally, amino acetate **4** also displays a relatively highly abundant ion at *m/e* 137 which corresponds to the elimination of acetic acid from the molecular ion to generate the bridgehead enamine radical cation **l** (eq 3). Of the

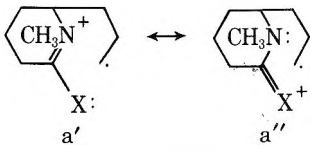


(3)

other substrates investigated, only the bridgehead chloride **6** presents a relatively important signal for the a → l transformation.[17]

The α amino chloride **6** gives rise to the base peak in its mass spectrum by still another primary fragmentation mechanism: the loss of atomic chlorine from the molecular ion to give immonium ion m (Chart IV). The **6a** → m transformation has been documented previously,[11] and has also recently been found to take place in the somewhat related 2-chloro-4-phenylquinuclidine system.[18,19] The fact that a *trans*-azacyclohexene (m) can indeed be generated derives support from the extraordinarily high rate of solvolysis of α-amino bridgehead chlorides.[6c] As indicated in Chart IV, immonium ion m eliminates ethylene to produce n. Among the other substrates examined here only the acetoxy derivative **4** shows a relatively intense signal for the bridgehead immonium ion m.

For the bicyclic amines **1–6**, the α-cleavage process within the molecular ion occurs predominantly (if not exclusively) at the 1,2 bond (see a in Chart I) so that the 1-heteroatom can assist in stabilizing the cleaved species a′ by resonance (a″).



With the bridgehead nitrile **7**, such resonance is not likely; moreover, cleavage of the 1,2 bond provides **7a′** which is destabilized via resonance and induction by the electron-withdrawing cyano group. Consequently, the 4,5 bond is preferentially cleaved in route to the base ion (Chart V). Radical **7o** attacks the cyano carbon to produce isomeric radical **7p** which undergoes α cleavage to afford the resonance-stabilized radical **7q** which loses 2-cyanoethyl radical to provide the base ion n. The **7o** → **7p** transformation is completely analogous to that observed in the condensed state with the bornyl radical.[20]

Chart IV

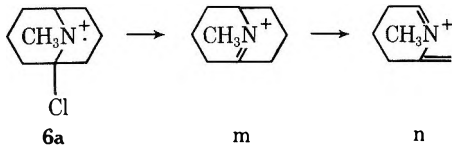
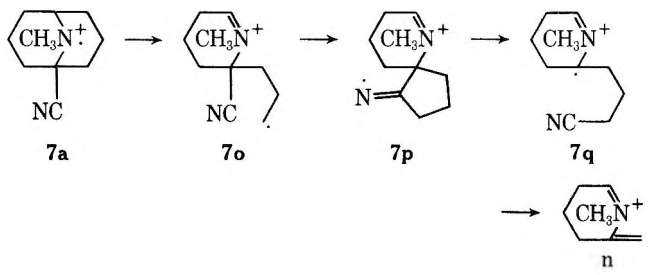


Chart V



Conclusion

It is clear from the above discussions that the nature of the bridgehead substituent plays an extremely important role in directing the fragmentation paths, particularly those leading to the base ions. The directive role of the α substituent manifests itself even though the fragmentations are triggered by the ionization of the nitrogen atom. In summary, it should be emphasized that four different initial fragmentations are responsible for the productions of the base ions: α cleavage of the 1,2 carbon–carbon bond (compounds **1, 2, 3, 5**), α cleavage of the bond between the bridgehead carbon and the substituent (compound **6**), α cleavage of the 4,5 carbon–carbon bond (compound **7**), and hydrogen abstraction from the side chain by nitrogen (compound **4**). The knowledge gained here on the strong dependence of the important fragmentation pathways on the nature of a substituent α to a nitrogen should be highly valuable in studies engaged in the elucidation of the structures of alkaloids utilizing mass spectrometry.

Experimental Section

Mass spectra were obtained with an A.E.I. MS-9 mass spectrometer operating at an ionization voltage of 70 eV and at a source temperature of about 175 °C. The mass-analyzed ion kinetic energy (MIKE) spectra were measured with the Varian MAT-311 instrument focused on the mass/charge value of 155 and operated at 3 kV. ^{1}H NMR spectra were measured on a Varian Associates T-60 instrument. Infrared spectra were recorded on a Perkin-Elmer 457 spectrophotometer. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are not corrected; boiling points are also uncorrected. All substrates were purified by preparative gas chromatography (with a Varian Aerograph 90-P apparatus equipped with a 5 ft. × 0.25 in. stainless-steel column packed with 20% SE-30 on Chromosorb G) immediately prior to mass spectral measurements; the column temperatures employed for sample collection were about 190 °C (which established that the substrates are thermally stable under the conditions used for mass spectrometry). Compounds **1**,[6] **2**,[6] **5**,[21] and **6**[6] are known and were prepared according to published procedures. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor Mich.

1-Methoxy-9-methyl-9-azabicyclo[3.3.1]nonane (3). To a 200-mL round-bottomed flask was added 3.10 g (0.02 mol) of amino alcohol **2** and 50 mL of cold thionyl chloride. After 1, the solution was heated at reflux for 60 h, after which the thionyl chloride was distilled. After cooling to room temperature, methanol and then saturated aqueous sodium carbonate solution were added, and the resulting solution was extracted with methylene chloride. The combined organic extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator to a liquid whose GC analysis indicated the presence of **2** and **3** in the ratio 14:86. Amino ether **3** was isolated by preparative thick-layer chromatography (silica gel, methanol) and distillation (bp ~85 °C, 0.25 Torr): NMR ($CDCl_3$) δ 3.09 (s, 3 H, OCH_3), 2.96 (m, 1 H, NCH), 2.20 (s, 3H, NCH_3), 2.2–1.2 (m, 12 H, CH_2).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 71.00; H, 11.27; N, 8.20.

9-Methyl-9-azabicyclo[3.3.1]non-1-yl Acetate (4). A solution of 646 mg (3.72 mmol) of amino chloride **6**, 7 mL of glacial acetic acid, 1 mL of acetic anhydride, and 1 g of anhydrous sodium acetate was stirred at room temperature for 2 days, after which methylene chloride and sufficient 10% aqueous sodium hydroxide solution to render the mixture basic were added. The layers were separated and the aqueous phase was extracted with methylene chloride. The combined organic extracts were dried over Na_2SO_4 and concentrated to 851 mg of liquid, most of which was acetic anhydride. Preparative GC provided pure amino acetate **4**: mp 63–66 °C; NMR ($CDCl_3$) δ 3.13 (m, 1 H, NCH), 2.52 (s, 3 H, NCH_3), 2.2–1.2 (m, 12 H, CH_2), 2.00 (s, 3 H, $OCOCH_3$); IR ($CHCl_3$) 1720 cm^{-1}.

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.62; H, 9.77; N, 7.02.

1-Cyano-9-methyl-9-azabicyclo[3.3.1]nonane (7). To a solution of 545 mg (3.14 mmol) of amino chloride **6** in 30 mL of *N,N*-dimeth-

ylformamide (distilled from CaO) was added 1.5 g of sodium cyanide. The mixture was stirred at room temperature under nitrogen for 4 days, after which methylene chloride and water were added. The layers were separated and the organic phase was washed with water, dried (Na_2SO_4), and concentrated to 40 mg of liquid from which pure amino nitrile **7** was obtained by preparative GC: NMR ($CDCl_3$) δ 2.88 (m, 1 H, NCH), 2.68 (s, 3 H, NCH_3), 2.3–1.2 (m, 12 H, CH_2); IR ($CHCl_3$) 2240 cm^{-1}.

Acknowledgments. The author is grateful to Mrs. Margaret Johnson for measuring the mass spectra of compounds **1–7**, to Dr. Woodfin V. Ligon, Jr., for the MIKE spectra, and to Professor John R. Wiseman for providing partial support.

Registry No.—Thionyl chloride, 7719-09-7; sodium cyanide, 143-33-9.

Supplementary Material Available. Bar graphs of the mass spectra of compounds **1–7** (7 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Correspondence concerning this manuscript should be directed to the author at the Organic and Polymer Chemistry Branch, General Electric Corporate Research and Development Center, Schenectady, N.Y. 12301.
(2) R. C. Fort, Jr., and P. v. R. Schleyer, *Adv. Alicycl. Chem.*, **1**, 283 (1966).
(3) R. C. Fort, Jr., "Carbonium Ions", Vol. 4, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N.Y., 1973; W. Parker, R. L. Tranter, C. I. F. Watt, L. W. K. Chang, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **96**, 7121 (1974), and references therein.
(4) Reduction of α-amino bridgehead ethers: P. G. Gassman and B. L. Fox, *J. Am. Chem. Soc.*, **89**, 338 (1967); J. O. Reed and W. Lwowski, *J. Org. Chem.*, **36**, 2864 (1971); P. Kovacic, J.-H. Liu, E. M. Levi, and P. D. Roskos, *J. Am. Chem. Soc.*, **93**, 5801 (1971); S. J. Padegimas and P. Kovacic, *J. Org. Chem.*, **37**, 2672 (1972).
(5) Solvolysis reactions: (a) R. D. Fisher, T. D. Bogard, and P. Kovacic, *J. Am. Chem. Soc.*, **95**, 3646 (1973); (b) P. G. Gassman, R. L. Cryberg, and K. Shudo, *J. Am. Chem. Soc.*, **94**, 7600 (1972); (c) C. A. Grob and A. Sieber, *Helv. Chim. Acta*, **50**, 2531 (1967); (d) T. A. Wnuk and P. Kovacic, *J. Am. Chem. Soc.*, **97**, 5807 (1975); (e) W. P. Meyer and J. C. Martin, *J. Am. Chem. Soc.*, **98**, 1231 (1976).
(6) Syntheses and properties of bridgehead olefins: (a) C. B. Quinn and J. R. Wiseman, *J. Am. Chem. Soc.*, **95**, 1342 (1973); (b) C. B. Quinn and J. R. Wiseman, *J. Am. Chem. Soc.*, **95**, 6120 (1973); (c) H. O. Krabbenhoft, J. R. Wiseman, and C. B. Quinn, *J. Am. Chem. Soc.*, **96**, 258 (1974).
(7) For reports dealing with the mass spectra bridgehead-substituted bridged bicyclic compounds; see: (a) Z. Dolejsek, S. Hala, V. Hanus, and S. Landa, *Collect. Czech. Chem. Commun.*, **31**, 435 (1966); (b) J. W. Greidanus, *Can. J. Chem.*, **49**, 3210 (1971); (c) D. C. DeJongh and S. H. Schrader, *J. Am. Chem. Soc.*, **88**, 3881 (1966); (d) A. G. Yurchenko, F. N. Stepanov, S. S. Isaeva, B. M. Zolotarev, V. I. Kadenstev, and O. S. Chizhov, *Org. Mass Spectrom.*, **3**, 1401 (1970).
(8) For reports dealing with the mass spectra of bicyclo[3.3.1]nonanes, see: (a) R. Nicoleti and A. Gambacurta, *Org. Mass. Spectrom.*, **7**, 699 (1973); (b) J. Cable, J. K. MacLeod, M. R. Vegar, and R. J. Wells, *Org. Mass. Spectrom.*, **7**, 1137 (1973); (c) J. R. Dalton, G. J. James, and J. G. Morris, *J. Chem. Eng. Data*, **20**, 125 (1975); (d) J. A. Peters, B. van de Graaf, P. J. W. Schuyl, T. M. Wortel, and H. van Bekkum, *Tetrahedron*, **32**, 2735 (1976).
(9) R. D. Guthrie and J. F. McCarthey, *J. Chem. Soc. C.*, 1207 (1966); (b) W. M. Bryant, III, A. L. Burlingame, H. O. House, C. G. Pitt, and B. A. Tefertiller, *J. Org. Chem.*, **31**, 3120 (1966).
(10) Similar results have been observed for the tropane system: (a) E. C. Blossey, H. Budzikiewicz, M. Ohashi, G. Fodor, and C. Djerassi, *Tetrahedron*, **20**, 585 (1964); (b) J. Parello, P. Longevaille, W. Vetter, and J. A. McCloskey, *Bull. Soc. Chim. Fr.*, 2787 (1963); (c) J. E. Dewhurst, J. J. Kaminski, and J. H. Supple, *J. Heterocycl. Chem.*, **9**, 507 (1972).
(11) H. O. Krabbenhoft, *J. Org. Chem.*, **41**, 1774 (1976).
(12) Bar graphs of the mass spectra of the compounds **1–7** appear in the microfilm edition; see paragraph at end of paper regarding supplementary material.
(13) For alcohol **2** the loss of hydrogen from radical ion b can occur from carbon 6 (to give **2c**) or from the hydroxyl group (to give **2f**). An attempt to distinguish between these two pathways by examining the mass spectrum of partially deuterated **2**-OD gave inconclusive results.
(14) R. G. Cooks, J. H. Beynon, R. M. Caprioli, and G. R. Lester, "Metastable Ions", Elsevier, Amsterdam, 1973, pp 42–44.
(15) F. Komitsky, Jr., J. E. Gurst, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 1398 (1965).
(16) M. M. Green, J. M. Moldowan, M. W. Armstrong, T. L. Thompson, K. L. Sprague, A. J. Hass, and J. J. Artus, *J. Am. Chem. Soc.*, **98**, 849 (1976).
(17) By measuring the mass spectrum of 9-methyl-9-azabicyclo[3.3.1]non-1-ene[6c] itself, it was found that the ions at *m/e* values of 136, 122, 109, 108, 94, 82, 81, 68, and 67 are daughters of **1** (H. O. Krabbenhoft, Ph.D. Thesis, University of Michigan, Ann Arbor, Mich., 1974).
(18) H. Achenbach, J. Worth, W. Schneider, and H. Bochow, *Org. Mass Spectrum*, **10**, 111 (1975); see also B. E. Maryanoff and R. O. Hutchins, *J. Org. Chem.*, **37**, 3475 (1972).
(19) The loss of bridgehead chloride is also responsible for the base peak in the bicyclo[3.3.1]nonane (H. O. Krabbenhoft, Ph.D. Thesis, University of Michigan, Ann Arbor, Mich., 1974) and adamantane[7a] systems.
(20) J. A. Berson, C. H. Olsen, and J. S. Walia, *J. Am. Chem. Soc.*, **84**, 3337 (1962).
(21) C. B. Quinn, Ph.D. Thesis, University of Michigan, Ann Arbor, Mich., 1973.

Effects of the Alkyl Portion of the Alkoxy Group on the Mass Spectrometric Fragmentation Pathways for the 1-Alkoxy-9-oxabicyclo[3.3.1]nonane System and Comparison with the 1-Alkoxy-9-methyl-9-azabicyclo[3.3.1]nonane System

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The mass spectral fragmentations of the 9-oxabicyclo[3.3.1]nonane nucleus substituted at a bridgehead position with OCH_3 (**1**), OC_2H_5 (**2**), $OCH(CH_3)_2$ (**3**), $OC(CH_3)_3$ (**4**), OH (**5**), and OC_6H_5 (**6**) are reported. The ketals **1** and **2** and hemiketal **5** give rise to their base peaks via α cleavage of the 1,2 bond, loss of ethylene, isomerization to the molecular ion of the corresponding 5-hexenoic acid derivative by means of homolytic scission of the 5,9 carbon–oxygen bond, and a McLafferty rearrangement; a combination of high resolution mass spectral measurements and mass-analyzed ion kinetic energy spectra, as well as the mass spectrum of methyl 5-hexenoate, were utilized to establish the fragmentation sequences leading to the base peaks of **1**, **2**, and **5**. For the branched chain ketals **3** and **4**, a hydrogen from the alkyl portion of the alkoxy group is transferred to an oxygen atom (probably the 9 oxygen atom via a Barton hydrogen-abstraction process within the molecular ion), after which expulsion of the hydrocarbon side chain as an alkene, loss of ethylene, and a McLafferty rearrangement (similar to that observed for compounds **1**, **2**, and **5**) take place. Comparison of the 1-alkoxy-9-oxabicyclo[3.3.1]nonane system with the 1-alkoxy-9-methyl-9-azabicyclo[3.3.1]nonane system revealed that the pathways leading to the base peaks in each system are unique.

In a recent report from this laboratory, the principal mass spectral fragmentation patterns of the 1-alkoxy-9-methyl-9-azabicyclo[3.3.1]nonane system were elucidated.[2] It was established that the nature of the alkoxy group exerts considerable influence on the fragmentation processes, particularly those leading to the base peaks. Thus, it was found that for the α-amino bridgehead ethers in which the R group is derived from a *primary* or *secondary* alcohol the base peaks occur without exception at *m/e* 112. Chart I contains the mechanistic pathway proposed to account for the generation of the *m/e* 112 ion. The molecular ion undergoes α cleavage to produce an ammonium ion which then consecutively expels cyclopropane and the R group to provide the base peak. On the other hand, while the *tertiary* alkoxy amines also display intense signals at *m/e* 112, the base ions are at *m/e* 113. Chart II summarizes the sequences presented to rationalize the formations of the *m/e* 113 ions. In a manner analogous to the hydrogen-transfer process of the Hofmann–Loeffler reaction,[3] the molecular ion (an amininium ion) abstracts a hydrogen from the alkoxy side chain and (sometimes simultaneously) expels the alkyl portion of the side chain to give an ammonium alkoxy radical which undergeos α cleavage and expulsion of cyclopropane to afford the base peak. (The *secondary* alkoxy amines also give rise to relatively abundant signals at *m/e* 113 on account of the availability of hydrogens conformationally suitable for abstraction by the initially generated nitrogen radical cation.)

In order to ascertain whether or not the conformational effects of the alkyl portion of the 1-alkoxy group found for the 9-azabicyclo[3.3.1]nonane system can be extended to other heterobicyclic frameworks, the mass spectra of some 1-alkoxy-9-oxabicyclo[3.3.1]nonanes (**1–4**) have been measured, as well as the hemiketal **5** and phenyl ketal **6**. Until now there have been no published reports dealing with the mass spectrometry of the 9-oxabicyclo[3.3.1]nonane skeleton.

Chart I

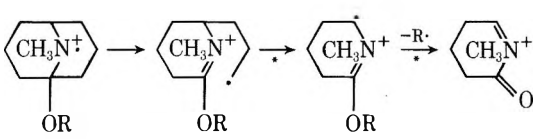
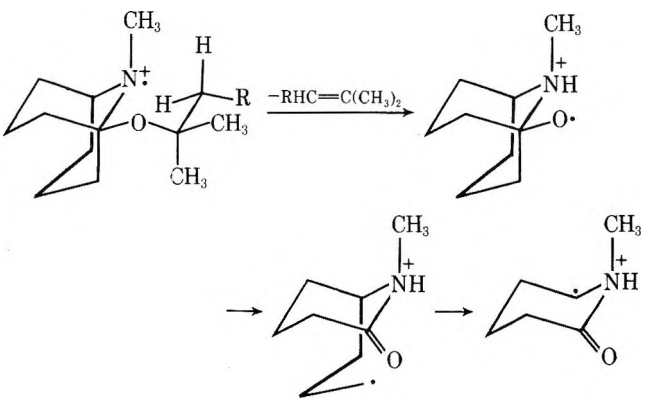
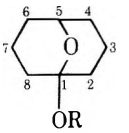


Chart II



Results and Discussion

Table I collects the relative intensity data for the important fragment ions in the mass spectra of compounds **1–6**.[4] Upon



1, R = CH_3 **4**, R = $(CH_3)_3C$
2, R = CH_3CH_2 **5**, R = H
3, R = $(CH_3)_2CH$ **6**, R = C_6H_5

inspection of the data in Table I, it is seen that the most striking features are: (1) that the ketals **1–4** show only *weak* signals at *m/e* values of 99 and 100, corresponding to the oxa analogues of the terminal aza ions shown in Charts I and II, respectively, which are the most abundant ions in the mass spectra of the 1-alkoxy-9-methyl-9-azabicyclo[3.3.1]nonanes;[2,5] and (2) that, while methyl ether **1** has its base peak at *m/e* 74 and its next higher homologue (ethyl ether **2**) gives rise to its base peak at *m/e* 88 (which is consistent with the 14 amu increment resulting from the additional methylene unit), isopropyl ether **3** and *tert*-butyl ether **4** show signals at *m/e* 102 and 116, respectively, with relative intensities *less* than 1%. Clearly, the 9-oxabicyclo[3.3.1]nonane system behaves significantly differently upon electron bombardment than the

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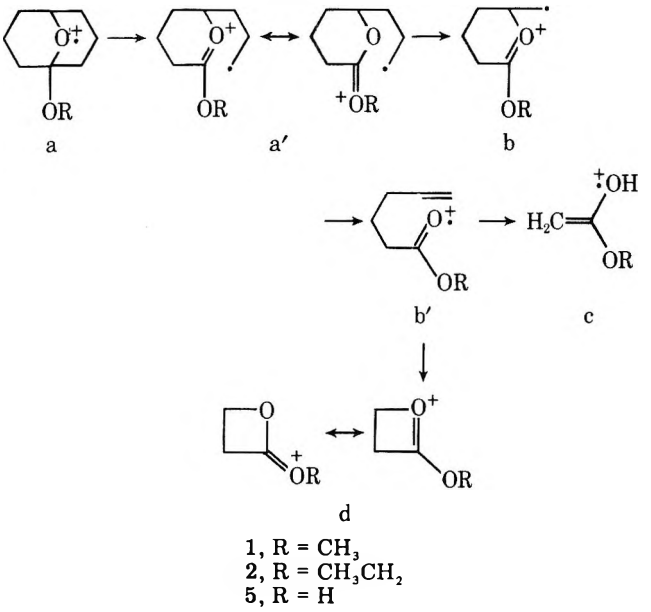
Table I. Relative Intensity Data For Bridgehead-Substituted Ethers

m/e; ion; %					
1[d]	2[d]	3[d]	4[a,d]	5[d]	6[b,d]
156; a; 29	170; a; 49	184; a; 57	198; a; 4	142; a; 75	218; a; 34
128; b; 12	142; b, e; 16	156; b; 1	170; b; <1	114; b; 90	190; b; <1
87; d; 30	101; d; 39	115; d; 2[c]	129; d; <1	73; d; 54	149; c; 2
74; c; 100	88; c; 100	102; c; <1	116; c; <1	60; c; 90	136; d; <1
125; i; 5	114; f; 8	142; e; 45	142; e; 80	125; i; 5	125; i; 20
99; <1	73; h; 21	114; f; 100	114; f; 74		
100; 2	60; g; 44	73; h; 48	73; h; 35		
	125; i; 9	60; g; 46	60; g; 32		
	99;7	125; i; 20	125; i; 29		
	100; 2	99; 11	99; 8		
		100; 17	100; 9		

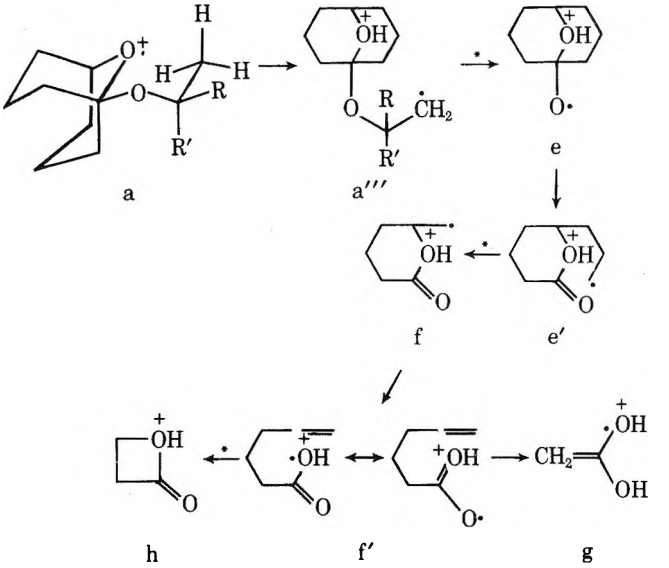
[a] The base peak occurs at *m/e* 41. [b] The base peak occurs at *m/e* 94. [c] Adjusted for the p + 1 contribution of the *m/e* 114 signal. [d] Registry no.: **1**, 63989-34-4; **2**, 63989-35-5; **3**, 63989-36-6; **4**, 63989-37-7; **5**, 37996-41-1; **6**, 63989-38-8.

Chart III



1, R = CH_3
2, R = CH_3CH_2
5, R = H

Chart IV



2, R = R′ = H
3, R = H; R′ = CH_3
4, R = R′ = CH_3

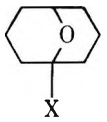
9-methyl-9-azabicyclo[3.3.1]nonane geometry when each framework is substituted at a bridgehead position with an alkoxy group, and (as with the azabicyclic skeleton) the nature of the alkyl portion of the alkoxy group plays a prominent role in the fragmentation pathways, particularly those leading to the formation of the base peaks.

Chart III details the proposed fragmentation scheme leading to the base ions for ketals 1 and 2. Cleavage of the 1,2 bond in the molecular ion a[6] produces the resonance-stabilized species a′ which expels ethylene to generate b which rearranges via homolytic cleavage of the 5,9 carbon–oxygen bond to the radical cation b′; fragment b′ is structurally (but not necessarily energetically) identical (or nearly so) to the molecular ion of methyl or ethyl 5-hexenoate. Radical cation b′ then takes part in a McLafferty rearrangement (a characteristic feature in the mass spectrometry of aliphatic carboxylic esters[7b]), expelling butadiene to provide the base peak c. Alternatively, intermediate b′ eliminates the relatively stable allyl radical to produce the resonance-stabilized cation d. The mass spectrum of hemiketal 5 (the next lower homologue of ketal 1) shows several similarities to the mass spectra of its methyl and ethyl ketals 1 and 2, respectively. Thus, it also contains a substantial (relative intensity = 90%) peak at *m/e* 60 corresponding to ion c (R = H) as well as a strong (relative intensity = 54%) signal at *m/e* 73 corresponding to ion d. Support for the correctness of the interpretations advanced in Chart III comes primarily from a detailed investigation of hemiketal 5. Thus, the utilization of high-resolution mass spectrometry established unequivocally that the ions at *m/e* 114, 60, and 73 correspond *exclusively* to elemental compositions consistent with ions **5b′–d**, respectively. Moreover, mass-analyzed ion kinetic energy (MIKE) spectra[9] confirmed the actuality of the steps **5a′** → **5b** and **5b′** → **5d**. In addition, the mass spectrum of methyl 5-hexenoate has been recorded;[10] the base peak occurs at *m/e* 74, just as it does for the methyl ketal 1.[11,12] Therefore, there can be little doubt that the pathways advocated in Chart III are reasonably accurate representations of the fragmentations occurring in the mass spectrometer for hemiketal 5 and ketals 1 and 2.

As mentioned above, the isopropyl and *tert*-butyl derivatives 3 and 4 do *not* follow the primary paths (Chart III) taken by the methyl and ethyl compounds 1 and 2; the ions **3b–d** and **4b–d** are present to the extent of less than 2% each. The principle fragmentations for ketals 3 and 4 are, however, *closely related* to the primary paths presented in Chart III for the ketals 1 and 2. The principal fragmentations for the isopropyl and *tert*-butyl substrates are triggered by an intramolecular transfer of a hydrogen from the alkyl portion of the alkoxy group to the 9-oxygen atom (Chart IV).[6] The side-chain hydrogen is abstracted by the 9-oxyl radical cation to provide the isomeric species a‴ which then loses the side chain as an olefin to afford e which rearranges to e′ and loses ethylene to give f which in turn isomerizes to f′. The a → a‴ step is another

example[13] of the Barton reaction[14] occurring in the mass spectrometer; additional support for the hydrogen abstraction process shown in Chart IV comes from the analogous step established for the 9-azabicyclo[3.3.1]nonane system illustrated in Chart II.[2] Radical cation f′ then goes on to ion g by way of a McLafferty rearrangement analogous to the b′ → c step exhibited by the methyl and ethyl ketals (Chart III); alternatively, f′ also goes on to h upon the elimination of allyl radical. Appropriate metastable peaks for the a‴ → e steps for ketals **3** and **4** were found at *m/e** values of 109.6 and 101.8, respectively; likewise, the mass spectra of **3** and **4** each displayed intense metastable peaks at *m/e** values of 91.5 and 46.7 corresponding to the e′ → f and f′ → h steps. Thus, the fragmentation scheme postulated in Chart IV is supported.[15]

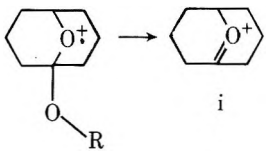
It is important to point out that *none* of the 1-alkoxy-9-methyl-9-azabicyclo[3.3.1]nonanes examined previously[2,5] show *m/e* values corresponding to the analogous terminal ions of Charts III and IV with relative intensities greater than 1%. It has also been found that neither the parent ether **7** nor its bridgehead chloride derivative **8** produce ions analogous to



7, X = H
8, X = Cl

ions c and d to any significant extent.[18] Thus, it appears as though the terminal fragmentations of Charts III and IV may be characteristic of 1-alkoxy- and 1-hydroxy-9-oxabicyclo-[3.3.1]nonanes, although further studies will be required to establish the generality of the selectivity found so far, since phenyl ketal **6** does *not* follow the paths outlined in Chart III.

The mass spectrum of phenyl ketal **6** shows an overwhelming base peak at *m/e* 94 which corresponds to the radical cation of phenol; only three other signals occur with relative intensities greater than 15%: the molecular ion (a), the



a i

ion at *m/e* 55, and the cation at *m/e* 125 for which structure i is suggested.[2] Clearly, the phenyl group brings about dramatic changes in the mass spectrometry of the 9-oxabicyclo[3.3.1]nonane system compared to the other ketals studied; such a phenomenon was also observed in the 9-methyl-9-azabicyclo[3.3.1]nonane system.[2]

Conclusions

Two important conclusions emerge from the present investigation: (1) The nature of the alkyl portion of the alkoxy group plays a dominant role in the fragmentation sequences involving the base ions. Thus, in the unbranched side-chain series O-$(CH_2)_nH$ (n = 0, 1, 2), the side chain is retained during the primary fragmentation pathway, while for the ketals bearing side chains derived from secondary or tertiary alcohols a hydrogen from the side chain is transferred to an oxygen atom and the remaining hydrocarbon portion of the side chain is lost during the primary fragmentation scheme. Furthermore, the straight-chain ketals (e.g., **2**) follow only to a minor extent the branched-chain primary fragmentation scheme (Chart IV), and the branched-chain ketals follow to a negligible degree the straight-chain primary fragmentation pathway (Chart III). Therefore, since the primary fragmentation sequences of 1-alkoxy-9-oxabicyclo[3.3.1]nonanes are strongly and highly selectively dependent upon the nature of branching in the 1-alkoxy side chain, mass spectrometry should prove to be extremely valuable in ascertaining the identity of a side chain in this system (and perhaps other related systems such as derivatives of multistriatin and other similar insect pheromone components[19]). In contrast to the alkoxy substrates **1–4**, the primary fragmentation path for phenyl ketal **6** produces the radical cation of phenol. (2) Although the molecular architectures of the 9-oxa- and 9-methyl-9-azabicyclo[3.3.1]nonane geometries are very similar, the primary fragmentation sequence for each system is specific, as evidenced by comparing Chart I with III and Chart II with IV.

Experimental Section

Mass spectra were obtained with an A.E.I. MS-9 mass spectrometer operating at an ionization voltage of 70 eV and a source temperature of about 175 °C. High-resolution measurements, MIKE spectra, and AVS spectra were obtained with a Varian MAT-311 instrument. Proton NMR spectra were measured on a Varian Associates T-60 machine, employing $CDCl_3$ solutions with internal Me_4Si. Infrared spectra were recorded on a Perkin-Elmer 457 spectrophotometer as neat films. All substrates were purified by preparative gas chromatography (with a Varian Aerograph 90-P apparatus equipped with a 5 ft × 0.25 in. stainless-steel column packed with 20% SE-30 on Chromosorb G) immediately prior to mass spectral measurements; the column temperatures employed for sample collection were about 190 °C (which established that the substrates were thermally stable to the conditions used with the mass spectrometer). Elemental analyses were performed by Spang Microanalytical Laboratories. Compounds **1, 2, 4, 5,** and **7–9** were previously known and were prepared according to published procedures.[20] Ketals **3** and **6** are new compounds and were synthesized by the solvolysis reactions of the bridgehead chloride **8** with 2-propanol and phenol, respectively, as described previously for the 9-methyl-9-azabicyclo[3.3.1]nonane system;[2] the spectral properties and analytical results of **3** and **6** (both of which are colorless oils at room temperature) are as follows.

1-(2-Propoxy)-9-oxabicyclo[3.3.1]nonane(3): NMR δ 4.2–4.5 [m, 1 H, bridgehead *H*], 4.22 [m, J = 6.5 Hz, 1 H, $CH(CH_3)_2$], 1.3–2.3 [m, 12 H, CH_2 groups], 1.16 [d, J = 6.5 Hz, 6 H, $CH(CH_3)_2$]; IR 2965, 2930, 1368, 1179, 1155, 1123, 1115, 1045, 1017 cm^{-1}.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 72.25; H, 10.96.

1-Phenoxy-9-oxabicyclo[3.3.1]nonane (6). NMR δ 7.3–6.8 [m, 5 H, aromatic *H*], 4.5–4.2 [m, 1 H, bridgehead *H*], 2.3–1.2 [m, 12 H, CH_2 groups]; IR 3050, 3030, 2930, 1595, 1585, 1490, 1370, 1240, 1225, 1215, 1145, 1098, 1015, 942, 898, 885, 778, 705 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.89; H, 8.33.

Registry No.—**8,** 40164-34-9; 2-propanol, 167-63-0; phenol, 108-95-2.

Supplementary Material Available. Bar graphs of the mass spectra of ketals **1–4** (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) The University of Michigan; (b) General Electric Co.; (c) correspondence concerning this manuscript should be directed to H. O. K. at the General Electric Co. address.
(2) H. O. Krabbenhoft, *J. Org. Chem.*, **41,** 1774 (1976).
(3) M. E. Wolff, *Chem. Rev.*, **63,** 55 (1963).
(4) Bar graphs of ketals **1–4** appear in the microfilm edition; see paragraph at end of paper regarding supplementary material.
(5) H. O. Krabbenhoft, *J. Org. Chem.*, the preceding article in this issue.
(6) There are two nonequivalent oxygen atoms which can be ionized upon electron impact (a and a″). None the less, several lines of evidence point to the preferential *effective* localization of charge on the 9-oxygen: (i) For ketals **2–4** the M − CH_3 peaks are of very low relative intensities (less than 1%); if the 1-oxyl radical cation a″ were generated, substantially higher intensity signals for the M − CH_3 ions would be expected.[7a] (ii) While abundant peaks are found at *m/e* 124 indicating the loss of the alkoxy group

a a″

in the form of a neutral alcohol and corresponding to the retention of the charge on the bridgehead enol ether, peaks associated with the elimination of a neutral bridgehead olefin and charged alcohols are virtually absent; such a situation also exists for 2-alkoxytetrahydropyrans.[6] (iii) The loss of alkoxy radical from the molecular ion to provide the oxonium ion i requires the 9-oxyl radical cation.
(7) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, Calif., 1967: (a) Chapters 2 and 6; (b) Chapter 4; (c) Chapter 3.
(8) S. J. Isser, A. M. Duffield, and C. Djerassi, *J. Org. Chem.*, **33**, 2266 (1968).
(9) R. G. Cooks, J. H. Beynon, R. M. Caprioli, and G. R. Lester, "Metastable Ions", Elsevier, Amsterdam, 1973, pp 42–44.
(10) W. K. Rohwedder, A. F. Mabrouk, and E. Selke, *J. Phys. Chem.*, **69**, 1711 (1965).
(11) We were unable to find any supportive data (mass-analyzed ion kinetic energy spectra, accelerated voltage scan spectra, or metastable peaks) for the b′ → c transformation; perhaps this indicates that the McLafferty rearrangement is occurring in the source of the mass spectrometer.
(12) J. R. Dias, Y. M. Sheikh, and C. Djerassi, *J. Am. Chem. Soc.*, **94**, 473 (1972).
(13) M. M. Green, J. G. McGrew, II, and J. M. Moldowan, *J. Am. Chem. Soc.*, **93**, 6700 (1971).
(14) R. H. Hesse, "Progress in Free Radical Chemistry", G. H. Williams, Ed., Academic Press, New York N.Y., 1969, Chapter 2.
(15) It is also possible that the hydrogen is transferred to the 9-oxygen atom via a McLafferty rearrangement within a′,[2,16] or to the 1-oxygen atom via the hydrogen migration/olefin elimination process (within a′) characteristic of ethers.[7a,17]
(16) D. G. I. Kingston, J. T. Bursey, and M. M. Bursey, *Chem. Rev.*, **74**, 215 (1974).
(17) C. Djerassi and C. Fenselau, *J. Am. Chem. Soc.*, **87**, 5747 (1965).
(18) H. O. Krabbenhoft, Ph.D. Thesis, University of Michigan, Ann Arbor, Mich., 1974.
(19) W. E. Gore, G. T. Pearce, and R. M. Silverstein, *J. Org. Chem.*, **41**, 607 (1976).
(20) C. B. Quinn, Ph.D. Thesis, University of Michigan, Ann Arbor, Mich., 1973.

Synthesis of 1-Azatricyclo[5.2.1.0^{4,10}]decane[1]

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Received June 14, 1977

The title compound (**1**) has been synthesized by the reductive cyclization of 2,5-bis(cyanomethyl)cyclopentanone (**5**) with a Raney Ni and, in better yield, with a Raney Co catalyst. The pK_a of **1** is 8.50. Attempts to introduce unsaturation into the system were unsuccessful. Treatment of the *N*-benzyl quaternary salt with butyllithium gave Hofmann elimination and Stevens rearrangement products, but fragmentation occurred with the *N*-methyl quaternary salt. Other cyclopentanone condensation experiments are described.

Our interest in the behavior of quaternary salts of cyclic amines with base[3] and in new heterocyclic, nonalternant, conjugate-unsaturated systems[4] led to consideration of the 1-azatricyclo[5.2.1.0^{4,10}]decane structure (**1**), a possible precursor to 7a*H*-cyclopent[*gh*]-1-azapentalene (**2**) which would

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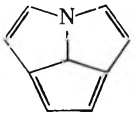

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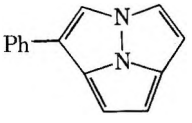

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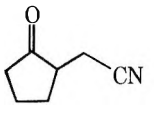
be an azaannulene with a 10 π-electron periphery distorted from planarity by the tetrahedral bridge atom. The closest analogy found was 1-phenyl-8-azacycl[2.2.2]azine (**3**) which was noted to exhibit ^{1}H NMR absorption only in the aromatic region,[5] but which has an unshared electron pair on the central nitrogen.

Leonard and Middleton[6] attempted to prepare **1** and the corresponding 1-azatricyclo[6.2.1.0^{4,11}]hendecane by the high-pressure hydrogenation of the oximes of diethyl cyclopentanone-2,5-diacetate and cyclohexanone-2,6-diacetate, respectively. They attributed the failure of the method to the assigned trans stereochemistry of the carbethoxymethyl groups (introduced by alkylation of the ketone enolate anion), and the formation of the trans product to steric factors. Later, however, Bohlmann et al.[7] showed the cyclohexanone diester to be the cis isomer. Thus, the failure to achieve the tricyclic system was apparently due to the reaction conditions. Subsequently, Mandell et al.[8] prepared *cis*-2,6-bis(cyanomethyl)cyclohexanone using Stork's enamine synthesis[9] and reductively cyclized it to the tricyclic amine in low yield.

Application of Mandell's procedure to the monoalkylation of cyclopentanone with chloroacetonitrile gave a 10% yield of the 2-cyanomethyl derivative (**4**) as compared to 35–45% reported[8] and verified by us for cyclohexanone. A comparable yield disparity has been observed with ethyl bromoacetate as the alkylating agent.[10] The use of dioxane as the solvent and morpholine as the base raised the yield of **4** to ca. 30%, which was still not satisfactory. The procedure of Gutsche et al.[11] of a one-pot reaction of cyclopentanone, pyrrolidine, and one equivalent of chloroacetonitrile was then tried and gave 31% of **4** plus a small amount of **5**. The use of two equivalents of



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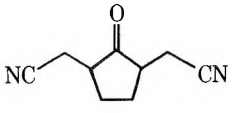

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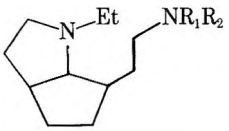
chloroacetonitrile and one additional equivalent of triethylamine afforded yields of 42 and 31%, respectively. A two-step procedure with the isolation of **4** gave appreciably lower yields of **5**. Hydrolysis of **5** formed the known corresponding dicarboxylic acid. An attempt to prepare **4** by the alkylation of the anion of *N*-cyclohexyliminocyclopentane[12] gave only tarry products.

High-pressure reduction of **5** in the presence of W-5 Raney nickel catalyst formed **1** (ca. 10%) along with three other compounds which were assigned structures as 1-ethyl-6-(2-aminoethyl)- (**6**), 1-ethyl-6-(2-ethylaminoethyl)- (**7**), and 1-ethyl-6-(2-diethylaminoethyl)cyclopentano[2,3]pyrrolidine (**8**) on the basis of their spectral characteristics. The ethyl groups in **6**–**8** came from the ethanol solvent.[13] Reduction in acetic acid gave essentially no **1**, but the use of glyme as the



6, $R_1 = R_2 = H$
7, $R_1 = H$; $R_2 = Et$
8, $R_1 = R_2 = Et$

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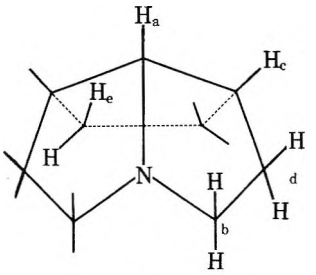
solvent increased the yield of 1 to ca. 25% and eliminated the ethylamine by-product formation. Predistillation of 5 from the Raney Ni to remove possible traces of halides toxic to the catalyst[14] did not improve the yield. Raney Co has also been used for the reduction of nitriles[15] and was found to give the highest yield (27%) of 1, but also by-products which were not separable by distillation.

The structure of 1 was indicated by its elemental composition, the molecular ion in the mass spectrum, and the ^{1}H NMR spectrum which consisted of a distinct triplet for the central CH (a), a multiplet for the CH_2's (b) adjacent to the N and the other CH groups (c), and a multiplet for the other CH_2 groups (d and e) (9). When successive scans were taken



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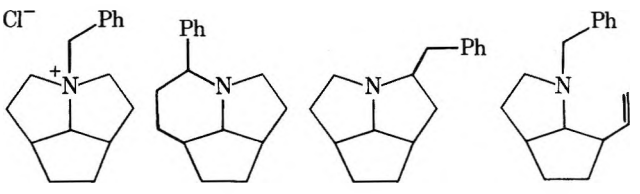
with increasing amounts of tris(dipivalomethanato)europium[16] present, the a signal showed the largest shift downfield and coalesced into a broad singlet and the b plus c signal was split into three 2H multiplets. For the latter, the multiplet which shifted the most was assigned to the exo b hydrogens which are nearer to the nitrogen electron pair and the europium, the next multiplet to the endo b hydrogens, and the last to the more remote c hydrogens. After the b and c multiplet had become resolved, the d plus e multiplet became a 4H quartet (d) and a triple-peaked 4H multiplet (e). Finally, at the point where resolution was lost, the d signal merged with the c signal.

The basicity of 1 and a series of tertiary amines was compared. The low solubility of 1 in water necessitated pK_a measurements in aqueous ethanol. The values obtained show that 1 is a stronger base than the others but not dramatically so. (See Table I.)

Treatment of benzyl quaternary salt 10 with strong base would be expected to give (i) benzylic hydrogen abstraction followed by a Stevens rearrangement to form 11, (ii) α-methylene hydrogen abstraction followed by a Stevens rearrangement to form 12, or a Sommelet rearrangement to form the 2-(o-tolyl) derivative of 1, or (iii) Hofmann β-elimination with ring opening to form 13. The benzyl group would hinder attack at the central CH and the rigid ring structure would make reaction of the benzylic carbon at this site less likely. With butyllithium as the base, two major products were isolated in a ratio of 2:3. Structure 11 is favored for one product



10 11 12 13

on the basis that this would arise from process i involving the more acidic benzylic α-hydrogens and that integration of the NMR spectrum showed only four hydrogens (α to N) in the region where the benzylic hydrogens in 12 would also be expected to be found.[17] The Sommelet product was excluded as the spectrum showed five phenyl hydrogens rather than four and no signal for a benzylic methyl group. The NMR spectrum

Table I. pK_a Values of 1 and Some Tertiary Amines[a]

Compound	Registry no.	pK_a
N-Ethylmorpholine	100-74-3	5.36
Triethylamine	121-44-8	7.45
N-Butylpyrrolidine	767-10-2	7.76
N-Ethylpiperidine	766-09-6	7.81
N-Ethylpyrrolidine	7335-06-0	8.01
1		8.50

[a] Aqueous ethanol solvent.

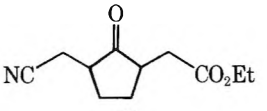
for 13 showed three hydrogens in the vinylic region and a pair of doublets for the nonequivalent benzylic hydrogens as has been noted by Reinecke for closely related compounds.[18] A third, very minor product was not characterized.

Heating 1 with sulfur (neat or in DMF) resulted in the evolution of hydrogen sulfide, but no volatile dehydrogenation product was obtained and heating with selenium caused only darkening. When 1 was heated at 350 °C with methyl oleate as hydrogen acceptor in the presence of Pd-C, no unsaturated product could be detected. Similarly, exposure of 1 to the Pd-C catalyst used for the dehydrogenative preparation of cyclopenta[c]thiapyran[19] in the vapor phase yielded no isolable unsaturated product. Unchanged 1 was recovered in good yield from both reactions with Pd-C.

Mercuric acetate has been used to introduce a double bond into the 1-azatricyclo[8.4.1.0^{6,15}]hexadecane[7a,20] and indolizine[13b,21] structures. However, this reagent did not oxidize 1 and, subsequently, it was learned that the analogous bicyclic pyrrolizidine is also unreactive.[22] The use of lead tetraacetate gave lead diacetate (ca. 50%) and acetic acid, but again no unsaturated product could be isolated.

Application of the trityl cation method for the introduction of conjugate unsaturation into tertiary alkylamines[23] to 1 in acetonitrile led, after workup, to the BF_3 adduct of 1 and triphenylcarbinol, but no triphenylmethane. With dichloromethane solvent a small amount of triphenylmethane was formed, but no new isolable product.

Several other approaches to 1 having a functional group on carbon were qualitatively explored. Catalytic reduction of 4 gave the known *cis*-cyclopentano[2,3]pyrrolidine but the desired reductive bis-cyclization of cyanoester 14 did not occur. Condensation of cyclopentanone with iminodiethanol required acid catalysis and gave a high yield of a product which was not the desired enamine (15). The spectral prop-



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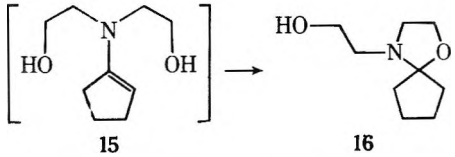

15 16

erties suggested 16 which could form from subsequent acid-catalyzed cyclization.[24]

Experimental Section

Melting points and boiling points are uncorrected. NMR spectra were taken on a Varian A-60 or T-60 spectrometer with Me_4Si as internal standard unless otherwise specified. Infrared spectra were recorded with a Perkin-Elmer Model 21 or 137 spectrophotometer with sodium chloride prisms on thin films unless stated otherwise. Ultraviolet spectra were obtained on a Cary Model 14 recording spectrophotometer with 1-cm cells. Mass spectra were taken on an Associated Electrical Industries MS-9 spectrometer with matching to perfluo-

rotributylamine. Elemental analyses were performed by Dr. Alfred Bernhardt, 5251 Elbach über Engelskirchen, West Germany. Vapor phase chromatography was carried out on a Varian Aerograph Model 90P-3 with 5% SE-30 on Chromosorb G columns.

2-Cyanomethylcyclopentanone (4) and 2,5-Bis(cyanomethyl)cyclopentanone (5). A solution of 420 g (5 mol) of cyclopentanone and 380 g of pyrrolidine in 1 L of dry benzene was refluxed under N_2 until H_2O evolution (Dean-Stark trap) ceased. Triethylamine (522 g, 5.15 mol) was added to the cooled solution which was then heated to reflux and stirred. Chloroacetonitrile (760 g, 10 mol) was added slowly. After 3 h, the solvent was removed (reduced pressure), 500 mL of H_2O was added, and the mixture was stirred under reflux for 1 h. The separated aqueous phase was extracted with 2:1 benzene–ether. The combined extracts and original nonaqueous layer were washed successively with 10% HCl, 5% $NaHCO_3$, H_2O, and saturated NaCl. The aqueous extracts were extracted (liquid–liquid extractor) for 1 day with benzene. Distillation of the residue after solvent removal (vacuum) from the combined, dried (Na_2SO_4) organic phases gave 257 g (41.8%) of **4**, bp 105–120 °C (3–4 mm),[11] and 249 g (30.8%) of **5**, bp 180–190 °C (1 mm): IR 1740 (C=O) and 2250 cm^{-1} (C≡N). Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.21. Found: C, 66.50; H, 6.37; N, 17.34.

From an analogous reaction of 21 g (0.25 mol) of cyclopentanone, 18 g (0.25 mol) of pyrrolidine and 19 g (0.25 mol) of chloroacetonitrile in 150 mL of benzene wherein triethylamine was absent,[11] the hydrolysis of the intermediate iminium salt was effected by refluxing for 1.5 h with 100 mL of 1:1 methanol–H_2O, and 100 mL of saturated NaCl was added prior to extraction with benzene–ether, giving 9.6 g (31%) of **4**, bp 105–120 °C (3–4 mm) and ca. 0.5 g of higher boiling material containing **5**.

2,5-Bis(carboxymethyl)cyclopentanone. A 1-g sample of **5** was refluxed for 1 h with 10 mL of concentrated HCl. Water (50 mL) was added and the solution was extracted with ether. Evaporation of the solvent from the combined, dried extracts gave 2,5-bis(carboxymethyl)cyclopentanone, mp 176–177.5 °C (lit.[25] 177 °C), after recrystallization from methanol: molecular ion at *m/e* 200.076 (Calcd for $C_9H_{12}O_5$: 200.068).

1-Azatricyclo[5.2.1.0^{4,10}]decane (1). A. With W-5 Ni in Ethanol. Reductive cyclization of a solution of 10 g (0.062 mol) of **5** in 130 mL of absolute ethanol in the presence of 4–5 g of W-5 Raney Ni catalyst was carried out in a stirring autoclave at 1650 psi of H_2 at 135 °C for 8 h. The catalyst was separated from the cooled (internal coil in autoclave) mixture by centrifugation, and the ethanol was removed under vacuum. Distillation of the residue gave 2.43 g of clear liquid, bp 75–130 °C (1 mm), which was separated into four fractions by preparative VPC on an SE-30 column at 190 °C.

The first fraction, ca. 1.5 g (11%), was identified as **1**: molecular ion at *m/e* 137.119 (calcd 137.120); NMR (CCl_4) δ 3.6 (t, 1 H), 2.7 (m, 6 H), 1.6 (m, 8 H). Anal. Calcd for $C_9H_{15}N$: C, 78.78; H, 11.02; N, 10.21. Found: C, 78.81; H, 11.07; N, 10.29.

The *picrate* crystallized from ethanol: mp 295 °C (dec) with block preheated to 280 °C. Anal. Calcd for $C_{15}H_{18}N_4O_7$: C, 49.18; H, 4.95; N, 15.29. Found: C, 49.53; H, 5.08; N, 15.24.

The properties of the second fraction (ca. 0.4 g) were in agreement with those expected for **6**: molecular ion at *m/e* 182.185 (Calcd for $C_{11}H_{22}N_2$: 182.178); NMR (CCl_4) δ 1.2 (t, 3 H, CH_2CH_3); IR poorly resolved doublet at 3350 cm^{-1} (NH_2); positive Hinsberg tests for primary and tertiary amino groups.

The third fraction (ca. 0.2 g) was not characterized beyond measurement of the molecular ion at *m/e* 199.166 and the observation of no signal for a methyl or ethyl group in the NMR spectrum.

B. With W-5 Ni in Ethanol (Dilute). The procedure in **A** was followed except that 500 mL of absolute ethanol was used. Fractionation of the crude product (4.7 g, bp 50–140 °C at 1.5 mm) by preparative VPC at 200 °C (exit tube packed with glass wool and effluent gas bubbled through ethanol) yielded ca. 0.5 g (3.75%) of **1** as the first fraction.

The second fraction gave ca. 2.2 g (17%) of **7**: molecular ion at *m/e* 210.209 (Calcd: 210.209); NMR (CCl_4) δ 1.1 (2 t, 6 H, CH_2CH_3). Anal. Calcd for $C_{13}H_{26}N_2$: C, 74.21; H, 12.46; N, 13.32. Found: C, 74.03; H, 12.43; N, 13.50.

The third fraction gave ca. 1.5 g (10%) of **8**: molecular ion at *m/e* 238.240 (Calcd: 238.241); NMR (CCl_4) δ 1.0 (t, 6 H, CH_2CH_3), 1.1 (t, 3 H, CH_2CH_3). Anal. Calcd. for $C_{15}H_{30}N_2$: C, 75.55; H, 12.69; N, 11.75. Found: C, 75.53; H, 12.68; N, 11.60.

Compounds **7** and **8** were unstable to air, and CCl_4 solutions became brown in a few hours.

C. With W-5 Co in DME. A solution of 15 g (0.093 mol) of **5** in 450 mL of 1,2-dimethoxyethane was treated with H_2 at 2000 psi and 170 °C in the presence of 7–8 g of W-5 Raney Co for 6 h. The contents were removed from the autoclave and the solution was decanted from the catalyst. Removal of the solvent under vacuum and distillation of the residue gave 3.8 g (30%) of **1**, bp 85–95 °C (15 mm), containing ca. 10% (VPC) of by-products.

***cis*-Cyclopentano[2,3]pyrrolidine.** A mixture of 15 g (0.122 mol) of **4**, 405 g of W-5 Raney Ni, and 450 mL of dry 1,2-dimethoxyethane was stirred and heated at 170 °C under 2500 psi of H_2 in an autoclave for 12 h. The contents of the reaction vessel were removed and centrifuged. The solvent was removed (vacuum) from decanted supernatant liquid. Distillation of the residue gave 5.03 g (37%) of *cis*-cyclopentano[2,3]pyrrolidine, bp 75–100 °C (30–40 mm): *picrate*, mp 111–113 °C (lit.[26] 111 °C); 3,5-dinitrobenzoate, mp 201–202 °C (lit.[26] 201–203 °C).

pK_a Measurements. A solution of 0.02 mol of the amine in 25 mL of 80% ethanol was titrated potentiometrically with 0.0996 N HCl on a Radiometer Type TTTlc automatic titrator recording pH change as a function of volume. At the midpoint (pH = pK_a)[27] the solution was 57% ethanol.

Reaction of Benzyl Quaternary Chloride 10 with *n*-Butyllithium. To 2 g of **1** dissolved in ethanol was added 2 g of benzyl chloride. The solvent was evaporated and the residual salt was extracted with hexane and then covered with 300 mL of hexane. To the stirred mixture was added 30 mL of 1.6 M butyllithium. After 5 days, 30 mL of H_2O was added and the separated aqueous layer was extracted with hexane. The solvent was removed from the combined, dried organic layer and extracts and the residue was chromatographed (neutral Al_2O_3, benzene). VPC showed three compounds (6:9:1) and the first two were collected on a preparative VPC (SE-30, 275 °C). The first fraction (1 g, 30%) was assigned the structure of 2-phenyl-1-azatricyclo[6.2.1.0^{5,11}]undecane (**11**): molecular ion at *m/e* 227.169 (Calcd: 227.167); NMR (CCl_4) δ 7.2 (s, 5 H), 3.2 (m, 1 H), 2.6 (m, 3 H), and 1.6 (m, 12 H). Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.39; H, 9.13; N, 6.05.

The second fraction (1.5 g, 47%) was assigned the structure 1-benzyl-6-vinylcyclopentano[2,3]pyrrolidine (**13**): molecular ion at *m/e* 227.19 (Calcd: 227.167); NMR (CCl_4) δ 7.2 (s, 5 H), 6.1 (p, 1 H, vinyl), 5.0 (t, 2 H, vinyl), 4.1 (d, 1 H, $PhCH_2$, J = 13 Hz), 2.98 (d, 1 H, $PhCH_2$, J = 13 Hz), 2.7 (m, 3 H, N–CH), and 1.6 (m, 8 H, ring CH_2). Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.47; H, 9.26; N, 6.13.

2-(Ethylcarboxymethyl)-5-(cyanomethyl)cyclopentanone (14). A solution of 61.5 g (0.5 mol) of **4**, 35.5 g (0.5 mol) of pyrrolidine, and 200 mL of dry toluene was refluxed until the evolution of H_2O (Dean-Stark trap) had ceased. To the cooled solution was added 61.5 g (0.4 mol) of ethyl chloroacetate and the mixture was refluxed with stirring overnight. Most of the solvent was removed. The residue was stirred with 100 mL of H_2O for 2 h, refluxed for 5 min, cooled, and extracted with 2:1 benzene–ether. Distillation of the residue after removal of the solvent from the combined, washed (10% HCl, 5% $NaHCO_3$, H_2O, saturated NaCl), dried extracts gave 37 g (60%) of unchanged **4**, bp 85–95 °C (0.5 mm), and 22.5 g of liquid, bp 95–135 °C (0.5 mm), which contained 85% (VPC) of one substance. Two further distillations gave ca. 15 g (17%) of pure product: bp 135 °C (0.3 mm); molecular ion at *m/e* 209.107 (Calcd: 209.105); IR 1750 and 2250 cm^{-1}; NMR (CCl_4) δ 4.1 (q, 2 H), 2.6 (m, 10 H), 1.3 (t, 3 H). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.17; H, 7.08; N, 6.79.

4-(2-Hydroxyethyl)-1-oxa-4-azaspiro[4.4]nonane (16). A solution of 8.4 g (0.1 mol) of cyclopentanone, 10.5 g (0.1 mol) of iminodiethanol, and 0.1 g of *p*-toluenesulfonic acid in 250 mL of benzene was refluxed under N_2 until 1.9 mL of H_2O (calcd: 1.8 mL) was evolved. The solvent was evaporated and distillation of the residue gave 15.3 g (90%) of **16**: bp 142–152 °C (15 mm); molecular ion at *m/e* 171.123 (Calcd for $C_9H_{17}NO_2$: 171.126); IR 3300, 1750, and 1050 cm^{-1}; NMR (CCl_4) δ 4.1 (s, 1 H), 3.8 (t, 2 H), 3.5 (t, 2 H), 2.9 (t, 2 H), 2.6 (t, 2 H) and 1.6 (s, 8 H).

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Registry no.—**1**, 38594-89-7; **1** picrate, 64010-75-9; **4**, 51004-14-9; **5**, 64010-74-8; **6**, 64010-73-7; **7**, 64010-72-6; **8**, 64010-71-5; **11**, 64010-70-4; **13**, 64010-69-1; **14**, 64010-68-0; **16**, 64034-89-5; chloroacetonitrile, 107-14-2; *cis*-cyclopentano[2,3]pyrrolidine, 2030-37-7; benzyl chloride, 100-44-7; ethyl chloroacetate, 105-39-5.

References and Notes

(1) From the Ph.D. Thesis of P. C. Wade, University of Washington.

(2) Shell Oil Fellow, 1969–1970; du Pont Research Fellow, 1971.
(3) A. G. Anderson, Jr., and M. T. Wills, *J. Org. Chem.*, **32**, 3241 (1967); **33**, 536, 2123, 3046 (1968); *Angew. Chem.*, **79**, 574 (1967); *Angew. Chem., Int. Ed. Engl.*, **6**, 557 (1967).
(4) A. G. Anderson, Jr., D. M. Forkey, and L. D. Grina, *J. Org. Chem.*, **37**, 3499 (1972); H. L. Ammon, P. H. Watts, Jr., A. G. Anderson, Jr., D. M. Forkey, L. D. Grina, and Q. Johnson, *Tetrahedron*, **26**, 5707 (1970); A. G. Anderson, Jr., and D. M. Forkey, *J. Am. Chem. Soc.*, **91**, 924 (1969).
(5) V. Boekelheide and N. A. Fedoruk, *Proc. Natl. Acad. Sci. U.S.A.*, **55**, 1385 (1966); N. A. Fedoruk, Ph.D. Thesis, University of Oregon, 1966.
(6) N. J. Leonard and W. J. Middleton, *J. Am. Chem. Soc.*, **74**, 5114 (1952).
(7) (a) F. Bohlmann and C. Arndt, *Chem. Ber.*, **91**, 2167 (1958); (b) F. Bohlmann, *ibid.*, **91**, 2157 (1958).
(8) L. Mandell, J. U. Piper, and K. P. Singh, *J. Org. Chem.*, **28**, 3440 (1963).
(9) G. Stork, A. Beizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
(10) J. Szmuzkovicz, "Advances in Organic Chemistry Methods and Results", Interscience, New York, N.Y., 1963, Vol. 4, Chapter 1.
(11) G. D. Gutsche, Washington University, St. Louis, Mo., personal communication, 1968; cf. D. M. Bailey, J. E. Bowles, and C. D. Gutsche, *J. Org. Chem.*, **28**, 610 (1963).
(12) G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).
(13) (a) R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, New York, N.Y., 1965, p 42; (b) M. G. Reinecke and L. R. Kray, *J. Org. Chem.*, **29**, 1736 (1964); (c) C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 1635 (1956).
(14) A. I. Vogel, "Practical Organic Chemistry", 3rd ed, Wiley, New York, N.Y., 1957, p 566.
(15) W. R. Grace and Co., Davison Chemical Division, Bulletin 1C-1268; ref 13, pp 32 and 98.
(16) J. K. M. Sanders and D. H. Williams, *Chem. Commun.*, **7**, 422 (1970).
(17) For example, cf. "High Resolution NMR Spectra Catalog", No. 265, Vol. 1, 1962, and No. 534, Vol. 2, 1963, Varian Associates, Palo Alto, Calif.
(18) We thank Professor Manfred Reinecke for bringing to our attention the spectral data and analysis for 1-benzyl-2-(3-butenyl)piperidine and 1-benzyl-2-(3-butenyl)pyrrolidine which provided the precedent for our assignment.
(19) A. G. Anderson, Jr., W. F. Harrison, and R. G. Anderson, *J. Am. Chem. Soc.*, **85**, 3448 (1963).
(20) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955).
(21) Reference 10, p 13.
(22) M. G. Reinecke and L. R. Kray, *J. Org. Chem.*, **32**, 225 (1967).
(23) R. Damico and C. D. Broaddus, *J. Org. Chem.*, **31**, 1607 (1966).
(24) T. D. Stewart and W. E. Bradley, *J. Am. Chem. Soc.*, **54**, 4177 (1932); R. F. Parcell and F. P. Hauck, Jr., *J. Org. Chem.*, **28**, 3468 (1963).
(25) N. N. Chaterjee, B. K. Das, and G. N. Barpujari, *J. Indian Chem. Soc.*, **17**, 161 (1940).
(26) H. Booth, F. E. King, and J. Patrick, *Chem. Ind. (London)*, 446 (1956).
(27) A. Albert and E. P. Sergent, "Ionization Constants of Acids and Bases", Wiley, New York, N.Y., 1962, p 7.

Synthesis and Structure of Stable Metal-Coordinated 1-Azirines[1a]

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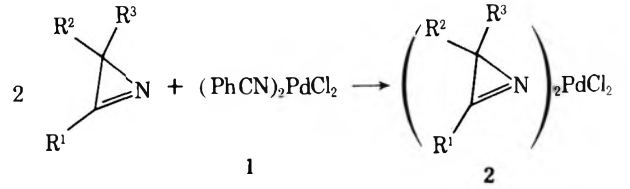
1-Azirines were found to form stable complexes with $PdCl_2$ or $PtCl_2$. These represent the first isolable transition-metal complexes of azirines. Compared to the free azirines, the palladium complexes **2** exhibit an unusually high stability toward air, moisture, and UV light. Thermolysis leads to formation of nitriles. An x-ray structural analysis of **2a** reveals coordination of the nitrogen with palladium, resulting in a 2:1 azirine/$PdCl_2$ complex with a trans configuration. The C–C–N bond angle is only 50.2° and the exocyclic C–C bond attaching the three-membered ring to a substituent is somewhat shortened (1.44 Å), suggesting a high degree of s character in the exocyclic bonds. Infrared and ^{13}C correlations for these complexes are discussed.

The strained 1-azirine ring system has been the subject of recent intensive studies.[2] Theoretical as well as practical considerations make the still unavailable 2-azirine ring system an interesting synthetic target.[3] In our efforts to prepare the elusive 2-azirine system stabilized by coordination to transition metals,[4] we felt that one possible route might involve transition-metal complexes of 1-azirines as precursors. Although 1-azirines are capable of acting as typical Schiff bases, coordinating via the nitrogen nonbonded electron pair, the few reported reactions of 1-azirines with metals have given only ring-opened products.[5–7] In the reaction of 2-phenyl-1-azirine with $CuBr_2$[5] or $M(CO)_6$ (M = Cr, W, MO),[6] no metal complexes containing azirine fragments were identified. Several complexes containing ring-opened fragments were isolated from the reaction of $Fe_2(CO)_9$ with 2-phenyl-1-azirine.[7]

Results

We have now been successful in preparing the first isolable transition metal–azirine complexes. Thus, we found that 2 equiv of a variety of 1-azirines, **1**, react with dichlorobis(benzonitrile)palladium(II) to give stable trans complexes, **2**, in good yield (Table I). Not only does the 1-azirine ring stay intact, but the azirine moiety seems to be protected from the usual decomposition 1-azirines undergo, without the necessity of exclusion of moisture and oxygen. For instance, complex **2d** stored at room temperature with no special precautions for over a year was unchanged. The azirine **1d** decomposes within days.



1 **2**

Coordination of the azirine also changes its susceptibility to photolysis. Thus, the complex **2c** was recovered (87%) unchanged after 14 h of irradiation. Under these conditions, the uncomplexed azirine **1c** converted into oxazole, **3** (89%), after 3.5 h.[8] We found that the oxazole itself reacts with $(PhCN)_2PdCl_2$ to give the bisoxazole complex **4**, but this product was not detected in the photolysis of **2c** in the presence of acetone. Since the azirines **1** can be regenerated from **2** by treatment with triphenylphosphine, the complex formation serves as a protection of the azirine moiety.

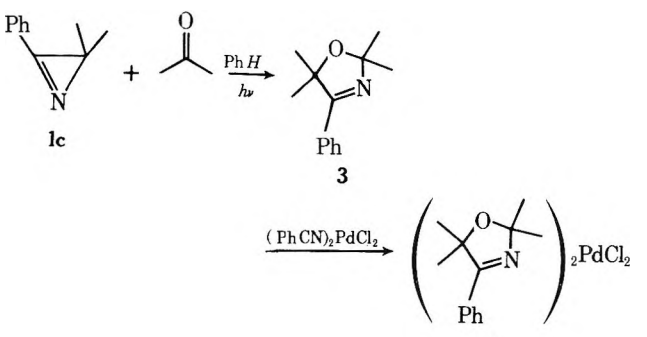


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Table I. (Azirine)$_2$·PdCl$_2$ Complexes (2)

Compd	R_1	R_2	R_3	Yield, %	mp,[a] °C
2a	*p*-Tolyl	H	H	91	*b*
2b	*p*-Anisyl	H	H	87	*c*
2c	Ph	Me	Me	89	143–147
2d	Ph	Me	H	89	126–128
2e	Ph	CO_2Me	H	95	165–170
2f	Ph	$CH(OMe)_2$	H	68	147–150
2g	Ph	CH_2OH	H	54	110–118
2h	Me	Me	H	64	*d*
2i	Me_2N	Me	Me	44	143–146

[a] Decomposition accompanied melting. [b] Darkened at 140–145 °C with decomposition at 195–205 °C without melting. [c] Darkened at 140–145 °C with decomposition at 175–180 °C without melting. [d] Darkened at 125–130 °C with decomposition at 185–190 °C without melting.

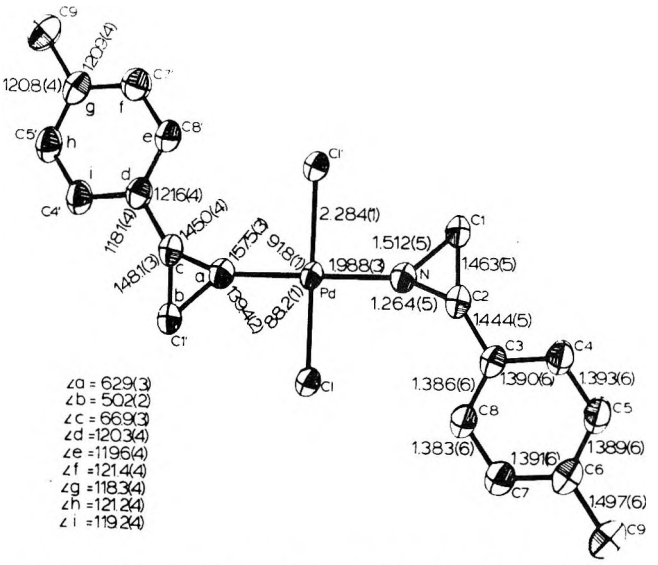


Figure 1. Bond lengths and angles for dichlorobis(2-*p*-tolyl-1-azirine)palladium(II), **2a**.

Thermal decomposition of the complexes **2** was somewhat dependent on conditions and was not a clean reaction. Pyrolysis of **2a** in refluxing chloroform or benzene gave a polymeric material. In the solid state at ca. 140 °C/0.1 mm, the major volatile product was *p*-tolunitrile, identified by IR and NMR. A number of minor products have not been identified.

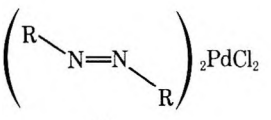
The stability of the azirine–Pd complexes contrasts the behavior of substituted cyclopropenes which opens to π-allyl complexes with paladium chloride.[9] The Pt analogues of **2** are more difficult to prepare.[10a] Compound **5** was obtained in 52% yield by refluxing $(PhCN)_2PtCl_2$ with excess azirine, **1c**, in methylene chloride overnight. Complex **5** was the only Pt

5

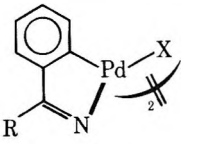
complex we were able to isolate in good purity, although the complexation of azirines **1a** and **1e** was also attempted. In general, the Pt compounds appeared to be less stable than the Pd ones.

Identification. Evidence for the structure of complexes **2** was provided by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy (Tables II–V). In addition, trans stereochemistry about the palladium atom in **2a** has been established by x-ray crystallography. It is assumed that the other Pd complexes also have trans stereochemistry. The stereochemistry for the Pt compound **5** is not certain, since the starting material, $(PhCN)_2PtCl_2$, has a cis configuration compared to *trans*-$(PhCN)_2PdCl_2$.[10b] However, the similarity between the ^{1}H NMR spectra of **5** and the Pd analogue **2c** suggest that **5** also has a trans configuration.

The infrared spectra of the complexes **2** show a strong band for the C=N bond. The position of the band (1762–1813 cm^{-1}) is shifted (27–42 cm^{-1}) to a higher frequency than found in the spectra of the uncomplexed azirines (Table II). This increase is consistent with several reports that Schiff bases show an increase in $\nu_{C=N}$ upon complexation.[11] The $\nu_{N=N}$ for coordinated azo compounds in the *trans*-Pd complexes **6** also increases relative to $\nu_{N=N}$ for the free ligand.[12] Complexes such as **7** are reported to have a lower $\nu_{C=N}$ than the nonmetalated, free Schiff base;[13] however, the metallocyclic structure of **7** mitigates a comparison with **2** in this regard.



6



7

The ^{1}H NMR spectra of the 1-azirine complexes **2** are very similar in appearance to the spectra of the free respective azirines **1**. There is, however, a consistent deshielding of the ortho protons in the 2-aryl-1-azirine complexes (Table III) of 0.3–0.5 ppm. Protons at the 3 position of the azirine ring are also deshielded considerably. For instance, the methylene protons of **2a** and **2b** show downfield shifts of 0.59 and 0.51 ppm, respectively, relative to the uncomplexed 1-azirine. The methine protons of **2d, 2e, 2f,** and **2g** show comparable deshielding (0.27–0.51 ppm).

In an effort to understand what may be responsible for the deshielding in the above complexes, we obtained ^{13}C NMR spectra for two of the 1-azirines, **1a** and **1c**, and their respective Pd complexes (Table IV). The results are somewhat surprising in that the chemical shift of C-2 of the azirine ring is affected very little by complexation.

Table II. IR Spectra[a] of 1-Azirines 1 and Complexed 1-Azirines 2

1-Azirine	Registry no.	$\nu_{C=N}$	Complexes	Registry no.	$\nu_{C=N}$	Other bands for 2
1a	**32687-33-5**	**1732**	**2a**	63989-17-3	1777	1608, 1322, 1187, 1034, 825
1b	32687-32-4	1730[b]	**2b**	63989-18-4	1772	1603, 1511, 1330, 1315, 1269, 1180, 1035, 844
1c	14492-02-2	1725	**2c**	63989-19-5	1762	1498, 1453, 1381, 1181
1d	16205-14-4	1738	**2d**	63989-20-8	1775	1600, 1455, 1385, 1328, 1168, 945
1e	18709-45-0	1768	**2e**	63989-21-9	1796	1740, 1598, 1455, 1440
1f	56900-68-6	1745	**2f**	63989-22-0	1780	1598, 1455
1g	52124-00-2	1730[c]	**2g**	63989-23-1	1769	3430 (br), 1600, 1450, 1325, 1315, 1158, 1085, 1035
1h	63989-39-9	1768[c]	**2h**	63989-24-2	1801	1385, 1365, 1091, 1052
1i	54856-83-6	1771	**2i**	63989-25-3	1813	1455, 1438, 1378, 1325, 1127, 1068, 1004

[a] $CHCl_3$ solution unless otherwise stated. [b] CCl_4 from ref 25, [c] CCl_4.

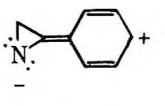
Table III. ^{1}H NMR Spectra of Dichlorobis(1-azirine)-palladium(II) Complexes (δ, $CDCl_3$)

Compd	Ortho H	Meta and para H	Other
2a	8.30	7.45	2.50 (3 H, s), 2.19 (2 H, s)
2b	8.32	7.08	3.95 (3 H, s), 2.15 (2 H, s)
2c	8.35	7.70	1.60 (6 H, s)
2d	8.27	7.60	2.75 (1 H, q, J = 4.9 Hz), 1.50 (6 H, d, J = 4.9 Hz)
2e	8.47	7.70	3.83 (3 H, s), 3.12 (1 H, s)
2f	8.38	7.63	4.80 (1 H, d, J = 1.5 Hz), 3.60 (3 H, s), 3.50 (3 H, s), 2.78 (1 H, d, J = 1.5 Hz)
2g	8.33	7.73	4.17 (1 H, ddd, J = 14, 7, 1 Hz), 3.63 (1 H, ddd, J = 14, 7, 3.5 Hz), 3.15 (1 H, d, J = 7 Hz), 2.90 (1 H, dd, J = 3, 1 Hz)
2h			2.70 (3 H, s), 2.30 (1 H, q, J = 4.5 Hz), 1.27 (3 H, d, J = 4.5 Hz)
2i			3.30 (3 H, s), 3.00 (3 H, s), 1.40 (6 H, s)

Table IV. ^{13}C NMR Spectra of 1a, 2a and 1c, 2c ($CDCl_3$, ppm Rel to Me_4Si)

Carbon	1a	2a	Δ	1c	2c	Δ
C-2	165.12	166.14	1.02	177.70	177.84	0.14
C-3	21.74	22.23	0.49	33.88	39.70	5.82
Subst C	123.09	119.21	−3.88	126.04	122.17	−3.87
o,m-C	129.54, 129.97	130.13 132.55		128.87, 129.11	129.25, 131.83	
p-C	143.57	147.07	3.50	132.41	134.84	2.43
CH_3	19.37	20.77	1.40	24.66	23.64	−1.02

By contrast, some atoms farther removed from the coordination site are affected much more. The para carbon (*p*-C) in the phenyl ring, for instance, is shifted downfield in both complexes **2a** and **2c**. This implies that the complexed azirine moiety acts as a greater electron sink than the free 1-azirine group. Electron-withdrawing groups are reported to lower (wrt benzene at 128.7 ppm) the ^{13}C NMR chemical shifts of para carbons in monosubstituted benzenes.[14] In a comprehensive study of ^{13}C NMR of 1-azirines,[15] the resonance contributor 8 was proposed to explain why the azirine moiety acts as an electron-withdrawing group.[16] A similar resonance contributor, **9**, enhanced by coordination to the Pd atom, could explain the downfield shift at *p*-C in **2a** and **2c**. On the other hand, contributions from structure **9** should decrease the $\nu_{C=N}$ in the IR spectra, which is opposite to our observation.



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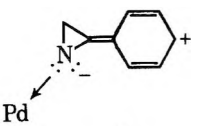

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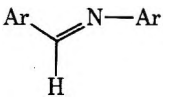
These results suggest that there is more than one effect controlling the ^{13}C chemical shifts in **2a** and **2c** and that for C-2 the effects fortuitously almost cancel each other.

X-ray structure. The crystal structure[17] of **2a** is shown in Figure 1. The ligands have a trans configuration about the planar Pd atom. The azirine and phenyl rings are essentially coplanar with a dihedral angle of 1.0° between them. The azirine ring is tilted about the Pd–N bond 11.6° from the coordination plane of the Pd.

The structure of the azirine portion of **2a** is of special importance, since there is no record of the bond lengths and angles in 1-azirines. The C(2)=N bond, 1.264 (5) Å, is somewhat shorter than the C=N bond found in salicylimine–Pd complexes, 1.286–1.294 Å,[18] or dichlorobis(cyclohexanone oxime)palladium(II), 1.29 Å.[19] However, the Schiff bases **10**



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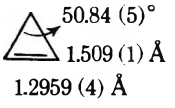

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are reported to have C=N bond lengths of 1.237–1.281 Å[20] so that the C(2)=N bond in **2a** is not unusually short.

It is also interesting to compare the structure of the azirine ring in **2a** with cyclopropene, **11**.[21] The small angle in the two rings is not significantly different, 50.84 (5)° for **11** and 50.2 (2)° for **2a**, but it does appear to be slightly smaller in the azirine ring. In order to accommodate the C=N bond in the three-membered ring, the C(1)–N bond has stretched to 1.512 (5) Å, an unusually long C–N bond distance.[21b] The C(1)–C(2) bond in the azirine is only 1.463 (5) Å, making the three-membered ring a somewhat lopsided triangle.[22] The corresponding C–C bond in cyclopropene is 1.509 (1) Å.

Finally, both the C(2)–C(3), 1.444 (5) Å, and Pd–N, 1.988 (3) Å, distances are slightly shorter than expected, 1.461–1.496 Å and and 2.00–2.09 Å,[23] respectively. This may be due to the high degree of s character found in the C(2) atom of 1-azirines[24] and assumed to be present in the nitrogen atom of the C=N bond as well. The short Pd–N bond may be due to metal backbonding. Otherwise, the bonds and angles are ordinary.

Table V. Formation of 2 from 1

Complex	$(PhCN)_2PdCl_2$, mmol	1, mmol	Solvent,[a] mL	Solvent,[b] mL	Yield of 2,[d] mmol	Comments
2a	3.94	7.94	50 B	100 P	3.58	Yellow powder–orange crystals from $CHCl_3$
2b	0.85	1.70	10 B	10 H	0.74	Yellow powder
2c	5.2	10.7	60 M	100 E	4.6	Orange crystals after 2 days at −25 °C
2d	1.31	2.75	10 M	20 P	1.16	Yellow crystals
2e	2.61	5.71	25 B	25 E	2.47	Yellow powder
2f	2.09	4.19	25 B	25 C	1.43	Yellow powder after 4 days at −4 °C
2g	0.78	2.38	30 B	40 E	0.43	E added after concentrating B to 10 mL—yellow powder
2h	2.74	*c*	50 B	75 P	1.75	Orange crystals after 12 h at −25 °C
2i	1.3	2.7	15 M	30 E	0.57	Orange needles after 2 days at −25 °C

[a] Reaction solvent: B, benzene; M, methylene chloride; CH, chloroform. [b] Precipitating solvent: P, pentane; H, hexane; E, ether; C, cyclohexane. [c] An excess of **1h** was generated in situ by photolysis of 2-azido-1-butene. [d] Consistent C, H, N analyses were obtained for the complex.

Experimental Section

General. All melting points were determined on a Fisher-Johns melting point block and are uncorrected. IR spectra were obtained on a Perkin-Elmer 267 spectrometer. ^1H NMR spectra were taken with either a Varian A60-A or EM-360 spectrometer. ^{13}C NMR spectra were recorded with a Varian HA-100 spectrometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

The 1-azirines, **1a**,[25] **1b**,[25] **1c**,[26] **1d**,[27] **1f**,[28] **1g**,[29] **1h**,[27] **1i**,[30] used for complex preparation were prepared by known methods.

Dichlorobis(1-azirine)palladium(II) (2). General Procedure. Method A. Two equivalents of 1-azirine was added to a suspension of $(PhCN)_2PdCl_2$ in benzene (10 mL/1.0 mmol), the mixture was stirred for 15 min, and twice the volume of pentane or ether was added. The product was collected by filtration, washed with ether, and was pure enough for most purposes.

Method B. Substituting CH_2Cl_2 (10 mL/1.0 mmol) as solvent, the solution was cooled to −25 °C overnight after adding 2 equiv of pentane or ether.

Recrystallization was carried out by dissolving the complex in a minimum amount of either $CHCl_3$ or CH_2Cl_2 and allowing ether to diffuse into the solution at −5 °C. Exact procedures and amounts for individual compounds are given in Table V.

Dichlorobis(2,2,5,5-tetramethyl-4-phenyl-3-oxazoline)palladium (II) (4). A solution of $(PhCN)_2PdCl_2$ (215 mg, 0.56 mmol) and **3** (230 mg, 1.13 mmol) in 50 mL of benzene was stirred several hours. Removal of the solvent gave a yellow solid which was washed with ether. Recrystallization from $CHCl_3$/ether by diffusion at −20 °C gave orange-yellow crystals (245 mg, 0.42 mmol, 75%): IR ($CHCl_3$) 1655 (m, br), 1465 (m), 1447 (m), 1389 (m), 1376 (s), 1368 (m), 1144 (m), 1018 (s), 910 (s), 841 (m) cm^{-1}; NMR ($CDCl_3$) δ 7.77 (2 H, m), 7.47 (3 H, m), 1.40 (6 H, s), and 1.30 (6 H, s).

Dichlorobis(3,3-dimethyl-2-phenyl-1-azirine)platinum(II) (5). $(PhCN)_2PtCl_2$[31] (500 mg, 1.06 mmol) and **1e** (600 mg, 4.14 mmol) were refluxed in 25 mL of CH_2Cl_2 (purified through Al_2O_3) for 24 h. An equal amount of ether was added and the solution was cooled to −25 °C. Yellow crystals (225 mg) were collected by filtration. A second crop (80 mg) was obtained giving 0.549 mmol (52%) of **5**: IR ($CHCl_3$) 1760, 1600 (m), 1455 (s), 1380 (s), 1180 (s) cm^{-1}; NMR ($CDCl_3$) δ 8.27 (2 H, m), 7.79 (3 H, m), and 1.67 (6 H, s).

Regeneration Azirine 1a from the Complex. To **2a** (100 mg, 0.23 mmol) in 5 mL of $CHCl_3$ and 20 mL of benzene was added triphenylphosphine (210 mg, 0.80 mmol) in 10 mL of benzene. After stirring overnight at 25 °C solvent was removed and the residue triturated with ether. Dichlorobis(triphenylphosphine)palladium (115 mg, 0.16 mmol, 72%) was collected as a yellow powder and recrystallized from $CHCl_3$/pentane at −20 °C, mp 268–272 °C. The filtrate was concentrated and ^1H NMR analysis indicated approximately equal amounts of **1a** and triphenylphosphine. Kugelrohr distillation gave **1a** (30 mg, 0.20 mmol, 49%), pure by NMR.

Crystallography. The yellow parallel-piped crystals of **2a** are monoclinic, space group $P2_1/n$,[32] with a = 8.963 (3), b = 11.268 (3), c = 8.991 (1) Å, and β = 99.98 (2)°. The observed density of 1.646 (5) g/mL is in agreement with the calculated density, 1.632 g/mL, for Z = 2.

Intensity measurements were made on a crystal ground to a spherical shape (d = 0.35 mm) using a Syntex Pl autodiffractometer equipped with a graphite monochromated Mo Kα source (θ–2θ scans). Some 1800 independent reciprocal lattice points were surveyed within a single quadrant to 2θ = 50° and 1358 were used in the refinement.

Since the Pd atom was in a special position, the determination of only one Cl atom from a Patterson map was sufficient. Three cycles of least-squares refinement on the Cl atom positional parameters, the scale factor, and the isotropic temperature factors for Pd and Cl gave R = 0.28 and wR = 0.36. From a difference Fourier map, the positions of all the nonhydrogen atoms were obtained. Inclusion of all these atoms as carbons in further isotropic refinement resulted in R = 0.10 and wR = 0.13. After determining the position of the N atom in the azirine ring,[33] anisotropic refinement converged at R = 0.047 and wR = 0.064. A difference map revealed the position of all nine H atoms. Idealized positions were used in the final refinement to give R = 0.039 and wR = 0.047. The standard deviation of an observation of unit weight was 1.88.[34]

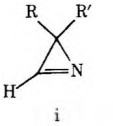
Acknowledgment. This investigation was supported by Grant CA-19203 awarded by the National Cancer Institute, Department of Health, Education, and Welfare.

Registry No.—**3**, 17582-72-8; **4**, 63989-26-4; **5**, 63989-27-5; $(PhCN)_2PdCl_2$, 15617-18-2.

Supplementary Material Available. Tables VI–VIII; structural parameters of **2a**, rms vibrational amplitudes, bond lengths, bond angles and least-square planes will appear following this article in the microfilm edition of this journal (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) Chemistry of Small Rings. 23. For the previous paper, see: A. Hassner and J. Keogh, *Tetrahedron Lett.*, 1575 (1975). (b) National Institutes of Health Postdoctoral Fellow.
(2) For a recent review, see: D. J. Anderson and A. Hassner, *Synthesis*, 483 (1975).
(3) (a) F. W. Fowler in *Adv. Heterocycl. Chem.*, **13**, 46–47 (1971). (b) D. J. Anderson, T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 550 (1973); (c) G. M. Rubottom, G. K. Stevenson, J. C. Chabala, and V. J. Pascucci, *Tetrahedron Lett.*, 3591 (1972); (d) F. W. Fowler and A. Hassner, *J. Am. Chem. Soc.*, **90**, 2875 (1968).
(4) Cyclobutadiene, another 4-π antiaromatic system, is well known to be stabilized in π-coordinated complexes. P. M. Maitlis, *Adv. Organomet. Chem.*, **4**, 95 (1966).
(5) K. I. Hayashi, K. Isomura, H. Taniguchi, *Chem. Lett.*, 1011 (1975).
(6) H. Alper and S. Wollowitz, *J. Am. Chem. Soc.*, **97**, 3541 (1975).
(7) H. Alper and J. E. Prickett, *J. Chem. Soc., Chem. Commun.*, **191**, 191, 483 (1976).
(8) Reported yield of **3** was 98%, P. Claus, P. Gilgen, H.-J. Hansen, H. Heimgartner, B. Jackson, and H. Schmid, *Helv. Chim. Acta*, **57**, 2173 (1974).
(9) M. A. Battiste, L. E. Friedrich, and R. A. Fiato, *Tetrahedron Lett.*, 45 (1975).
(10) (a) It is known that $(PhCN)_2PtCl_2$ reacts very slowly with olefins, whereas $(PhCN)_2PdCl_2$ reacts rapidly to give olefin complexes. M. S. Kharasch, R. C. Seyler, and F. R. Mayo, *J. Am. Chem. Soc.*, **60**, 882 (1938); (b) F. R. Hartley, "The Chemistry of Platinum and Palladium", Wiley, New York, N.Y., 1973, p 126.
(11) (a) N. I. Pirskhalava and K. P. Giorgadze, *Russ. J. Inorg. Chem.*, **20**, 1796 (1975); (b) L. A. Ugulava, N. I. Pirskhalava, V. A. Kogan, A. S. Egorov, and O. A. Osipov, *J. Gen. Chem. USSR (Engl. Transl.)*, **45**, 1539 (1974); (c) V. A. Kogan, N. N. Kharabaev, and O. A. Osipov, *J. Gen. Chem. USSR (Engl. Transl.)*, **45**, 346 (1975), and references therein.
(12) L. Caglioti, L. Cattalini, F. Gasparrini, G. Marangoni, and P. A. Vigato, *J. Chem. Soc. A*, 324 (1971).
(13) H. Onone and I. Moritani, *J. Organomet. Chem.*, **43**, 431 (1972).
(14) G. L. Nelsen, G. C. Levy, and J. D. Cargioli, *J. Am. Chem. Soc.*, **94**, 3089 (1972).
(15) K. Isomura, H. Taniguchi, M. Mishima, M. Fujio, and Y. Tsuno, submitted for publication. We thank Professor Taniguchi for a copy of this paper prior to publication.
(16) The 1-azirine fragment is electron withdrawing only when the phenyl group is attached at the 2 position of the 1-azirine. 1-Azirines are considered electron donating on a phenyl group at the 3 position.[15]
(17) Detailed parameters will be available on microfilm.
(18) (a) R. L. Braun and E. C. Lingafelter, *Acta Crystallogr.*, **22**, 787 (1967); (b) P. C. Jain and E. C. Lingafelter, *Acta Crystallogr.*, **23**, 127 (1967).
(19) M. Tanimura, T. Mizushima, and Y. Kinoshita, *Bull. Chem. Soc. Jpn.*, **40**, 2777 (1967).
(20) H. B. Gingi and J. D. Dunitz, *Helv. Chim. Acta*, **54**, 1255 (1971).
(21) (a) W. M. Stigliani, V. W. Laurie, and J. C. Li, *J. Chem. Phys.*, **31**, 1890 (1975); (b) A. J. Gordan and R. A. Ford, "The Chemist's Companion", Wiley, New York, N.Y., 1972, p 108.
(22) There is evidence that the C(1)–N bond is cleaved preferentially in the thermal decomposition and hydrogenation of **2a**. C. A. Bunnell and A. Hassner, unpublished results.
(23) P. M. Maitlis, "The Organic Chemistry of Palladium", Vol. 1, Academic Press, New York, N.Y., 1971, pp 38–39.
(24) Hassner and Fowler deduced from ^{13}C–H coupling data that C(3) in azirines possesses 36% s character.[3d] Similarly, Taniguchi[15] found that the unsaturated carbon atom in i displayed 46% s character.



i

(25) A. G. Hortmann, D. A. Robertson, and B. K. Gillard, *J. Org. Chem.*, **37**, 322 (1972).
(26) R. F. Parcell, *Chem. Ind. (London)*, 1396 (1963).
(27) A. Hassner and F. W. Fowler, *J. Am. Chem. Soc.*, **90**, 2869 (1968).
(28) A. Padwa, J. Smolanoff, and A. Tremper, *J. Am. Chem. Soc.*, **97**, 4682 (1975).
(29) R. J. Isbister, Ph.D. Thesis, University of Colorado, 1968.
(30) M. Reno and L. Ghosez, *Tetrahedron Lett.*, 3765 (1970).
(31) See ref 10b, p 462.
(32) The equivalent positions for $P2_1/n$ are x, y, z; $\bar{x}, \bar{y}, \bar{z}$; $\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z$; $\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z$. The Pd atom is located at a special position; thus, an asymetric unit contains one half of the compound.
(33) One of the atoms included as carbon had an isotropic temperature factor significantly less than the others (2.1 vs. 3.0–4.8) and was in a position consistent with a N atom in the azirine ring.
(34) In the calculations, the scattering factors for Pd^{2+} and Cl^- were those of

Cromer and Waber,[35] and these light atom scattering curves were taken from the tabulations of Hanson et al.[36] The effects of anomolous dispersion were included in the calculated structure factors with the values of $\Delta D'$ and $\Delta f''$ for Pd and Cl taken from the report of Cromer.[37] The data were reduced and the Patterson maps calculated on a Data General NOVA 1200 using programs written in this laboratory. All further calculations were done on the CDC 6400 at the University of Colorado using programs supplied by Dr. James Ibers.

(35) D. T. Cromer and J. T. Waber, *Acta Crystallogr.*, **18**, 104 (1965).
(36) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr.*, **17**, 1040 (1964).
(37) D. T. Cromer, *Acta Crystallogr.*, **18**, 17 (1965).

Attempted Synthesis of a Keto Diazene: Reactions of Propargylic Amines, Sulfamides, and Ureas

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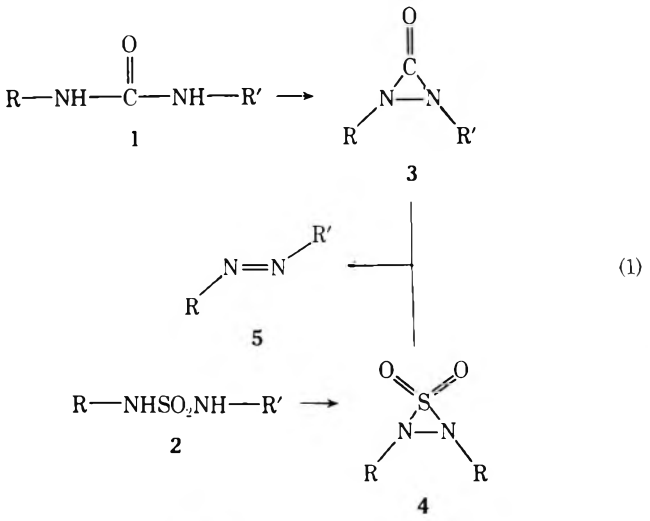
Several attempts to prepare bis(2-oxo-1,1-dimethylpropyl)diazene (**5e**) from propargylic derivatives led to a number of interesting cyclizations giving nitrogen heterocycles (isoxazole **11**, imidazolidinones **22**, and pyrazole **27**). One of these provides an alternate synthesis of hydantoins (imidazolidinediones **23**).

Ureas **1**,[1] sulfamides **2**,[2] diaziridinones **3**,[3,4] and thiadiaziridine 1,1-dioxides **4**[5,6] have been used as precursors to dialkyldiazenes (**5**, eq 1).[1] In a continuation[7] of our study of



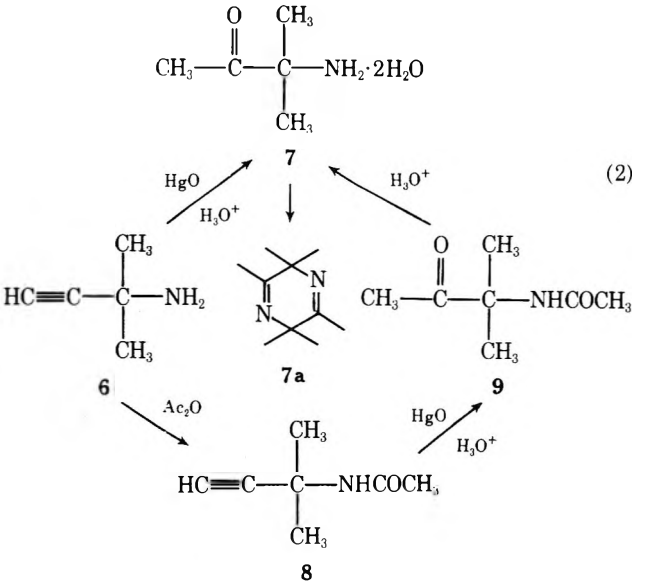
(1)

(a) R = $HC{\equiv}CC(CH_3)_2$—; R′ = $(CH_3)_3C$—
(b) R = R′ = $HC{\equiv}CC(CH_3)_2$—
(c) R = $CH_3COC(CH_3)_2$—, R′ = $(CH_3)_3C$—
(d) R = $HC{\equiv}CC(CH_3)_2$—, R′ = $CH_3COC(CH_3)_2$—
(e) R = R′ = $CH_3COC(CH_3)_2$—

diazenes as models of radical stabilities, we were interested in synthesizing a diazene with a β keto R group such as **5c** or **5e**. Since substituted acetylenes can be considered synthons of keto groups by hydration of the triple bond, we considered the four following methods as possible routes to ketodiazene **5c,e:** (a) hydration of 1,1-dimethylpropargylamine (**6**), (b) hydration of β-substituted propargylsulfamides **2a,b,** (c) hydration of propargyldiaziridinones **3a,b** or thiadiaziridine 1,1-dioxides **4a,b,** and (d) hydration of propargyldiazenes **5a,b.** These attempts have not been completely successful, but have led to some interesting chemistry described herein.

Results and Discussion

(a) Hydration of 1,1-Dimethylpropargylamine. 1,1-Dimethylpropargylamine (**6**) was considered as a precursor to 3-amino-3-methyl-2-butanone (**7**) so that the latter could be directly converted to diazene **5e** with IF_5[1,8] or first converted to urea **1e** or sulfamide **2e** and then to the diazene **5e.**[1] However, hydration of the propargylamine **6** proceeded in very low yield (<5%). Similarly, hydration of acetylated propargylamine **8** followed by acidic hydrolysis also gave unsatisfactory results (~13% overall from **6**, eq 2). While this amine



(2)

has been reported previously as the monomeric amine hydrochloride salt,[9] spectral data seem to indicate that in completely dehydrated form the "amine" appears to be dimeric (**7a**, see Experimental Section). An x-ray analysis is presently being attempted.

The Ritter reaction of 3-hydroxyl-3-methyl-2-butanone (**10**) was selected as an alternative route to **7** by hydrolysis of the expected amide. However, our initial attempts employing the normal aqueous workup recovered only "unreacted" starting material. More careful low-temperature workup gave two products, 4-hydroxy-2,4,5,5-tetramethyl-2-oxazoline (**11**, 17% yield) and 3-oxo-2-methyl-2-butyl acetate (**12**, 22% yield). A reaction sequence explaining the recovery of starting material is illustrated in eq 3. Isolated oxazoline **11** was converted to ester **12** under mild hydrolytic conditions and **12** was converted back to **10** by hydrolysis of the ester under more rigorous conditions.

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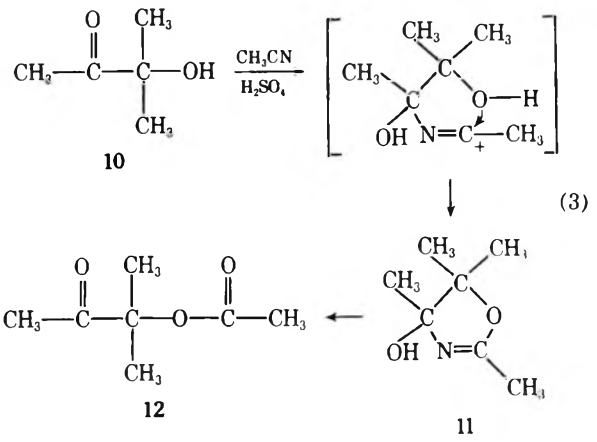
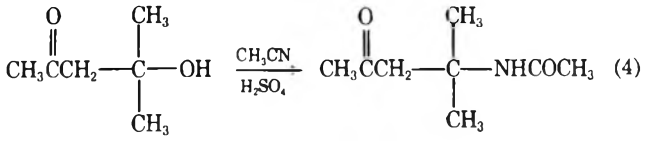


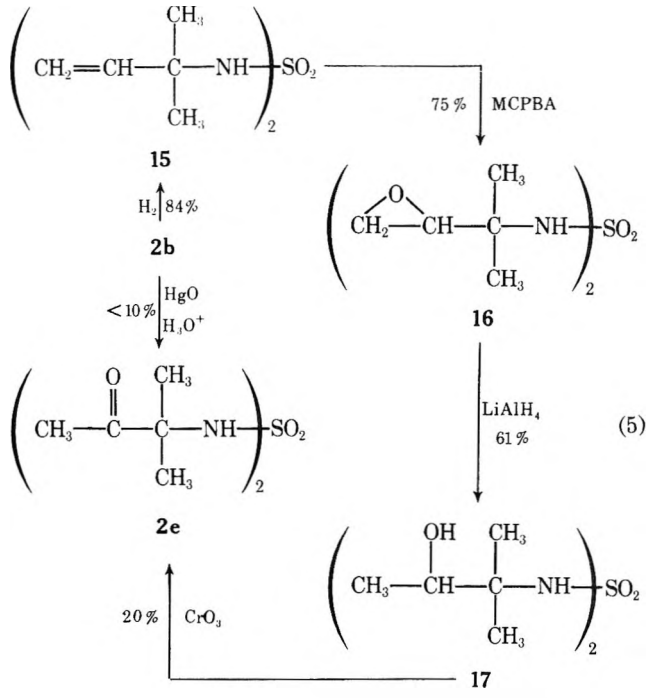
10 (3) 12 11

It is interesting to note that diacetone alcohol **13** (4-hydroxy-4-methyl-2-pentanone, **13**) gives the normal Ritter product amide **14**; undoubtedly, this reflects the difference between **10** and **13** in their respective cation stabilities.



13 14 (4)

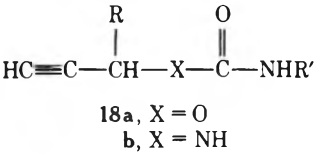
(b) Hydration of Sulfamides. Hydration of *N,N'*-bis(1,1-dimethylpropynyl)sulfamide (**2b**), prepared from the corresponding propargylamine with sulfuryl chloride according to Engel and Bishop,[10] was also a low-yield process (1%). Alternatively, we have prepared the bisketo sulfamide **2e** by the sequence shown in eq 5. Hydrogenation of **2b** to the



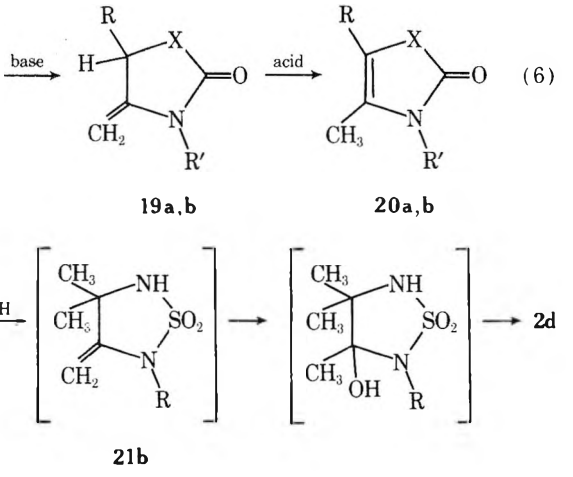
15 2b 16 2e 17 (5)

bisallylic sulfamide **15** is known,[10] and compound **15** can be epoxidized to **16** (75%), reduced to alcohol **17** (61%), and oxidized to sulfamide **2e** (20%). However, neither the aqueous conversion (NaOCl, NaOH)[2] of **2e** to **5e** nor nonaqueous conversion of **2e** to **5e** (NaH, *t*-BuOCl)[5] was successful.

(c) Attempted Preparation of Propargyldiaziridinones and Thiadiaziridine 1,1-Dioxides. The preferred method of preparing thiadiaziridine 1,1-dioxides (**4**, eq 1) involves treating the sodium salt of the sulfamide (**2** + NaH) with *tert*-butyl hypochlorite.[6,11] However, it is known that propargylic urethanes[12] **18a** and ureas[13] **18b** cyclize with sodium methoxide, pyridine, or sodium acetate to give 5-methylene-2-oxazolidinones **19a** and imidazolidinones **19b.** We believe this same cyclization occurs with propargylic sulfamide **2b** with sodium hydride to give thiadiazolidine 1,1-dioxide (**21b**). However, because of the extreme lability its presence could only be conjectured from NMR data (see Experimental Section) and from the corresponding keto sulfamide **2d** isolated from the aqueous workup. The oxazolidinones **19a** and imidazolidinones **19b** previously obtained by this cyclization all contained hydrogen at C-4, and acid treatment resulted in tautomerization from the exocyclic isomer **19a,b** to the endocyclic isomer **20a,b**[14]. Because the thiadiazolidine dioxide **21b** was only presumed as an intermediate, the corresponding *N,N'*-bis(1,1-dimethylpropynyl)ureas were cyclized to imidazolidinones **22a,b** as further evidence of the intermediacy of **21b.** Even though unlikely, we had to establish that the keto sulfamide **2d** was not produced directly from basic hydration of the propargylsulfamide (**2b**). The cyclic ureas **22a,b** were more stable than the cyclic sulfamide and could be isolated in good yields. As expected, these imidazolidinones **22a,b** with two methyls at C-4 were blocked toward tautomerization, and hydrolysis to the keto ureas **1c** and **1d** resulted.



18a, X = O
b, X = NH

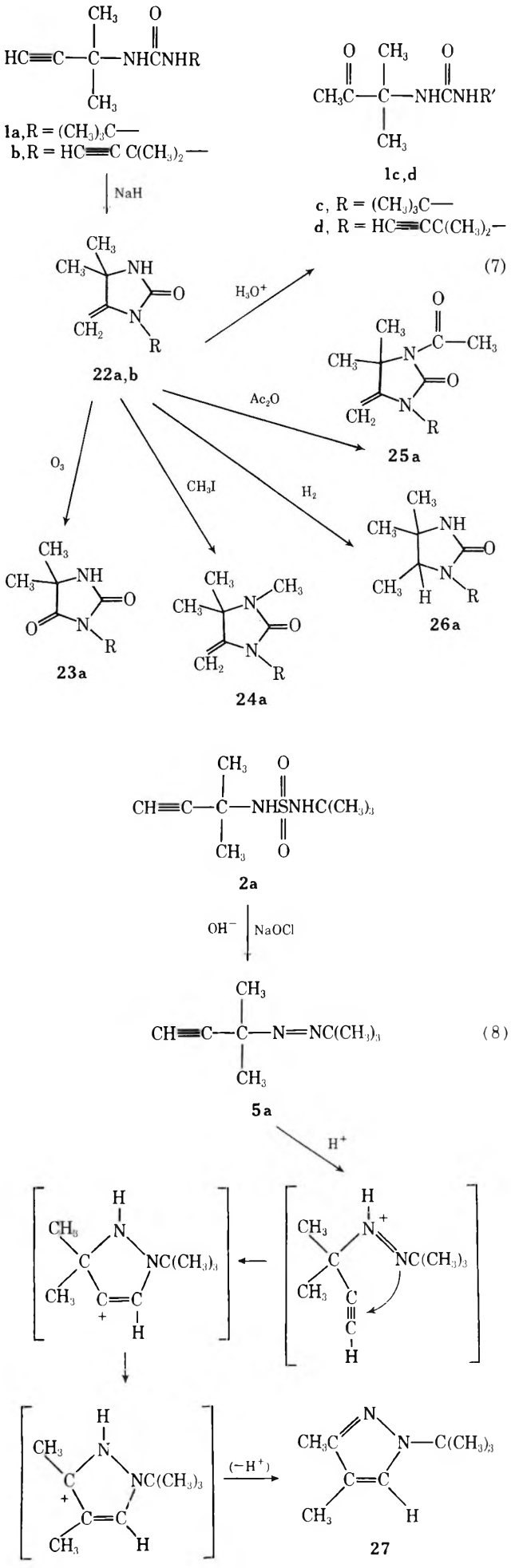


19a,b 20a,b (6)

21b

The imidazolidinones can be alkylated (**24a**) or acetylated (**25a**) on nitrogen and the exocyclic double bond can be reduced to a methyl group (**26a**) or ozonolyzed to hydantoin (2,4-imidazolidinedione) **23a.** Hydantoins represent a class of compounds with an extensive history and find use as herbicides and antibacterial, antifungal, antiarrhythmatic, and anticonvulsant agents.[15,16] We are presently investigating this method as a procedure for making functionalized hydantoins which are difficult to obtain by other procedures.

(d) Attempted Hydration of Propargyldiazenes. Alkylsulfamides **2** are readily converted to alkyldiazenes **5** using aqueous base and hypochlorite.[2] Bis(1,1-dimethylpropynyl)-diazene has been prepared by Engel[10] using this procedure (**2b** to **5b**). Following this lead, sulfamide **2a** was converted to *N-tert*-butyl-*N'*-1,1-dimethylpropynyldiazene (**5a**) with aqueous hypochlorite and base. The NMR of the pentane extract showed signals expected for diazene **5a,** but the compound rapidly rearranged to 1-*tert*-butyl-3,4-dimethylpyrazole (**27**). The reaction appears to be acid catalyzed and yields up to 70% can be obtained by treating the pentane extract with



formic acid. The formation of pyrazole **27** can be rationalized as shown in eq 8 and clearly indicates that acid-catalyzed hydration of propargyldiazenes is not feasible.

Summary

Attempts to prepare β-ketodiazenes **5c,e** have uncovered a number of interesting side reactions. In particular, one of these, the closure of propargylureas **1** followed by ozonolysis could provide a useful synthetic route to hydantoins **23.**

Experimental Section

3-Amino-3-methyl-2-butanone Hydrate (7). To a stirred solution of 0.83 g (3.8 mmol) of red mercuric oxide in 60 mL of 10% H_2SO_4 heated to 70 °C was added dropwise 5.58 g (67 mmol) of 1,1-dimethylpropargylamine (Aldrich). After stirring for 1 h at room temperature, ether was added and the aqueous solution was neutralized with 5 M KOH. The ether layer was dried over $MgSO_4$ and distilled. The crude amine was sublimed to yield colorless cubic crystals of 3-amino-3-methyl-2-butanone dihydrate (**7,** 0.03 g, 0.5%), mp 77–84 °C, or **7a** hexahydrate: NMR (CCl_4 solution dried over Na_2SO_4) δ 1.22 (s, 3 H) and 1.95 ppm (s, 1 H); IR (CCl_4 solution dried) 3291, 2971, 1655, 1368, 1357 and 1161 cm^{-1}; mass spectrum *m/e* 166.

Anal. Calcd for $C_5H_{11}NO{\cdot}2H_2O$ or $C_{10}H_{18}N_2{\cdot}6H_2O$: C, 43.77; H, 11.04; N, 10.21. Found: C, 44.05; H, 11.04; N, 10.30.

***N*-1,1-Dimethyl-2-propynylacetamide (8).** To a solution of 4 g (0.048 mol) of 1,1-dimethylpropargylamine in 50 mL of ether cooled to 0 °C was added dropwise 6 g (0.058 mol) of acetic anhydride. The mixture was stirred at reflux overnight. The etheral solution was washed with several portions of 5% $NaHCO_3$ and combined with several chloroform extracts of the aqueous layer. The organic extracts were dried ($MgSO_4$), concentrated, and recrystallized from $CHCl_3$–hexane to give 4.1 g (68%) of white crystals: mp 104.5–106 °C; NMR ($CDCl_3$) δ 1.64 (s, 6 H), 1.95 (s, 3 H), 2.32 (s, 2 H) and 5.60 ppm (br s, ~1 H); IR ($CHCl_3$) 3441, 3302, and 1692 cm^{-1}.

Anal. Calcd for $C_7H_{11}NO$: C, 67.21; H, 8.80; N, 11.20. Found: C, 67.34; H, 9.02; N, 11.16.

2-Methyl-3-oxo-2-butylacetamide (9). *N*-1,1-Dimethyl-2-propynylacetamide (**8,** 6.0 g, 48 mmol) and red mercuric oxide (1 g, 5.0 mmol) were dissolved in 130 mL of 24% H_2SO_4 and stirred overnight at room temperature. The solution was neutralized with K_2CO_3 and continuously extracted with $CHCl_3$ for 24 h. The $CHCl_3$ extract was dried ($MgSO_4$) and concentrated. The crude product was recrystallized from $CHCl_3$–hexane to give 4.0 g (70%) of white needles: mp 109–111 °C; IR ($CHCl_3$) 3395, 3440, 1725 and 1665 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (s, 6 H), 1.98 (s, 3 H), and 6.4 ppm (br s, ~1 H); mass spectrum *m/e* 143.

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.75; H, 9.09; N, 9.79. Found: C, 58.94; H, 9.18; N, 9.80.

3-Amino-3-methyl-2-butanone (7). 2-Methyl-3-oxo-2-butylacetamide (**9,** 3.3 g, 0.023 mol) in 40 mL of 20% HCl was heated to reflux for 12 h. The solution was neutralized with K_2CO_3 and continuously extracted with $CHCl_3$ for 60 h. After drying the $CHCl_3$ extract ($MgSO_4$) and distilling off the $CHCl_3$, a yellow oil remained which was recrystallized from pentane at −80 °C to give 0.65 g (28%) of white needles, mp 82–85 °C, identical with material (**7**) obtained as above.

***N,N'*-Bis(1,1-dimethyl-2,3-epoxypropyl)sulfamide (16).** To a refluxing solution of 21.0 g (0.09 mol) of *N,N'*-bis(1,1-dimethylallyl)sulfamide (**15**)[10] in 250 mL of CH_2Cl_2 was added 55.1 g (0.226 mol) of *m*-chloroperbenzoic acid (85%, Aldrich) in 200 mL of CH_2Cl_2 at a rate sufficient to maintain reflux. The solution was heated at reflux for 20 h at which time a white solid had formed. The excess peracid was destroyed by washing twice with 100-mL portions of 10% $NaHSO_3$. The solution was washed with two portions of 100 mL of 5% $NaHCO_3$, followed by water and a saturated NaCl solution. The organic layer was dried ($MgSO_4$) and concentrated to give 18.0 g (0.068 mol, 75% crude) of a viscous yellow oil which could not be crystallized and was used in the subsequent steps without further purification: NMR ($CDCl_3$) δ 1.40 (q, 6 H), 2.78 (d, 2 H), 3.08 (t, 1 H), and 4.5 ppm (br s, 1 H); IR ($CHCl_3$) 3683, 3375, 3050, 3040, 1370, 1270, and 1122 cm^{-1}.

***N,N'*-Bis(3-hydroxy-2-methyl-2-butyl)sulfamide (17).** To a solution of 10.6 g (0.04 mol) of the epoxide **16** in 100 mL of anhydrous ether was added 3.1 g (0.08 mol) of $LiAlH_4$. The mixture was stirred at reflux overnight. A saturated Na_2SO_4 solution was added to destroy the excess $LiAlH_4$. Enough $MgSO_4$ was added to contain the aqueous layer. The dry ether layer was concentrated to yield 5.62 g (0.021 mol, 54% crude) of a light-yellow oil which could not be crystallized and

was used in the next step without further purification: NMR ($CDCl_3$) δ 1.34 (m, 9 H), 3.45 (q, 1 H), and 5.0 ppm (br exchangable protons); IR ($CHCl_3$) 3492, 3380, 1369, and 1138 cm^{-1}.

***N,N'*-Bis(2-methyl-3-oxo-2-butyl)sulfamide (2e) by Oxidation of 17.** To a solution of *N,N'*-bis(2-methyl-3-oxo-2-butyl)sulfamide (**17**, 5.6 g, 0.02 mol) in 100 mL of acetone cooled to 0 °C was added dropwise 33 mL of a Jones reagent solution prepared by dissolving 7.0 g of CrO_3 in 10 mL of water followed by the addition of 6.1 mL of concentrated H_2SO_4 followed by 20 mL of water. The mixture was stirred for 3 h at room temperature. Solid $NaHSO_3$ was added until the brown color disappeared. The ether extract was washed successively with 100-mL portions of saturated NaCl, 5% $NaHCO_3$, saturated NaCl solutions, and dried over $MgSO_4$. Concentration yielded a semisolid which was purified by chromatography on neutral alumina and recrystallized from $CHCl_3$–hexane to yield 1.0 g (3.38 mmol, 18%) of white solid, mp 147–149 °C. This compound was identical in every respect with the keto sulfamide prepared below.

***N,N'*-Bis(2-methyl-3-oxo-2-butyl)sulfamide (2e) by Hydration of 2b.** *N,N'*-bis(1,1-dimethylpropynyl)sulfamide[10](**2b**, 5g, 22 mmol) was combined with 0.1 g (4.6 mmol) of red mercuric oxide and 60 mL of 25% H_2SO_4. After stirring for 24 h, the solution was extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated to give a brown oil which was crystallized from ether at −78 °C to yield 0.05 g (1%) of white crystals: mp 149–151 °C; NMR ($CDCl_3$) δ 1.56 (s, 6 H), 2.25 (s, 3 H), and 5.34 ppm (br s, 1 H); IR ($CHCl_3$) 3333, 1710, 1325 and 1147 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}N_2O_4S$: C, 45.42; H, 7.62; N, 10.63. Found: C, 45.20; H, 7.57; N, 10.49.

Ritter Reaction of 3-Hydroxy-3-methyl-2-butanone (10). To a 250-mL flask equipped with an overhead stirrer and cooled to 0 °C was added 16 g (0.14 mol) of acetonitrile, 25 mL of concentrated H_2SO_4, and 50 mL of glacial acetic acid. To this mixture was added 10 g (0.102 mol) of 3-hydroxy-3-methyl-2-butanone (Aldrich). The solution was stirred for 24 h. In rapid succession the mixture was poured over ice, rapidly neutralized with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried ($MgSO_4$) and concentrated to give a thick yellow liquid which afforded 3.2 g (22%) of 2-methyl-3-oxo-2-butyl acetate (**12**) with vacuum distillation: bp 28 °C/0.1 mm; NMR ($CDCl_3$) δ 1.47 (s, 6 H), 2.08 (s, 3 H) and 2.11 ppm (s, 3 H); IR ($CHCl_3$) 1734, 1719, and 1252 cm^{-1}; mass spectrum *m/e* 144.

Anal. Calcd for $C_7H_{12}O_3$: C, 58.33; H, 8.33. Found: C, 58.11; H, 8.59.

The crude solid which remained was recrystallized from pentane to give 2.5 g (17%) of 4,5-dihydro-2,4,5,5-tetramethyl-4-hydroxyoxazole (**11**) as white needles: mp 93–94 °C; NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.41 (s, 6 H), 1.96 (s, 3 H), and 2.96 ppm (s, 1 H); IR ($CHCl_3$) 3605, 3160, 1655, and 1140 cm^{-1}; mass spectrum *m/e* 143.

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.75; H, 9.09; N, 9.79. Found: C, 58.61; H, 9.20; N, 9.69.

Oxazole (**11**) was hydrolyzed in 15 mL of 5% HCl to a mixture of 2-methyl-3-oxo-2-butyl acetate (**12**) and 3-methyl-3-hydroxy-2-butanone (**10**) as determined by NMR. Refluxing the oxazole in 5% HCl showed only keto alcohol **10** as the product.

2-Methyl-4-oxo-2-pentylacetamide (14). To 7.15 g (0.174 mol) of acetonitrile, 20 mL of concentrated H_2SO_4, and 40 mL of glacial acetic acid was added 13.5 g (0.116 mol) of diacetone alcohol (4-methyl-4-hydroxy-2-pentanone, Aldrich). After stirring for 24 h, the mixture was poured over ice, neutralized with K_2CO_3, and extracted with $CHCl_3$. The dried $CHCl_3$ extract ($MgSO_4$) was concentrated to give an orange-red liquid. Distillation gave a yellow liquid (bp 115–118 °C/~1 mm) which crystallized from pentane at −78 °C to give 9.1 g (50%) of amide **14** which was recrystallized from pentane to give pure 2-methyl-4-oxo-2-pentylacetamide (**14**): mp 44–45 °C (lit. 46 °C);[17] NMR ($CDCl_3$) δ 1.42 (s, 6 H), 1.96 (s, 3 H), 2.18 (s, 3 H) and 3.0 ppm (s, 2 H); IR ($CHCl_3$) 3440, 1746, 1710, and 1658 cm^{-1}.

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.30; H, 9.55; N, 8.93.

***N*-*tert*-Butyl-*N'*-1,1-dimethylpropynylurea (1a).** To a solution of 39 g (0.47 mol) of 1,1-dimethylpropargylamine in 150 mL of purified hexane at 0 °C under a nitrogen atmosphere was added 46.5 g (0.47 mol) of freshly distilled *tert*-butyl isocyanate. The mixture was stirred for 2 h at room temperature. The solid which formed was filtered and recrystallized from ethanol–water to yield 73.6 g (87%) of *N*-*tert*-butyl-*N'*-1,1-dimethylpropynylurea: mp 202–203 °C; NMR ($CDCl_3$) δ 1.38 (s, 9 H), 1.58 (s, 6 H), 2.46 (s, 1 H), 4.30 (br s, 1 H), and 5.10 ppm (br s, 1 H); IR ($CHCl_3$) 3406, 3297, 2285, and 1662 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.88; H, 9.97; N, 15.37. Found: C, 65.81; H, 10.12; N, 15.30.

***N,N'*-Bis(1,1-dimethylpropynyl)urea (1b).** To 45.8 g (0.55 mol) of 1,1-dimethylpropargylamine and 55.7 g (0.55 mol) of triethylamine in 250 mL of dry benzene in a flask cooled in an ice bath was added 27.3 g (0.27 mol) of phosgene in 200 mL of dry benzene. The mixture was stirred for 2 h followed by the careful addition of 200 mL of 5% $NaHCO_3$ solution. The solid formed was filtered, redissolved in $CHCl_3$, dried ($MgSO_4$), concentrated, and recrystallized from ethanol–H_2O to give 35 g (66%) of urea **1b**: mp 189–190 °C; NMR ($CDCl_3$) δ 1.60 (s, 6 H), 2.40 (s, 1 H), and 5.20 ppm (br s, 1 H); IR ($CHCl_3$) 3394, 3300, 2111, and 1670 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.70; H, 8.40; N, 14.57. Found: C, 68.75; H, 8.31; N, 14.51.

1-*tert*-Butyl-5-methylene-4,4-dimethyl-2-imidazolidinone (22a). To 2.0 g of sodium hydride dispersion washed with dry THF (~42 mmol) suspended in 50 mL of THF was added 1 g (5.5 mmol) of *N*-*tert*-butyl-*N'*-1,1-dimethylpropynylurea. The mixture was heated to reflux for 3 h followed by the careful addition of 50 mL of water. After stirring 1 h at room temperature, the THF was removed in vacuo. Extraction with ether, drying over K_2CO_3, and removal of the ether left a white solid which was recrystallized from pentane to yield 0.5 g (50%) of 1-*tert*-butyl-5-methylene-4,4-dimethyl-2-imidazolidinone (**22a**): mp 104–105 °C; ^1H NMR ($CDCl_3$) δ 1.30 (s, 6 H), 1.59 (s, 9 H), 4.02 (d, 1 H, J = 3 Hz) and 4.32 ppm (d, 1 H, J = 3 Hz); ^{13}C NMR ($CDCl_3$ relative to Me_4Si) δ 28.8 [$(C^*H_3)_2C$–], 29.6 [$(C^*H_3)_3C$–], 55.2 [$(CH_3)_2C^*$–], 55.9 [$(CH_3)_3C^*$–], 82.8[H_2C^*=C], 154.0 [H_2C=C^*], and 158.8 ppm [C^*=O]; mass spectrum *m/e* 182; IR ($CHCl_3$) 3445, 1710, and 1664 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.88; H, 9.97; N, 15.37. Found: C, 65.93; H, 9.89; N, 15.17.

1-(1,1-Dimethylpropynyl)-5-methylene-4,4-dimethyl-2-imidazolidinone (22b). To 5.5 g (~90 mmol) of sodium hydride suspension washed with THF suspended in 150 mL of THF was added 18.0 g (94 mmol) of *N,N'*-bis(1,1-dimethylpropynyl)urea (**1b**). After stirring for 24 h the solution was filtered and the THF removed in vacuo. The yellow solid was recrystallized four times from hexane to yield 14 g (78%) of 1-(1,1-dimethylpropynyl)-5-methylene-4,4-dimethyl-2-imidazolidinone (**22b**): mp 110–111 °C; NMR ($CDCl_3$) δ 1.32 (s, 6 H), 1.77 (s, 1 H), 1.88 (s, 6 H), 2.45 (s, 1 H), 4.17 (d, 1 H, J = 3 Hz), and 4.82 ppm (d, 1 H, J = 3 Hz); IR ($CHCl_3$) 3410, 3395, 3300, 1710, and 1665 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.70; H, 8.39; N, 14.57. Found: C, 68.57; H, 8.50; N, 14.60.

Hydrolysis of 1-(1,1-Dimethylpropynyl)-5-methylene-4,4-dimethyl-2-imidazolidinone (22b). To 4.1 g (0.021 mol) of 3-(1,1-dimethylpropynyl)-5-methylene-4,4-dimethyl-2-imidazolidinone (**22b**) was added 80 mL of 6% H_2SO_4. The mixture was stirred for 15 min, extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated to give 3.6 g (82%) of crude yellow solid. The solid was chromatographed on a Florisil column and eluted with $CHCl_3$. After decolorizing with Norite, and recrystallizing from $CHCl_3$–hexane, there was obtained *N*-2-methyl-3-oxo-2-butyl-*N'*-1,1-dimethylpropynylurea (**1d**) as white needles: mp 174–177 °C; NMR ($CDCl_3$) δ 1.46 (s, 6 H), 1.60 (s, 6 H), 2.22 (s, 3 H), 2.46 (s, 1 H), and 4.87 ppm (br s, 2 H); IR ($CHCl_3$) 3392, 3295, 1708 and 1664 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}N_2O$: C, 62.86; H, 8.57; N, 13.33. Found: C, 62.65; H, 8.54; N, 12.95.

Hydrolysis of 1-*tert*-Butyl-5-methylene-4,4-dimethyl-2-imidazolidinone (22a). A mixture of 0.5 g (2.8 mmol) of imidazolidinone **22a** and 50 mL of 5% hydrochloric acid was stirred for 12 h at room temperature. The solution was extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated, and the solid was recrystallized from hexane to give 0.2 g (36%) of *N*-*tert*-butyl-*N'*-2-methyl-3-oxo-2-butylurea (**2c**): mp 201–202 °C; NMR ($CDCl_3$) δ 1.32 (s, 9 H), 1.41 (s, 6 H), 2.21 (s, 3 H), 4.50 (br s, 1 H) and 5.10 ppm (br s, 1 H); IR ($CHCl_3$) 3431, 1711, and 1680 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.80; H, 10.11; N, 13.80.

3-*tert*-Butyl-5,5-dimethyl-2,4-imidazolidinedione (Hydantoin 23a). Ozone was passed through a solution of 1 g (5.5 mmol) of 1-*tert*-butyl-5-methylene-4,4-dimethyl-2-imidazolidinone (**22a**) in 100 mL of $CHCl_3$ maintained at 0 °C for 1 h. Water (50 mL) was added to the mixture which was stirred at room temperature for 2 h. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residual white solid was recrystallized from $CHCl_3$–hexane to give 0.43 g (45%) of 3-*tert*-butyl-5,5-dimethyl-2,4-imidazolidinedione (**23a**): mp 147–148 °C; NMR ($CDCl_3$) δ 1.34 (s, 6 H), 1.60 (s, 9 H), and 5.60 ppm (br s, 1 H); IR ($CHCl_3$) 3665, 1769, and 1702 cm^{-1}.

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.77; H, 8.94; N, 15.17.

3-Acyl-1-*tert*-butyl-5-methylene-4,4-dimethyl-2-imidazolidinone (25a). To 2.0 g (~42 mmol) of sodium hydride dispersion in 50 mL of THF was added 1.0 g (5.5 mmol) of 1-*tert*-butyl-5-

methylene-4,4-dimethyl-2-imidazolidinone (**22a**). The solution was heated to reflux for 2 h and cooled to room temperature, and 0.60 g (5.8 mmol) of acetic anhydrite was added. After stirring for 1 h, 50 mL of water was cautiously added and the THF was removed in vacuo. An ether extract was dried ($MgSO_4$) and the solid concentrate was recrystallized from pentane to give 0.99 g (50%) of the acylated product (**25a**); mp 64–65 °C; NMR ($CDCl_3$) δ 1.60 (s, 6 H), 1.62 (s, 9 H), 2.45 (s, 3 H), 4.02 (d, 1 H, J = 2.5 Hz), and 4.32 ppm (d, 1 H, J = 2.5 Hz).

Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.30; H, 9.00; N, 12.50.

3-Methyl-1-*tert*-butyl-5-methylene-4,4-dimethyl-2-imidazolidinone (24a). Following the procedure outlined above, a THF solution of 2.0 g of sodium hydride dispersion and 1.0 g of imidazolidinone **22a** was heated to reflux for 2 h. After cooling to room temperature, 0.78 g (5.5 mmol) of iodomethane was added, Workup and distillation, 137 °C/35 mm, gave a liquid tentatively identified as the methylated imidazolidinone by lack of a N–H stretch: NMR ($CDCl_3$) δ 1.25 (s, 6 H), 1.57 (s, 9 H), 2.72 (s, 3 H), 4.04 (d, 1 H J = 3 Hz) and 4.32 ppm (d, 1 H, J = 3 Hz); mass spectrum m/e 196.

The compound was somewhat unstable and was analyzed as the hydantoin derivative, mp 81-82 °C, obtained by ozonolysis of **24a.**

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.49; H, 9.04; N, 13.95.

1-*tert*-Butyl-4,4,5-trimethyl-2-imidazolidinone (26a). To a solution of 2.0 g (11 mmol) of 1-*tert*-butyl-5-methylene-4,4-dimethyl-2-imidazolidinone in 50 mL of ethanol was hydrogenated at room temperature for 3 h at 50 psi with 1.5 g of 10% Pd/C catalyst. The solution was filtered and the residue after solvent removal was recrystallized from hexane to give 1.62 g (80%) of 1-*tert*-butyl-4,4,5-trimethyl-2-imidazolidinone (**26a**): mp 138–139 °C; NMR ($CDCl_3$) δ 1.13 (s, 4.5 H), 1.23 (s, 4.5 H), 1.42 (s, 9 H), 3.37 (q, 1 H, J = 6 Hz), and 4.48 ppm (br s, 1 H). The peaks at 1.13 and 1.23 (4.5 H each) are the result of coincidental equivalence of the chemical-shift difference of the C-4 diastereotopic methyl groups and the coupling constant (J = 6 Hz) between the methyl at C-3 and the ring hydrogen: NMR (C_6H_6) δ 0.78 (s, 1.5 H), 0.88 (s, 4.5 H), 1.37 (s, 9 H), and 2.88 (q, 1 H, J = 6 Hz); IR ($CHCl_3$) 3425 and 1691 cm^{-1}; mass spectrum (relative intensity) 184 (4), 168 (100), 126 (71), 112 (73), 57 (71), 56 (50), and 40 (61).

Anal. Calcd for $C_{10}H_{20}N_2O$: C, 65.18; H, 10.94; N, 15.20. Found: C, 65.21; H, 11.09; N, 15.33.

Conversion of *N,N'*-Bis(1,1-dimethylpropynyl)sulfamide (2b) to *N*-1,1-Dimethylpropynyl-*N'*-2-methyl-3-oxo-2-butylsulfamide (2d) Via 2-(1,1-Dimethylpropynyl)-4,4-dimethyl-3-methylene-1,2,5-thiadiazolidine *S,S*-Dioxide (21b). To 50 mL of dry THF were added 2.0 g (~35 mmol) of NaH dispersion washed with THF and 5.0 g (22 mmol) of sulfamide **2b**.[10] The solution was allowed to reflux for 10 h. The deep-brown solution was cooled to 0 °C and treated with just enough water to destroy the excess NaH. A small portion removed for spectral analysis showed the following NMR peaks: δ 1.52 (s, ~6 H), 1.89 (s, ~6 H), 2.55 (s, ~1 H), 4.30 (d, ~1 H, J = 3 Hz) and 4.85 ppm (d, ~1 H, J = 3 Hz), consistent with **21b.** A number of smaller extraneous peaks were also present. An additional 20 mL of water was added to the remaining solution which was allowed to stir overnight. The addition of 50 mL of a saturated NaCl solution caused the THF layer to separate. This organic layer was dried and concentrated to give 4.8 g of a viscous yellow oil. The NMR indicated the major component to be *N*-1,1-dimethylpropynyl-*N'*-2-methyl-3-oxo-2-butylsulfamide (**2d**). A small sample of pure **2d** was obtained by extracting the oil with ether and cooling the ether to −78 °C. Recrystallization from $CHCl_3$–hexane gave pure **2d:** mp 125–125.5; NMR δ 1.55 (s, 6 H), 1.62 (s, 6 H), 2.27 (s, 3 H), 2.50 (s, 1 H), 4.55 (br s, 1 H) and 5.60 ppm (br s, 1 H); IR ($CHCl_3$) 3392, 3295, 1708, and 1664 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}N_2SO_3$: C, 48.76; H, 7.36; N, 11.37. Found: C, 48.60; H, 7.48; N, 11.30.

1-*tert*-Butyl-3,4-dimethylpyrazole (27). To 100 mL of commercial bleach, 5 g of NaOH and 100 mL of pentane cooled at 0 °C was added 1.2 g (5.5 mmol) of *N*-*tert*-butyl-*N'*-1,1-dimethylpropynylsulfamide.[10] The mixture was stirred for 3 h at 0 °C. A portion of the pentane layer concentrated in vacuo at 0 °C and dissolved in $CDCl_3$ showed NMR signals consistent with *tert*-butyl-1,1-dimethylpropynyldiazene (**5a**): δ 1.41 (s, 6 H), 1.18 (s, 9 H), and 2.20 ppm (s, 1 H). For example, di-*tert*-butyldiazene, δ 1.12 ppm, and bis(1,1-dimethylpropynyl)diazene, δ 1.46 (s, 12 H) and 2.43 ppm (s, 2 H).

To the remaining pentane layer was added 3 mL of *tert*-butyl alcohol and 1 mL of HCO_2H. After stirring for 1 h at 0 °C, the pentane layer was dried over K_2CO_3 and concentrated to ~10 mL. Preparative GLC from a 9 ft 10% SE-30/Chromosorb P column at 100 °C with a 170 mL/min flow rate yielded 0.61 g (73%) of pure 1-*tert*-butyl-3,4-dimethylpyrazole: NMR (CCl_4) δ 1.42 (s, 9 H), 1.92 (s, 3 H), 2.07 (s, 3 H), and 6.96 ppm (s, 1 H); ^{13}C NMR (rel Me_4Si) δ 8.4 and 11.6 (2 CH_3), 29.9 [$(C^*H_3)_3C$–], 57.3 [$(CH_3)_3C^*$–], 112.9 [CH_3–C^*=CH], 124.8 [C^*H=C], and 146.3 ppm [CH_3–C^*=N]; mass spectrum m/e 152 (53%, parent ion), 137 (100%, –CH_3), and 95 [89%, –$C(CH_3)_3$].

Anal. Calcd for $C_9H_{16}N_2$: C, 71.05; H, 10.53; N, 18.42. Found: C, 71.28; H, 10.64; N, 18.18.

Acknowledgments. The authors appreciate financial support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, from the Army Research Office, and the Diamond Shamrock Corp.

Registry No.—**1a,** 59863-61-5; **1b,** 63989-51-5; **1d,** 63989-52-6; **2a,** 57542-31-1; **2b,** 57542-27-5; **2c,** 63989-53-7; **2d,** 63989-54-8; **2e,** 63989-55-9; **5a,** 63989-56-0; **6,** 2978-58-7; **7,** 63989-57-1; **7a,** 36848-44-9; **8,** 21604-47-7; **9,** 10201-12-4; **10,** 115-22-0; **11,** 63989-58-2; **12,** 10235-71-9; **13,** 123-42-2; **4,** 40652-47-9; **15,** 57542-28-6; **16,** 63989-59-3; **17,** 63989-60-6; **21b,** 63989-61-7; **22a,** 63989-62-8; **22b,** 63989-63-9; **23a,** 63989-64-0; **24a,** 63989-65-1; **25a,** 63989-66-2; **26a,** 63989-67-3; **27,** 63989-68-4; acetonitrile, 75-05-8; *tert*-butyl isocyanate, 1609-86-5.

References and Notes

(1) J. W. Timberlake and J. C. Stowell in "The Chemistry of the Hydrazo, Azo and Azoxy Groups", Part 1, S. Patai, Ed., Wiley, New York, N.Y., 1975, p 69.
(2) R. Ohme, H. Preuschhof, and H.-U. Heyne, *Org. Synth.*, **52,** 11 (1972).
(3) F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, **34,** 2254 (1969).
(4) F. D. Greene, W. R. Bergmark, and J. G. Pacifi, *J. Org. Chem.*, **34,** 2263 (1969).
(5) J. W. Timberlake, M. L. Hodges, and K. Betterton, *Synthesis,* 632 (1972).
(6) J. W. Timberlake and M. L. Hodges, *J. Am. Chem. Soc.*, **95,** 634 (1973).
(7) B. K. Bandlish, A. W. Garner, M. L. Hodges, and J. W. Timberlake *J. Am. Chem. Soc.*, **97,** 5856 (1975).
(8) T. E. Stevens, *J. Org. Chem.*, **26,** 2531 (1961).
(9) S. Gabriel, *Chem. Ber.*, **44,** 57 (1911).
(10) P. S. Engel and D. J. Bishop, *J. Am. Chem. Soc.*, **97,** 6754 (1975).
(11) J. W. Timberlake, M. L. Hodges, and A. W. Garner, *Tetrahedron Lett.*, 3843 (1973).
(12) P. J. Stoffel and A. J. Speziale, *J. Org. Chem.*, **28,** 2814 (1963).
(13) P. J. Stoffel and A. J. Speziale, *J. Org. Chem.*, **27,** 3079 (1962).
(14) P. J. Stoffel and W. D. Dixon, *J. Org. Chem.*, **29,** 978 (1964).
(15) E. Ware, *Chem. Rev.*, **46,** 403 (1950).
(16) See, for example, Chemical Abstracts under 2,4-imidazolidinediones for almost any year.
(17) M. E. Smith and H. Adkins, *J. Am. Chem. Soc.*, **60,** 407 (1938).

Intramolecular Cycloaddition Reactions of Vinyl Azides Bearing Alkenyl and Alkynyl Groups

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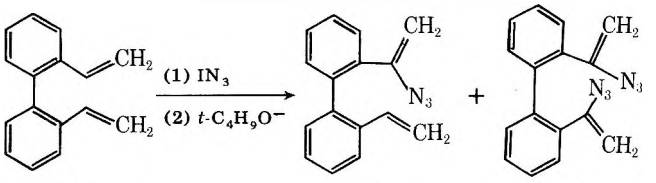
Vinyl azides containing dipolarophile groups in close proximity to the azide moiety were synthesized from a series of *o*-divinyl-substituted biphenyls and propargyl-substituted phenyl ethers. The biphenyl-substituted vinyl azides were found to undergo intramolecular 1,3-dipolar cycloaddition to give an insoluble triazoline. Further thermolysis of the triazoline results in the formation of a 1-vinylaziridine. Intramolecular dipolar cycloaddition of the vinyl azido group to a neighboring triple bond was also observed to occur in the propargyl *o*-(1-azidovinyl)phenyl ether system.

During the past decade unsaturated azides have acquired considerable importance as intermediates in organic synthesis.[1-3] Since the discovery of several methods for the synthesis of vinyl azides,[4] their chemistry has been extensively studied and a large amount of information is now available.[1-3] The reactive azide function is susceptible to thermolysis,[5-9] photolysis,[10-16] cycloaddition,[17-19] and attack by nucleophiles[20-23] and electrophiles.[24-27] Pyrolysis or photolysis of vinyl azides serves as a general method for the synthesis of 2*H*-azirines.[5-16] Vinyl azides are also known to participate in thermally allowed [π_4s + π_2s] cycloadditions as dipolarophiles[28,29] or 1,3-dipoles.[17-19] Although several examples of bimolecular 1,3-dipolar cycloadditions of vinyl azides have appeared in the literature,[17-19,30,31] intramolecular cycloadditions of this 1,3-dipole have not been described.[32] Intramolecular 1,3-dipolar cycloaddition is an extremely versatile and important reaction. The range of synthetic possibilities which it opens for the construction of fused heterocycles is extremely large.[33] With azides, intramolecular cycloadditions have been occasionally reported,[34-37] but systematic data are available only for a series of azidoalkenes.[36] As part of a program directed toward a study of the intramolecular dipolar cycloaddition reactions of unsaturated 2*H*-azirines,[38] we had occasion to prepare several vinyl azides containing a π bond in close proximity to the azide functionality. In this paper, we describe the smooth intramolecular 1,3-dipolar cycloaddition reaction of these unsaturated vinyl azides.

Results and Discussion

A general synthetic method for vinyl azides, discovered by Hassner and co-workers,[4] involves the addition of halogen azides to olefins followed by treatment of the resulting β-haloalkyl azides with potassium *tert*-butoxide. Application of this procedure to 2,2′-divinylbiphenyl (1) gave a mixture

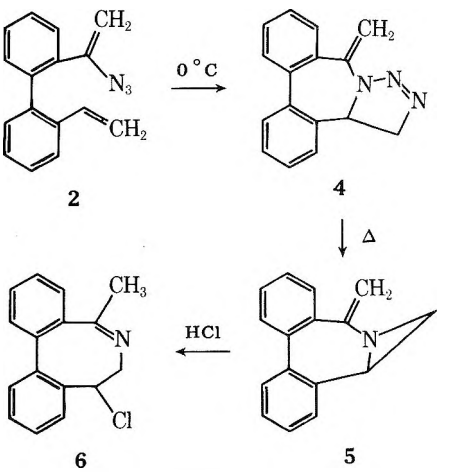


1 2 3

of vinyl azides **2** and **3**. The minor component of the reaction mixture was established as 2-(1-azidovinyl)-2′-vinylbiphenyl (**2**); the major component, isolated as a crystalline solid, mp 72–73 °C, was 2,2′-(1-azidovinyl)biphenyl (**3**). Evidently, the initially formed iodine azide adduct undergoes further reaction at a somewhat faster rate than starting material. This explanation would account for the large amount of starting material that can be recovered when equivalent amounts of iodine azide were used. When a 2-mol excess of iodine azide was employed, a quantitative yield of **3** could be obtained after elimination of hydrogen iodide.

When **2** was allowed to stand at 0 °C for 3 days, it quantitatively cyclized to give 5,13b-dihydro-5-methylene-1*H*-dibenzo[c,e]-*v*-triazolo[1,5-*a*]azepine (**4**): mp 141–142 °C; NMR (100 MHz) τ 6.00 (dd, 1 H, J = 17.0 and 10.0 Hz), 5.62 (s, 1 H), 5.31 (dd, 1 H, J = 10.0 and 3.0 Hz), 4.90 (dd, 1 H, J = 17.0 and 3.0 Hz), 4.73 (s, 1 H) and 2.32–2.92 (m, 8 H). Further heating of this material resulted in the loss of nitrogen and formation of 3,11b-dihydro-3-methylene-1*H*-azirino [1,2-*a*]dibenz[c,e]azepine (**5**): NMR (100 MHz) τ 8.01 (d, 1 H, J = 3.0 Hz), 7.49 (d, 1 H, J = 6.0 Hz), 6.67 (dd, 1 H, J = 6.0 and 3.0 Hz), 5.57 (s, 1 H), 5.43 (s, 1 H), and 2.37–2.88 (m, 8 H). The thermal decomposition of 1,2,3-triazolines has previously been reported[39-41] to produce the corresponding aziridines and provides good analogy for the conversion of **4** to **5**. Alder and Stein's comprehensive study, however, has shown that aziridine formation is usually complicated, and frequently excluded by the formation of isomeric imines.[42] The thermal decomposition of triazolines is therefore not regarded as a generally useful route to aziridines.[43,44] In the above system, however, the thermolysis of Δ^2-1,2,3-triazoline **4** results in the quantitative formation of vinyl aziridine **5** and provides a convenient synthesis of this unusual ring system.

Aziridines possessing unsaturated substituents on nitrogen are known to readily undergo ring expansion to 1-azacyclopentene derivatives.[45,46] Formally analogous to the vinylcyclopropane–cyclopentene isomerization, these rearrangements have been effected by nucleophiles, acids, and heat. Simple 2-vinylaziridines have also been found to rearrange on heating to 3-pyrrolines,[47-50] probably by way of a homolytic mechanism proceeding via an allylic–hydrazino diradical which collapses with allylic rearrangement. It therefore became of interest to examine the thermal behavior of *N*-vinylaziridine **5**, since this system is sterically prohibited from undergoing an analogous rearrangement. One possible reaction which could be imagined would involve the rearrangement of **5** into



2 4 6 5

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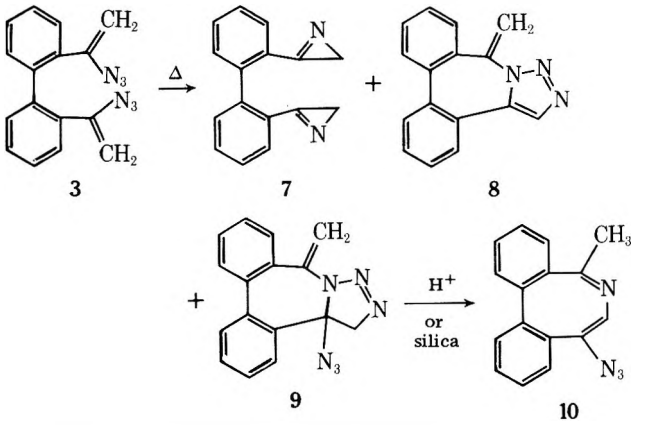
3-(2′-vinyl-2-biphenylyl)-2*H*-azirine by a cheletropic fragmentation of the aziridine ring followed by reorganization of the resulting vinyl nitrene. However, all attempts to isolate a characterizable product from the thermolysis of **5** failed. Treatment of **5** with hydrochloric acid, however, was found to give chloride **6** in high yield. This reaction may be interpreted as involving an acid-induced cleavage of the C–N bond of the aziridine followed by chloride attack and tautomerization of the initially produced enamine.

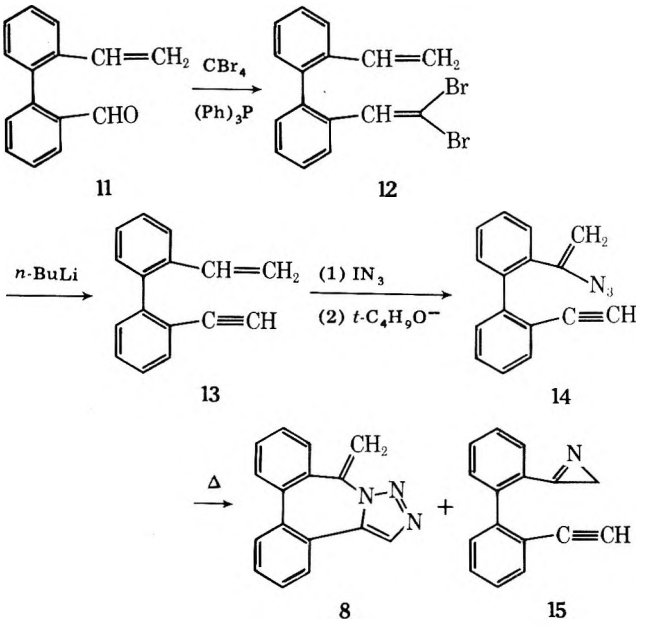
Although the isolation of Δ^2-1,2,3-triazoline **4** from vinyl azide **2** is not surprising, it is noteworthy as the first example of intramolecular cycloaddition of a vinyl azide. Thermolysis of vinyl azides generally produce 2*H*-azirines by a process involving ring closure simultaneous with loss of nitrogen.[2] The facile formation of **2** is also unusual in light of the earlier work by Logothetis[36] who found that azidoalkenes require heating at 50 °C for 18 h before intramolecular cycloaddition will occur. The high reactivity of vinyl azide **2** toward dipolar cycloaddition can be nicely rationalized by the frontier molecular orbital method. 1,3-Dipolar cycloadditions of azides with olefins may be classified as a set which involves dipolar LUMO-dipolarophile HOMO control.[51,52] Attachment of a phenyl group to the π system will raise the HOMO and lower the LUMO energy levels of the olefin and thus bring about an acceleration of the rate of 1,3-dipolar cycloaddition with azides. Another factor which undoubtedly plays an important role in the intramolecular cycloaddition reaction of vinyl azide **2** is the high degree of order present in the transition state. Bimolecular cycloadditions exhibit large negative entropies of activation,[53] since the reactants must be precisely aligned with respect to each other. The interplay of favorable entropy and enthalpy factors in the above system undoubtedly facilitates the rate of cycloaddition over that of azirine formation.

As a continuation of our work in this area, we also studied the thermal behavior of 2,2′-(1-azidovinyl)biphenyl (**3**). Heating a sample of **3** in benzene produced a mixture of three products which were identified as **7** (61%), **8** (17%), and **9**



(22%). The major component isolated from the mixture was established as 3,3′-(2,2′-biphenylylene)bis(2*H*-azirine) (**7**), mp 84–85 °C, through a combination of infrared, ultraviolet, and NMR spectroscopy. The conversion of **3** into **7** represents a typical example of azirine formation from a vinyl azide.[5-16] The minor component of the reaction mixture was a white crystalline solid, mp 165–166 °C, whose structure is assigned as 9-methylene-9*H*-dibenzo[c,*e*]-*v*-triazolo[1,5-*a*]azepine (**8**) on the basis of its elemental analysis and spectroscopic data [NMR (60 MHz) τ 4.39 (s, 1 H), 4.10 (s, 1 H), 2.20–2.70 (m, 8 H), and 2.08 (s, 1 H)]. This structure was further established by the independent synthesis outlined in Scheme I. 2-(1-Azidovinyl)-2′-ethynylbiphenyl (**14**) was prepared by treating 2′-vinyl-2-biphenylcarboxaldehyde (**11**) with carbon tetrabromide and triphenylphosphine to give dibromide **12**. This

Scheme I

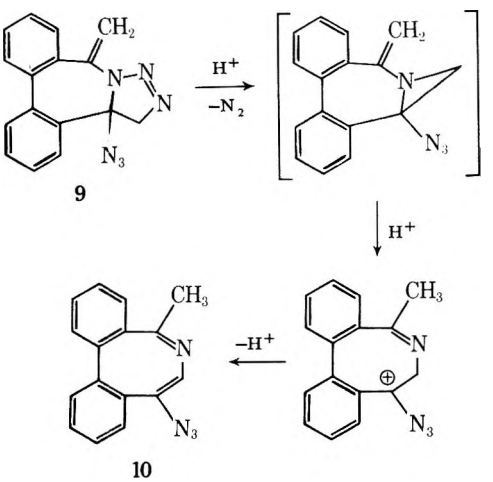


material was converted to acetylene **13** on treatment with *n*-butyllithium which, in turn, was transformed into **14** with iodine azide and potassium *tert*-butoxide. The thermolysis of **14** resulted in both azirine formation (**14**) and intramolecular 1,3-dipolar cycloaddition to give **8** which was identical with the minor product obtained from the thermolysis of **3**.

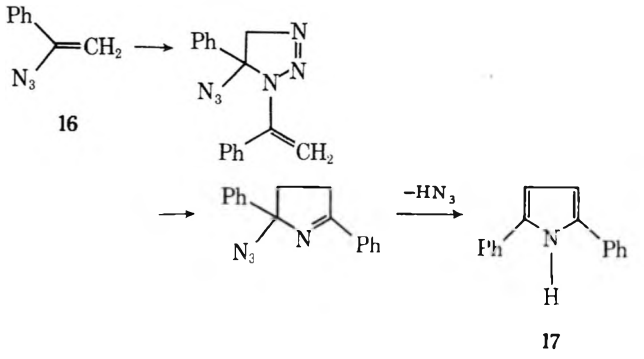
The remaining component (**9**) present in the reaction mixture obtained from the thermolysis of **3** could not be isolated by column chromatography. Instead, a new compound was obtained whose structure was assigned a 8-azido-5-methyldibenz[*c*,*e*]azocine (**10**), mp 102–103 °C, on the basis of its spectral properties (see Experimental Section). The formation of **10** was shown by control experiments to be the result of an acid-induced reaction of **9** and which presumably occurs via the path shown in Scheme II. The structure of **9** was established from its spectral properties and was further confirmed by its based-induced conversion to **8**.

The nature of the products obtained from the thermolysis of bis(vinyl azide) **3** suggests that the thermal chemistry of this system proceeds via two distinct paths. The major path involves formation of bis(azirine) **7**. The minor process, which ultimately leads to the formation of **8**, is best explained as proceeding via an intramolecular dipolar cycloaddition of the azide functionality across the neighboring double bond of the adjacent vinyl azide to give structure **9**. On further thermolysis, this material loses the elements of HN_3 to give **8**.

Scheme II



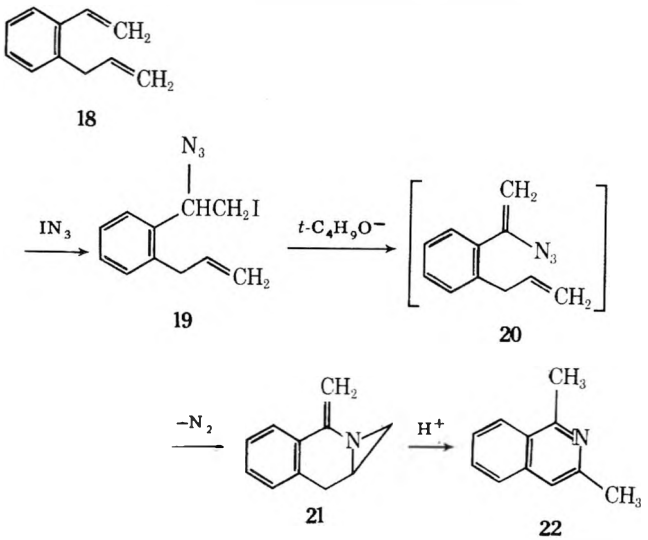
It is interesting to note that the presence of an azide function together with a C=C double bond in the same molecule should allow self-addition of vinyl azides to occur, but this has never been reported explicitly. However, one example exists in the literature where this process might have occurred. Boyer had previously reported[54] that α-azidostyrene (**16**) decomposes slowly at room temperature to give a mixture of 2-phenylazirine, 3,6-diphenylpyridazine, and 2,5-diphenylpyrrole (**17**). The formation of 2,5-diphenylpyrrole (**17**) can



16 **17**

be interpreted in terms of 1,3-dipolar cycloaddition of the azide onto the electron-rich double bond of a second molecule to give a 2-triazoline which decomposes by loss of nitrogen and elimination of HN_3. This reaction scheme was discussed by L'abbe' in a recent review dealing with the reaction of vinyl azides[2] and provides good analogy for the formation of structure **9**.[55]

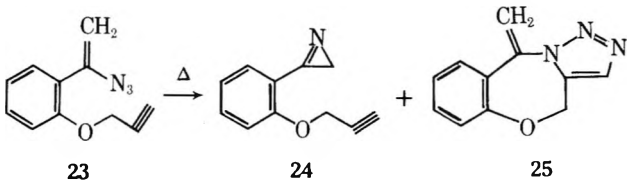
We also attempted to study the intramolecular 1,3-dipolar cycloaddition reaction of the closely related vinyl azide system **20** in order to assess the generality of this cycloaddition. Treatment of *o*-allylstyrene (**18**) with iodine azide gave the expected iodo azide adduct **19.** Elimination of hydrogen iodide from this adduct gave 1,3,8,8a-tetrahydro-3-methyleneazirino[1,2-*b*]isoquinoline (**21**) presumably by way of a transient vinyl azide intermediate **20.** The structure of **21** was assigned



18 **19** **20** **21** **22**

on the basis of its characteristic spectral properties [NMR (100 MHz) τ 7.24–7.40 (m, 2 H), 6.1–6.6 (m, 1 H), 5.90 (dd, 1 H, J = 17.0 and 8.0 Hz), 5.58 (dd, 1 H, J = 17.0 and 11.0 Hz), 2.2–3.0 (m, 4 H)]. Thick-layer chromatography of **21** resulted in the opening of the three-membered ring and gave 1,3-dimethylisoquinoline (**22**) in quantitative yield. The formation of **21** from **19** can reasonably be interpreted in terms of a rapid intramolecular 1,3-dipolar cycloaddition of an initially formed vinyl azide **20** followed by loss of nitrogen.

Another case where a vinyl azide was found to undergo smooth intramolecular dipolar cycloaddition was encountered in the thermolysis of propargyl o-(1-azidovinyl)phenyl ether

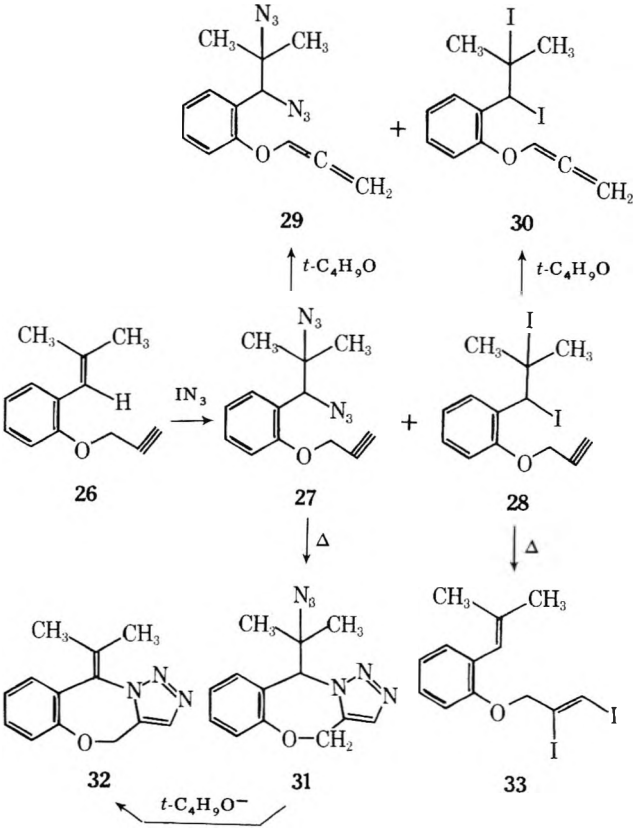


23 **24** **25**

(**23**). Refluxing a solution of **23** in toluene for 2 h afforded a mixture of 3-[o-(2-propynyloxy)phenyl]-2*H*-azirine (**24**), mp 57–58 °C (20%), and 10-methylene-4*H*,10*H*-[1,2,3]triazolo[5,1-c][1,4]benzoxazepine (**25**) (80%) which could be readily separated by column chromatography. In this case, the internal cycloaddition reaction occurred across the acetylenic functionality to give **25** as the major reaction product (see Experimental Section for spectral data).

One additional system which was also studied involved the reaction of 1-[o-(2-propynyloxy)phenyl]-2-methyl-1-propene (**26**) with iodine azide. With this system, the addition of IN_3 proceeded to give a mixture of 1,2-diazido- (**27**) (80%) and 1,2-diodo-1-[o-(2-propynyloxy)phenyl]-2-methylpropane (**28**) (20%). Treatment of this mixture with potassium *tert*-butoxide resulted in a base-induced isomerization of the acetylenic moiety and gave rise to the isomeric o-(allenyloxy)phenyl substituted olefins **29** and **30.** Heating the mixture of **27** and **28** at 120 °C in toluene, on the other hand, resulted in the formation of benzoxazepine **31** and diiodide **33.** The structure of the major reaction product (i.e. **31**) was based on its elemental analysis and characteristic spectral data [NMR (100 MHz) τ 8.66 (s, 3 H), 8.62 (s, 3 H), 5.12 (d, 1 H, J = 14.0 Hz), 4.48 (d, 1 H, J = 14.0 Hz), 4.40 (s, 1 H), 2.60–3.18 (m, 4 H), and 2.70 (s, 1 H)]. Structure **31** was further confirmed by elimination of HN_3 with base to give **32.** The structure of the minor component obtained from the thermolysis was established as diiodide **33** by comparison with an independently synthesized sample prepared by treating olefin **26** with iodine.

The formation of a mixture of **27** and **28** from the reaction of **26** with iodine azide presumably proceeds through an iodonium ion[4] which is trapped by iodide ion to give **28** or reacts with azide ion to give an iodoazide adduct. It would seem as



26 **27** **28** **29** **30** **31** **32** **33**

though the transient iodo azide adduct rapidly loses iodide to give a tertiary carbonium ion which is subsequently trapped by azide to give **27**. The isolation of a vicinal diazide from the reaction of an olefin with iodine azide has been described in the literature.[56] Although it was not possible to obtain the vinyl azide derived from **26**, the isolation of **32** by the above sequence provides an alternate synthesis of this novel ring system. It should also be pointed out that the internal cycloaddition reactions of **23** and **27** represent one of the few available examples of intramolecular cycloadditions of the azido group to a triple bond.[57]

In summary, we have shown that vinyl azides can undergo intramolecular dipolar cycloaddition to a neighboring site of unsaturation to give an isolable triazoline in competition with nitrogen loss and formation of the 2*H*-azirine ring system. Further thermolysis of the triazoline results in the formation of a 1-vinylaziridine. Though 1-vinylaziridines have the structure of an enamine, they are not obtained by the conventional method of enamine synthesis involving the condensation of a carbonyl compound with an aziridine. Only a few of them have so far been prepared by the addition of aziridine to acetylenic compounds possessing strong electron-withdrawing substituents.[58,59] By analogy, we assume that triazolines are also intermediates in the bimolecular reaction of vinyl azides with electron-deficient olefins to give 1-vinylaziridines.[60]

Experimental Section

All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by Scandinavian Microanalytical 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 spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 100 MHz using a Varian XL-100 spectrometer and at 60 MHz with a Varian T-60 spectrometer. All NMR spectra were recorded using deuteriochloroform as the solvent unless otherwise stated.

Preparation of 2-(1-Azidovinyl)-2′-vinylbiphenyl (2). To a solution containing 1.30 g of sodium azide in 50 mL of acetonitrile at −5 °C was added a solution containing 1.62 g of iodide monochloride in 5 mL of acetonitrile. The mixture was allowed to stir for an additional 30 min and was then added to a solution of 1.03 g of 2,2′-divinylbiphenyl[61] (**1**) in 50 mL of acetonitrile. After the addition was completed, the orange slurry was allowed to stir for 10 min at room temperature. The mixture was diluted with 100 mL of water and then extracted with ether. The ethereal extracts were washed with a 5% aqueous sodium thiosulfate solution and then with water. After drying the organic layer with anhydrous magnesium sulfate, the solvent was removed under reduced pressure to give a yellow oil which was used immediately in the next step.

To a solution containing the above iodine azide adduct in 40 mL of ether at −5 °C was added 1.68 g of potassium *tert*-butoxide. The mixture was allowed to stir at 5 °C for 14 h and was then washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure left a yellow oil which was chromatographed on a 2 × 40 cm neutral alumina column using a 5% acetone–hexane mixture as the eluent. The middle fractions contained 150 mg of 2-(1-azidovinyl)-2′-vinylbiphenyl (**2**) as a pale yellow oil: NMR (100 MHz, $CDCl_3$) τ 5.43 (s, 1 H), 5.24 (s, 1 H), 4.97 (d, 1 H, J = 11.0 Hz), 4.43 (d, 1 H, J = 18.0 Hz), 3.55 (dd, 1 H, J = 18.0 and 11.0 Hz), and 2.31–2.99 (m, 8 H).

Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.48; H, 5.21; N, 16.86.

Further elution of the column gave 970 mg of 2,2′-di(1-azidovinyl)biphenyl (**3**) as a crystalline solid: mp 72–73 °C; IR (KBr) 4.75, 6.13, 6.80, 7.20, 7.70, 8.20, 9.35, 9.95, 11.30, 12.85, and 13.55 μm; NMR (60 MHz) τ 5.42 (d, 2 H, J = 2.0 Hz), 5.20 (d, 2 H, J = 2.0 Hz), 2.50–2.80 (m, 8 H).

Anal. Calcd for $C_{16}H_{12}N_6$: C, 66.65; H, 4.19; N, 29.15. Found: C, 66.62; H, 4.08; N, 29.07.

Thermolysis of 2-(1-Azidovinyl)-2′-vinylbiphenyl (2). A 125-mg sample of **2** was allowed to stand at 0 °C for 3 days. The pale-yellow needles which had formed were filtered and washed with hexane. Recrystallization of the solid from chloroform–hexane gave 100 mg (90%) of 5,13b-dihydro-5-methylene-1*H*-dibenzo[*c*,*e*]-*v*-triazolo[1,5-*a*]azepine (**4**): mp 141–142 °C; IR (KBr) 4.72, 6.18, 6.71, 6.90, 7.39, 7.49, 8.34, 8.91, 9.74, 10.70, 11.90, 13.20, and 13.41 μm; UV (cyclohexane) 247 (ε 12 700) and 300 nm (ε 3600); NMR (100 MHz, $CDCl_3$) τ 6.00 (dd, 1 H, J = 17.0 and 10.0 Hz), 5.62 (s, 1 H), 5.31 (dd, 1 H, J = 10.0 and 3.0 Hz), 4.90 (dd, 1 H, J = 17.0 and 3.0 Hz), 4.73 (s, 1 H), and 2.32–2.92 (m, 8 H); MS *m*/*e* 219 (base), 218, 217, 205, 191, 178, 152, and 151.

Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.36; H, 5.30; N, 16.95.

A solution containing 100 mg of the above compound in 25 mL of benzene was heated at reflux for 14 h. Removal of the solvent left a yellow oil which was purified by chromatography on a 1 × 15 cm florosil column using a 1:1 mixture of ether–pentane as the eluent. The major fraction isolated contained 70 mg (77%) of a pale-yellow oil which was identified as 3,11b-dihydro-3-methylene-1*H*-azirino[1,2-*a*]dibenz[*c*,*e*]azepine (**5**) on the basis of its spectral properties: IR (neat) 3.26, 6.11, 6.74, 6.95, 7.46, 8.36, 9.94, 10.33, 11.74, and 13.16 μm; NMR (100 MHz, $CDCl_3$) τ 8.01 (d, 1 H, J = 3.0 Hz), 7.49 (d, 1 H, J = 6.0 Hz), 6.67 (dd, 1 H, J = 6.0 and 3.0 Hz), 5.57 (s, 1 H), 5.43 (s, 1 H), and 2.37–2.88 (m, 8 H); *m*/*e* 219 (M^+ and base), 204, 192, 165.

Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.52; H, 5.81; N, 6.32.

To a solution containing 100 mg of **5** in 20 mL of benzene was added 5 drops of a 10% hydrochloric acid solution. The solution was allowed to stir for 20 min at room temperature and then was washed with a saturated sodium bicarbonate solution and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 75 mg (68%) of 8-chloro-7,8-dihydro-5-methyldibenz[*c*,*e*]azocine (**6**) as a crystalline solid: mp 124–125 °C; IR (KBr) 6.16, 7.11, 7.31, 7.80, 8.31, 12.41, 12.81, 13.13, and 14.19 μm; NMR (100 MHz) τ 7.85 (s, 3 H), 6.40 (t, 1 H, J = 11.0 Hz), 5.80 (dd, 1 H, J = 11.0 and 7.0 Hz), 4.52 (dd, 1 H, J = 11.0 and 7.0 Hz), 2.40–2.90 (m, 8 H); MS *m*/*e* 255 (M^+), 220, 219, 218, 206, 191, 178 (base), 165, 151, and 139.

Anal. Calcd for $C_{16}H_{14}NCl$: C, 75.14; H, 5.52; N, 5.50. Found: C, 75.13; H, 5.54; N, 5.49.

Thermolysis of 2,2′-Di(1-azidovinyl)biphenyl (3). A 2.0-g sample of **3** was heated at reflux in 20 mL of benzene under a nitrogen atmosphere for 24 h. Removal of the solvent left a yellow oil which was subjected to silica gel chromatography using a 15% ether–hexane mixture as the eluent. The first fraction collected contained 330 mg of a yellow solid whose structure was assigned as 8-azido-5-methyldibenz[*c*,*e*]azocine (**10**) on the basis of its spectroscopic data: mp 102–103 °C; IR (KBr) 4.77, 6.09, 6.68, 6.90, 7.13, 7.40, 7.58, 7.90, 10.40, 11.85, 12.35, 13.00, 13.50, and 14.50 μm; NMR (60 MHz) τ 7.50 (s, 3 H), 4.56 (s, 1 H), 2.30–2.70 (m, 8 H); UV (methanol) 280 nm (ε 11 200); MS *m*/*e* 260 (M^+), 232 (base), 219, 204, 192, 178, 165 and 152.

Anal. Calcd for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.53. Found: C, 74.19; H, 4.69; N, 21.07.

Examination of the crude reaction mixture before chromatography showed that **10** was not present. Instead, a series of peaks associated with 5,13b-dihydro-5-methylene-13b-azido-1*H*-dibenzo[*c*,*e*]-*v*-triazolo[1,5-*a*]azepine (**9**) could be found in the NMR spectrum [NMR (60 MHz) τ 5.78 (s, 2 H), 5.46 (s, 1 H), and 5.28 (s, 1 H)]. On treatment of the crude mixture with acid, the peaks associated with **9** disappeared while those of **10** appeared.

The second component isolated from the chromatography column amounted to 980 mg and was a white crystalline solid, mp 84–85 °C, whose structure was assigned as 3,3′-(2,2′-biphenylylene)bis(2*H*-azirine) (**7**) on the basis of the following data: IR (KBr) 5.71, 6.20, 6.38, 6.90, 7.59, 8.58, 8 90, 9.10, 10.05, 12.80, 13.00, 13.40 and 13.60 μm; NMR (100 MHz) τ 8.72 (s, 4 H), 2.36–2.64 (m, 6 H), 1.98–2.08 (m, 2 H); UV (methanol) 242 nm (ε 20 300); MS *m*/*e* 232 (M^+), 231, 230, 229, 205, 204 (base), 192, 190, 178, 165, 151 and 102.

Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.61; H, 5.26; N, 11.97.

The last component isolated from the silica gel column contained 240 mg of a crystalline solid, mp 165–166 °C, whose structure was assigned as 9-methylene-9*H*-dibenzo[ε,*e*]-*v*-triazolo[1,5-*a*]acepine (**8**) on the basis of the following data: IR (KBr) 6.10, 6.87, 7.00, 7.70, 7.78, 8.16, 8.95, 9.95, 10.35, 11.05, 11.67, 13.10, 13.70 and 14.32 μm; NMR (60 MHz) τ 4.39 (s, 1 H), 4.10 (s, 1 H), 2.20–2.70 (m, 8 H), and 2.08 (s, 1 H), UV (methanol) 233 nm (ε 27 200).

Anal. Calcd for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.25; H, 4.50; N, 17.08.

The structure of azepine **8** was further verified by an independent synthesis. A solution containing 5.9 g of 2′-vinyl-2-biphenylcarboxaldehyde (**11**), 15 5 g of carbon tetrabromide, and 25.0 g of triphenylphosphine in 250 mL of methylene chloride was allowed to stir at 0 °C for 20 min. At the end of this time 20 mL of water was added and

the mixture was separated. The organic layer was filtered and the solvent was removed under reduced pressure. The resulting yellow residue was chromatographed on a silica gel column using a 10% ether–pentane mixture as the eluent. The major fraction isolated contained 6.4 g (73%) of 2-vinyl-2′-(2,2-dibromovinyl)biphenyl (**12**) as a light yellow oil: IR (neat) 3.30, 3.45, 6.14, 6.29, 6.82, 6.98, 8.00, 8.36, 8.60, 10.00, 10.40, 10.80, 11.15, 11.50, and 12.25 μm; NMR (100 MHz) τ 4.92 (d, 1 H, J = 10.0 Hz), 4.40 (d, 1 H, J = 18.0 Hz), 3.62 (dd, 1 H, J = 18.0 and 10.0 Hz), 3.06 (s, 1 H), 2.40–3.00 (m, 8 H).

To a solution containing 2.40 g of sodium azide in 40 mL of acetonitrile at −5 °C was added a solution containing 2.8 g of iodine monochloride in 5 mL of acetonitrile. The mixture was allowed to stir for 30 min and was then added to a solution of 4.70 g of **12** in 20 mL of acetonitrile. After the addition was completed, the mixture was allowed to stir at room temperature for 2 h. The mixture was diluted with water and extracted with ether. The ether extracts were washed with a 10% sodium thiosulfate solution followed by water. After drying the organic layer, the solvent was removed to leave behind a dark-orange oil which was used immediately in the next step.

To a solution containing the above iodine azide adduct in 100 mL of tehrahydrofuran was added 18.0 mL of a 2.2 M n-butyllithium solution. After stirring for 1 h at −78 °C, the solution was allowed to warm up to room temperature and was then diluted with water and extracted with ether. The ether solution was dried over magnesium sulfate and the solvent was removed under reduced pressure. The resulting residue was distilled at 95–97 °C at 0.05 mm to give 2.3 g of 2-ethynyl-2′-vinylbiphenyl (**13**) as a clear oil: IR (neat) 3.06, 3.32, 3.44, 6.14, 6.84, 6.96, 8.96, 10.10, 10.94, and 13.20 μm; NMR (100 MHz) τ 7.20 (s, 1 H), 4.96 (d, 1 H, J = 11.0 Hz), 4.50 (d, 1 H, J = 17.0 Hz), 3.56 (dd, 1 H, J = 17.0 and 11.0 Hz), 2.50–3.00 (m, 8 H).

To a solution containing 1.5 g of sodium azide in 20 mL of acetonitrile at −5 °C was added a solution containing 1.9 g of iodine monochloride in 3 mL of acetonitrile. The solution was allowed to stir for 30 min at −5 °C and then a solution containing 1.7 g of 2-ethynyl-2′-vinylbiphenyl (**13**) in 3 mL of acetonitrile was added. The resulting mixture was allowed to stir at room temperature for an additional 2 h. The mixture was diluted with water and extracted with ether. The extracts were washed with a 10% sodium thiosulfate solution, dried, and concentrated under reduced pressure. The residue was taken up in 100 mL of ether and 3.4 g of potassium *tert*-butoxide was added. The mixture was stirred at 0 °C for 12 h and was then washed with water and dried over magnesium sulfate. Removal of the solvent left 1.55 g (67%) of 2-(1-azidovinyl)-2′-ethynylbiphenyl (**14**): IR (neat) 3.06, 3.29, 3.41, 4.77, 6.12, 6.80, 6.97, 7.70, 9.55, 9.92, 10.50, 11.70, and 13.0 μm; NMR (100 MHz) τ 7.12 (s, 1 H), 5.50 (s, 1 H), 5.25 (s, 1 H), and 2.40–3.30 (m, 8 H).

A 200-mg sample of **14** in 5 mL of benzene was heated at 30 °C for 3 days. Removal of the solvent left a pale-yellow oil which was chromatographed on a thick-layer plate. The minor component isolated from the plate contained 30 mg (15%) of an oil which was identical in every detail (IR, NMR) with that of a sample of 8 obtained from the thermolysis of **3**.

Treatment of 2-Azido-1-iodo-1-(o-allylphenyl)ethane with Potassium *tert*-Butoxide. A solution containing 0.26 g of sodium azide in 10 mL of acetonitrile was cooled in a methanol–ice bath and then a solution containing 0.35 g of iodine monochloride in 5 mL of acetonitrile was added dropwise. The mixture was allowed to stir for 30 min at 0 °C and then a mixture containing 0.29 g of *o*-allylstyrene[62] (**18**) in 5 mL of acetonitrile was added and the mixture was stirred at 0 °C for 4 h. The resulting orange slurry was added to 10 mL of water and extracted with ether. The ether extracts were washed with a 5% sodium thiosulfate solution and then water. The ethereal layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 0.59 g (95%) of a clear oil whose structure was assigned as 2-azido-1-iodo-1-(o-allylphenyl)ethane (**19**): NMR ($CDCl_3$, 100 MHz) τ 6.80 (d, 2 H, J = 8.0 Hz), 6.70 (d, 2 H, J = 6.0 Hz), 5.0–5.26 (m, 3 H), 4.0–4.40 (m, 1 H), 2.20–3.00 (m, 4 H).

To a solution containing 200 mg of **19** in 25 mL of ether at −10 °C was added 0.12 g of potassium *tert*-butoxide. The mixture was allowed to stir at 0 °C for 14 h and was then diluted with 75 mL of ether and washed with water. Removal of the solvent under reduced pressure left a pale-yellow oil whose structure is assigned as 1,3,8,8a-tetrahydro-3-methyleneazirino[1,2-*b*]isoquinoline (**21**) on the basis of its characteristic NMR spectrum: (100 MHz, $CDCl_3$) τ 7.32 (m, 2 H), 6.1–6.60 (m, 1 H), 5.92 (dd, 1 H, J = 16.0 and 7.0 Hz), 5.56 (dd, 1 H, J = 16.0 and 11.0 Hz), 4.94 (s, 1 H), 4.60 (s, 1 H), 2.20–3.00 (m, 4 H). Chromatography of this material on a thick-layer plate using a 15% ethyl acetate–hexane mixture as the eluent resulted in a rearrangement and gave 32 mg of a clear oil which was identified as 1,3-dimethylisoquinoline (**22**) on the basis of its spectral properties [NMR (100 MHz, $CDCl_3$) τ 7.32 (s, 3 H), 7.03 (s, 3 H), 1.90–2.70 (m, 5 H)] and by comparison with an authentic sample prepared by the method of Fitton and co-workers.[63]

Preparation of Propargyl o-(1-Azidovinyl)phenyl Ether (23). To a stirred solution containing 8.2 g of sodium hydroxide in 300 mL of a 75% aqueous ethanol solution was added 25 g of salicylaldehyde and 23 mL of propargyl bromide. The reaction mixture was heated at 75 °C for 24 h and then the solvent was removed under reduced pressure. The residue was taken up in ether, washed with water, and concentrated under reduced pressure. The resulting solid was sublimed at 30 °C (0.01 mm) to give 20 g (62%) of *o*-(2-propynyloxy)-benzaldehyde as a crystalline solid: mp 68–69 °C; IR (KBr) 3.00, 3.40, 4.65, 5.85, 6.70, 7.70, 8.10, 9.85, 10.65, 11.90, 13.10 and 14.30 μm; NMR ($CDCl_3$, 100 MHz) τ 7.40 (t, 1 H, J = 2.0 Hz), 5.20 (d, 2 H, J = 2.0 Hz), 2.84–3.04 (m, 2 H), 2.16–2.58 (m, 2 H), −0.44 (s, 1 H).

To a mixture containing 11.2 g of methyltriphenylphosphonium bromide in 250 mL of dry ether was added 13.5 mL of a 2.4 M n-butyllithium solution at room temperature under a nitrogen atmosphere. The resulting orange solution was allowed to stir at room temperature for 20 min prior to the addition of 4.0 g of o-(2-propynyloxy)benzaldehyde in 15 mL of ether. The mixture was allowed to stir at room temperature for 14 h and was then filtered to remove the precipitated triphenylphosphine oxide. Removal of the solvent under reduced pressure left a yellow oil which was distilled at 65 °C (0.4 mm) to give 1.7 g (43%) of a colorless oil whose structure was assigned as o-(2-propynyloxy)phenylethylene: IR (neat) 3.0, 3.30, 4.65, 6.02, 6.70, 10.00, 10.85, and 13.00 μm; NMR ($CDCl_3$, 100 MHz) τ 7.48 (t, 1 H, J = 2.0 Hz), 5.22 (d, 2 H, J = 2.0 Hz), 4.64 (d, 1 H, J = 12.0 Hz), 4.16 (d, 1 H, J = 18.0 Hz), 2.26–3.00 (m, 5 H).

To a solution of 2.5 g of sodium azide in 40 mL of acetonitrile cooled in a methanol–ice bath was added a solution of 3.6 g of iodine monochloride in 10 mL of acetonitrile. The mixture was allowed to stir for an additional 30 min while maintaining the temperature at 0 °C. To this solution was added 3.16 g of *o*-(2-propynyloxy)phenylethylene. The mixture was kept at room temperature for 3 h and the resultant orange slurry was added to water and extracted with ether. The ether extracts were washed with a 5% sodium thiosulfate solution and dried over anhydrous magnesium sulfate. Removal of the solvent left 6.6 g (100%) of an oil whose structure was assigned as 1-azido-2-iodo-1-[o-(2-propynyloxy)phenyl]ethane: NMR ($CDCl_3$, 100 MHz) τ 7.46 (t, 1 H, J = 2.0 Hz), 6.5–6.80 (m, 2 H), 5.20 (d, 2 H, J = 2.0 Hz), 4.82 (dd, 1 H, J = 6.0 and 4.0 Hz), 2.60–3.0 (m, 4 H).

To a stirred and cooled solution of 6.6 g of the above iodine azide adduct in 100 mL of ether was added 2.68 g of potassium *tert*-butoxide. The mixture was then allowed to stir at 5 °C for 8 h. The slurry was extracted with ether, washed with water, and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 3.0 g of an orange oil which was purified by passing it through a neutral alumina column with benzene. The resulting light yellow oil was identified as propargyl *o*-(1-azidovinyl)phenyl ether (**23**): IR (neat) 3.00, 4.70, 6.60, 7.70, 8.10, 9.80, and 13.20 μm; NMR ($CDCl_3$, 100 MHz), τ 7.46 (t, 1 H, J = 2.0 Hz), 5.18 (d, 2 H, J = 2.0 Hz), 4.94 (s, 1 H), 4.88 (s, 1 H), 2.40–3.04 (m, 4 H).

Thermolysis of Propargyl o-(1-Azidovinyl)phenyl Ether. A 100-mg sample of the above azide was refluxed for 2 h in 5 mL of toluene. After being concentrated under reduced pressure, the residue was subjected to thick-layer chromatography using a 15% ethyl acetate–hexane mixture as the eluent. The first band obtained contained 20 mg (20%) of a pale-yellow solid whose structure was assigned as 3-[o-(2-propynyloxy)phenyl]-2*H*-azirine (**24**): mp 57–58 °C; IR (KBr) 3.00, 4.65, 6.15, 8.05, 9.70, 10.65, and 13.20 μm; NMR ($CDCl_3$, 100 MHz) τ 8.38 (s, 2 H), 7.46 (t, 1 H, J = 2.0 Hz), 5.14 (d, 2 H, J = 2.0 Hz), 2.25–3.00 (m, 4 H); UV (methanol) 302 and 245 nm (ε 9300 and 23 000); m/e 171 (M^+), 170 (base), 115, 90, and 77.

Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.02; H, 5.46; N, 7.92.

The second band isolated from the thick-layer plate was a pale-yellow oil (80 mg, 80%) whose structure was assigned as 10-methylene-4*H*,10*H*-[1,2,3]triazolo[5,1-c][1,4]benzoxazepine (**25**) on the basis of its characteristic spectral properties: IR (neat) 3.00, 5.95, 6.75, 8.10, 9.70, 10.95, 11.80, and 13.00 μm; NMR ($CDCl_3$, 100 MHz) τ 4.80 (s, 2 H), 4.32 (s, 1 H), 3.86 (s, 1 H), 2.40–2.96 (m, 4 H), and 2.36 (s, 1 H); UV (methanol) 290 nm (ε 7000); MS m/e 199 (M^+), 118 (base), 90, and 89.

Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.65; N, 21.10. Found: C, 66.32; H, 5.09; N, 20.82.

Preparation of 1-[o-(2-Propynyloxy)phenyl]-2-methyl-1-propene (26). To a mixture containing 3.0 g of isopropyltriphenylphosphonium bromide[64] in 50 mL of anhydrous ether was added 3.4 mL of a 2.4 M n-butyllithium solution at room temperature under a

nitrogen atmosphere. The resulting solution was allowed to stir at room temperature for 7 h prior to the addition of 1.0 g of *o*-(2-propynyloxy)benzaldehyde in 125 mL of ether. The mixture was allowed to stir at room temperature for 18 h and was then filtered to remove the precipitated triphenylphosphine oxide. Concentration of the solution under reduced pressure left a yellow oil which was distilled to give 620 mg (50%) of 1-[o-(2-propynyloxy)phenyl]-2-methyl-1-propene (**26**), bp 55–57 °C (0.01 mm): IR (neat) 3.00, 3.35, 4.60, 5.95, 6.65, 7.20, 8.05, 9.65, 10.70, 12.00, and 13.50 μm; NMR ($CDCl_3$, 100 MHz) τ 8.26 (s, 3 H), 8.12 (s, 3 H), 7.60 (t, 1 H, J = 2.0 Hz), 5.34 (d, 2 H, J = 2.0 Hz), 3.78 (br s, 1 H), 2.60–3.12 (m, 4 H).

Treatment of 1-[o-(2-Propynyloxy)phenyl]-2-methyl-1-propene (26) with Iodine Azide. To a solution of 312 mg of sodium azide in 5 mL of acetonitrile cooled in a methanol–ice bath was added a solution of 780 mg of iodine monochloride in 2 mL of acetonitrile. The mixture was allowed to stir for an additional 30 min at 0 °C, and then a solution containing 774 mg of **26** in 5 mL of acetonitrile was added. The mixture was kept at room temperature for 18 h and the resultant orange slurry was added to water and extracted with ether. The ether extracts were washed with a 5% sodium thiosulfate solution and dried over anhydrous magnesium sulfate. Removal of the solvent left 1 g of an oil whose NMR spectrum showed it to be a 4:1 mixture of 1,2-diazido-2-[o-(2-propynyloxy)phenyl]-2-methylpropane (**27**) and 1,2-diodo-1-[o-(2-propynyloxy)phenyl]-2-methylpropane (**28**). The NMR spectrum of the mixture showed peaks at τ 8.80 (s, 3 H), 8.68 (s, 3 H), 7.50 (t, 1 H, J = 2.0 Hz), 5.30 (d, 2 H, J = 2.0 Hz), 4.86 (s, 1 H), and 2.40–3.00 (m, 4 H) for **27** and peaks at τ 8.76 (s, 3 H), 8.52 (s, 3 H), 7.50 (t, 1 H, J = 2.0 Hz), 5.30 (d, 2 H, J = 2.0 Hz), 4.20 (s, 1 H), and 2.08–3.12 (m, 4 H) for **28**.

Treatment of 300 mg of the above mixture with potassium *tert*-butoxide resulted in the isomerization of the triple bond. To a stirred and cooled solution of the above mixture of adducts (**27** and **28**) in 40 mL of anhydrous ether was added 140 mg of potassium *tert*-butoxide. The mixture was allowed to stir at 5 °C for 12 h. The slurry was washed with water and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 300 mg of a light yellow oil whose NMR spectrum indicated it to be a mixture of 1,2-diazido- (**29**) and 2,2-diodo-1-[o-(allenyloxy)phenyl]-2-methylpropane (**30**): NMR ($CDCl_3$, 100 MHz) of **29:** τ 8.80 (s, 3 H), 8.68 (s, 3 H), 4.82 (s, 1 H), 4.48 (d, 2 H, J = 6.0 Hz), 3.10 (t, 1 H, J = 6.0 Hz), 2.32–2.92 (m, 4 H), while the NMR spectrum of **30** showed signals at τ 8.62 (s, 3 H), 8.50 (s, 3 H), 4.56 (d, 2 H, J = 6.0 Hz), 4.28 (s, 1 H), 3.20 (t, 1 H, J = 6.0 Hz), 2.08–3.04 (m, 4 H).

A 300-mg sample of the mixture (**27** and **28**) obtained from the iodine azide treatment of **26** was heated at reflux for 1 h in toluene. The solution was concentrated under reduced pressure and the resulting residue was subjected to thick-layer chromatography using a 15% ethyl acetate–hexane mixture as the eluent. The major band obtained was a light yellow solid which was recrystallized from ether to give 150 mg (50%) of a white solid, mp 119–120 °C, whose structure was assigned as 10-[(1-azido-1-methyl)ethyl]-4*H*,10*H*-[1,2,3]triazolo[5,1-c][1,4]benzoxazepine (**31**) on the basis of its spectral properties: IR (KBr) 4.60, 6.60, 8.10, 9.40 and 13.00 μm; NMR ($CDCl_3$, 100 MHz) τ 8.66 (s, 3 H), 8.62 (s, 3 H), 5.12 (d, 1 H, J = 14.0 Hz), 4.48 (d, 1 H, J = 14.0 Hz), 4.40 (s, 1 H), 2.60–3.18 (m, 4 H), 2.70 (s, 1 H); UV (methanol) 265 nm (ε 200); MS *m/e* 270 (M^+), 228, 187, 186, 159, 158 (base), 132, 106, 93, and 78.

Anal. Calcd for $C_{13}H_{14}N_6O$: C, 57.76; H, 5.22; N, 31.10. Found: C, 58.09; H, 5.35; N, 31.42.

The structure of this material was further verified by treatment with base. A 30-mg sample of **31** in 10 mL of anhydrous ether was treated with 60 mg of potassium *tert*-butoxide for 12 h. The reaction mixture was then diluted with ether, washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting yellow solid was recrystallized from ether–hexane to give 22 mg (97%) of a white solid, mp 140–141 °C, whose structure was assayed as 10-isopropylidene-4*H*,10*H*-[1,2,3]-triazolo[5,1-*c*][1,4]benzoxazepine (**32**) on the basis of the following data; IR (KBr) 6.65, 7.15, 8.10, 9.80, 12.50 and 13.10 μm; NMR ($CDCl_3$, 100 MHz) τ 8.08 (s, 1 H), 7.92 (s, 3 H), 4.76 (br s, 2 H), 2.76–3.20 (m, 4 H), 2.48 (s, 1 H); UV (methanol) 287 (ε 1200); MS *m/e* 227 (M^+), 183, 182, 172, 145, 131, 91, and 77 (base).

Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.55; H, 5.92; N, 18.37.

The minor component isolated from the thick-layer plate from the thermolysis of the mixture **27** and **28** contained 40 mg of a solid, mp 40–41 °C, whose structure was assigned as 1-[o-(2,3-diodoallyloxy)-phenyl]-2-methylprop-1-ene (**33**): IR (KBr) 3.30, 6.60, 6.80, 8.00, 9.50, and 13.25 μm; NMR ($CDCl_3$, 100 MHz) τ 8.18 (s, 3 H), 8.00 (s, 3 H), 5.36 (s, 2 H), 3.62 (s, 1 H), 2.86–3.32 (m, 5 H); UV (methanol) 280 and 240 nm (ε 1340 and 4800).

Anal. Calcd for $C_{13}H_{14}OI_2$: C, 35.45; H, 3.21; I, 57.69. Found: C, 35.50; H, 3.32; I, 57.52.

An authentic sample of **33** was prepared by treating 186 mg of **26** in 10 mL of acetonitrile with 300 mg of iodine. The reaction mixture was maintained at 40 °C for 24 h. At the end of this time the solution was taken up in ether and washed with a 5% sodium thiosulfate solution followed by water. The ethereal layer was dried over magnesium sulfate and concentrated under reduced pressure to give 200 mg (45%) of a solid, mp 40–41 °C, whose spectral properties were identical in every detail with **33** obtained above.

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Registry No.—**1**, 34919-47-6; **2**, 63375-55-3; **3**, 63626-09-5; **4**, 63375-56-4; **5**, 63375-57-5; **6**, 63375-59-7; **7**, 63626-10-8; **8**, 63641-41-8; **9**, 63657-91-0; **10**, 63626-11-9; **11**, 63626-12-0; **12**, 63626-13-1; **13**, 63626-14-2; **14**, 63626-15-3; **18**, 21919-44-8; **19**, 63626-16-4; **21**, 63375-68-6; **22**, 1721-94-4; **23**, 63626-17-5; **24**, 63626-18-6; **25**, 63626-19-7; **26**, 63626-20-0; **27**, 63626-21-1; **28**, 63626-22-2; **29**, 63626-23-3; **30**, 63626-24-4; **31**, 63626-25-5; **32**, 63626-26-6; **33**, 63626-27-7; salicylaldehyde, 90-02-8; propargyl bromide, 106-96-7; o-(2-propynyloxy)benzaldehyde, 29978-83-4; *o*-(2-propynyloxy)-phenylethylene, 63626-28-8; 1-azido-2-iodo-1-[*o*-(2-propynyloxy)-phenyl]ethane, 63626-29-9; iodine azide, 14696-82-3; methyltriphenylphosphonium bromide, 1779-49-3.

References and Notes

(1) G. L'abbe and A. Hassner, *Angew. Chem., Int. Ed. Engl.*, **10**, 98 (1971).
(2) G. L'abbe, *Angew. Chem., Int. Ed. Engl.*, **14**, 775 (1975).
(3) G. L'abbe, *Chem. Rev.*, 69, 345 (1969); *Ind. Chim. Belge*, **34**, 519 (1969).
(4) A. Hassner and L. A. Levy, *J. Am. Chem. Soc.*, **87**, 4203 (1965); F. W. Fowler, A. Hassner, and L. A. Levy, *ibid.*, **89**, 2077 (1967); A. Hassner and F. W. Fowler, *J. Org. Chem.*, **33**, 2686 (1968); A. Hassner and F. Boerwinkle, *J. Am. Chem. Soc.*, **90**, 216 (1968); *Tetrahedron Lett.*, 3309 (1969); A. Hassner, F. P. Boerwinkle, and A. B. Levy, *J. Am. Chem. Soc.*, **92**, 4879 (1970); A. Hassner, *Acc. Chem. Res.*, **4**, 9 (1971).
(5) F. W. Fowler, *Adv. Heterocycl. Chem.*, **13**, 45 (1971).
(6) G. Smolinsky, *J. Am. Chem. Soc.*, **83**, 4483 (1961); *J. Org. Chem.*, **27**, 3556 (1962); G. Smolinsky and C. A. Pryde, *ibid.*, **33**, 2411 (1968).
(7) C. S. Cleaver and C. G. Krespan, *J. Am. Chem. Soc.*, **87**, 3716 (1965).
(8) R. E. Banks and G. J. Moore, *J. Chem. Soc. C*, 2304 (1966).
(9) A. G. Hartmann, D. A. Robertson, and B. K. Gillard, *J. Org. Chem.*, **37**, 322 (1972).
(10) A. Hassner and F. W. Fowler, *Tetrahedron Lett.*, 1545 (1967); *J. Am. Chem. Soc.*, **90**, 2869 (1968).
(11) A. Padwa and J. Smolanoff, *J. Am. Chem. Soc.*, **93**, 548 (1971).
(12) A. Padwa, *Acc. Chem. Res.*, **9**, 371 (1976).
(13) L. Horner, A. Christmann, and A. Gross, *Chem. Ber.*, **96**, 399 (1963).
(14) J. S. Meek and J. S. Fowler, *J. Org. Chem.*, **33**, 3418 (1968).
(15) F. P. Woerner, H. Reimlinger, and D. R. Arnold, *Angew. Chem., Int. Ed. Engl.*, **7**, 130 (1969).
(16) K. Isomura, M. Okada, and H. Taniguchi, *Tetrahedron Lett.*, 4073 (1969).
(17) A. N. Thakore, J. Buschshriber, and A. C. Oehlschlager, *Can. J. Chem.*, **51**, 2406 (1973).
(18) G. L'abbe, J. E. Gaulle, and A. Hassner, *Tetrahedron Lett.*, 303 (1970); *Bull. Soc. Chim. Belg.*, **80**, 209 (1971).
(19) P. Ykman, G Mathys, G. L'abbe, and C. Smets, *J. Org. Chem.*, **37**, 3213 (1972).
(20) A. N. Nasmeyanov and M. I. Rybinskaya, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 761 (1962).
(21) G. L'abbe, *Ind. Chim. Belge*, **34**, 519 (1969).
(22) G. L'abbe and A. Hassner, *J. Org. Chem.*, **36**, 258 (1971).
(23) E. Ciganek, *J. Org. Chem.*, **35**, 3631 (1970).
(24) A. Hassner, E. S. Ferdinandi, and R. J. Isbister, *J. Am. Chem. Soc.*, **92**, 1672 (1970).
(25) A. Hassner and A. B. Levy, *J. Am. Chem. Soc.*, **93**, 5469 (1971); **93**, 2051 (1971).
(27) A. Hassner, A. S. Miller, and M. J. Haddadin, *J. Org. Chem.*, **37**, 2682 (1972).
(28) G. L'abbe and G. Mathys, *J. Heterocycl. Chem.*, **11**, 613 (1974).
(29) G. L'abbe and G. Mathys, *J. Org. Chem.*, **39**, 1221 (1974).
(30) J. H. Boyer, W. E. Krueger, and R. Modler, *Tetrahedron Lett.*, 5979 (1968).
(31) G. L'abbe and A. Hassner, *J. Heterocycl. Chem.*, **7**, 361 (1970).
(32) For a preliminary report, see: A. Padwa, A. Ku, H. Ku, and A. Massu, *Tetrahedron Lett.*, 551 (1977).
(33) A. Padwa, *Angew. Chem., Int. Ed. Engl.*, **15**, 123 (1976).
(34) F. C. Uhle, *J. Org. Chem.*, **32**, 1596 (1967).
(35) P. A. Smith, J. M. Clegg, and J. H. Hall, *J. Org. Chem.*, **23**, 524 (1958).
(36) A. L. Logothetis, *J. Am. Chem. Soc.*, **87**, 749 (1965).
(37) J. H. Hall, F. E. Behr, and R. L. Reed, *J. Am. Chem. Soc.*, **94**, 4952 (1972).
(38) For some recent work in this area, see: A. Padwa and P. H. J. Carlsen, *J.*

Am. Chem. Soc., **99**, 1514 (1977); A. Padwa and N. Kamigata, *ibid.*, **99**, 1871 (1977).
(39) F. D. Chattaway and G. D. Parkes, *J. Chem. Soc.*, **127**, 1307 (1925).
(40) A. Mustafa, S. Zayed, and S. Khattab, *J. Am. Chem. Soc.*, **78**, 145 (1956).
(41) P. Scheiner and W. R. Vaughan, *J. Org. Chem.*, **26**, 1923 (1961).
(42) K. Alder and G. Stein, *Ann.*, **501**, 1 (1933).
(43) P. K. Kadaba and J. O. Edwards, *J. Org. Chem.*, **26**, 2331 (1961).
(44) S. M. Gurvich and A. P. Terentev, *Sb. Statei, Obshch. Khim. Akad. Nank SSSR*, **1**, 409 (1953).
(45) H. W. Heine, *Angew. Chem., Int. Ed. Engl.*, **1**, 528 (1962).
(46) H. W. Whitlock and G. L. Smith, *Tetrahedron Lett.*, 1389 (1965); *ibid.*, 2711 (1966); *J. Am. Chem. Soc.*, **89**, 3600 (1967).
(47) R. V. Stevens and M. C. Ellis, *Tetrahedron Lett.*, 5185 (1967).
(48) R. S. Atkinson and C. W. Rees, *Chem. Commun.*, 1232 (1967); *J. Chem. Soc. C*, 778 (1969).
(49) S. L. Keely and F. C. Tahk, *Chem., Commun.*, 441 (1968).
(50) P. Scheiner, *J. Org. Chem.*, **32**, 2628 (1967).
(51) K. Houk, R. Duke, J. George, J. Sims, and R. Strozier, *J. Am. Chem. Soc.*, **95**, 7287 (1973).
(52) R. Sustmann, *Tetrahedron Lett.*, 2717 (1971).
(53) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **14**, 775 (1975).
(54) J. H. Boyer, W. E. Krueger, and R. Modler, *Tetrahedron Lett.*, 5979 (1968).
(55) For a closely related reaction of 1-azido-1-pyridinylethylene, see: V. Nair and K. H. Kim, *J. Heterocycl. Chem.*, **13**, 873 (1976).
(56) S. Kwon, T. Okada, M. Ikeda, and Y. Tamura, *Heterocycles*, **6**, 33 (1977).
(57) R. Fusco, L. Garanti, and G. Zecchi, *J. Org. Chem.*, **40**, 1906 (1975).
(58) W. E. Truce and G. G. Brady, *J. Org. Chem.*, **31**, 3542 (1966).
(59) T. Sasaki, T. Yoshioka, and K. Shoji, *J. Chem. Soc. C*, 1086 (1969).
(60) Y. Nomura, N. Hatanaka, and Y. Takenchi, *Chem. Lett.*, 901 (1976).
(61) D. Hall, J. Ladbury, M. Lesslie, and E. Turner, *J. Chem. Soc.*, 3475 (1956).
(62) Y. Kazuaki and T. Yashiyuki, *Kobuashi Kagaku*, **26**, 317 (1969).
(63) A. O. Fitton, J. R. Frost, M. M. Zakaria, and G. Andrew, *Chem. Commun.*, 889 (1973).
(64) U. H. M. Fargerlund and D. Idler, *J. Am. Chem. Soc.*, **79**, 6473 (1957).

Reaction of Nicotine and Sodium Nitrite: Formation of Nitrosamines and Fragmentation of the Pyrrolidine Ring[1,2]

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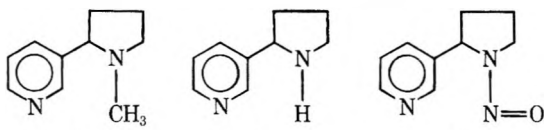
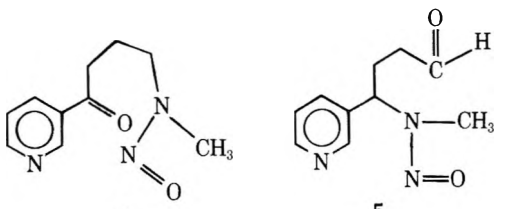
The reaction of nicotine and sodium nitrite was investigated in order to provide insight on the formation of potentially carcinogenic tobacco-specific nitrosamines. Reaction at 25 °C resulted in the formation of *N'*-nitrosonornicotine (**3**), 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone (**4**), and 4-(*N*-methyl-*N*-nitrosamino)-4-(3-pyridyl)butanal (**5**) in yields of 0.1–2.8%, with most of the nicotine being unreacted. When the reaction was carried out at 90 °C, with a fivefold excess of $NaNO_2$, 75–85% of the nicotine reacted. The nitrosamines **3** and **4** were formed in higher yield [up to 13.5 (**3**) and 4.3% (**4**)], but **5** was not observed. Both **4** and **5** gave secondary products under these conditions; **4** was nitrosated further to give 4-(*N*-methyl-*N*-nitrosamino)-2-oximino-1-(3-pyridyl)-1-butanone (**6**), and **5** gave rise to 1-methyl-5-(3-pyridyl)pyrazole (**7**). The major products resulting from fragmentation of the pyrrolidine ring were *cis*- and *trans*-3-(3-pyridyl)acrylonitrile (**8a,b**), *N*-methylnicotinamide (**9**), and nicotinic acid (**10**). The nitrosamines **3–5** and the fragmentation products **8a**, **8b**, and **9** most probably arise via cyclic iminium salts.

Recent studies have shown that both unburned, cured tobacco and tobacco smoke contain significant quantities of the carcinogenic compound, *N'*-nitrosonornicotine (**3**) (0.3–10 ppm in smoking tobacco, 3–90 ppm in chewing tobacco, 40–250 ng/cigarette in smoke).[3-9] This compound induces esophageal and nasal cavity tumors in rats, respiratory tract tumors in hamsters, and lung adenomas in mice, and displays carcinogenic activity and organ specificity which is typical of nitrosamines in general.[10-14] The major precursor in tobacco for **3** is the tertiary amine nicotine (**1**), which is converted to **3** during curing of tobacco.[15] Nornicotine (**2**) can also serve as



1 **2** **3**

precursor for **3**, but its concentration in tobacco is significantly lower.[3,15] About half of **3** present in tobacco smoke is formed during smoking, and model studies have shown that **1** is more important than **2** as a precursor to **3** during cigarette smoking.[7,9] In view of these facts, studies on the reaction of **1** with nitrite were undertaken in order to provide insight on the possible formation of other nitrosamines, such as 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone (**4**) and 4-(*N*-methyl-*N*-nitrosamino)-4-(3-pyridyl)butanal (**5**), which



4 **5**

could result from ring cleavage of the 1′–2′ or 1′–5′ bonds of **1** and nitrosation, respectively. In previous studies on the reaction of **1** with nitrite under various conditions, the presence of **3** was demonstrated and the possible formation of **4** and **5** discussed.[5,7,16]

Results and Discussion

When **1** was allowed to react with 1 equiv of $NaNO_2$ in aqueous solution at 20 °C for 17 h, the nitrosamines **3–5** were formed. Under these mild conditions, **1** was mostly (80–90%) unreacted. The nitrosamines were identified by comparison of GC retention times and mass spectra to those of reference standards, which were independently synthesized.[17-19] Compounds **4** and **5** are, to our knowledge, the first examples of nitrosamines which are primary products of cleavage of a ring C–N bond in the nitrosation of a cyclic tertiary amine. The yields of **3–5** under these conditions are summarized in Table I and are typical of the reaction of tertiary amines with

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Table I. Formation of Nitrosamines 3–5 from Nicotine and $NaNO_2$

Conditions				% yields[a]		
$[NaNO_2]$/[Nicotine]	pH[b]	T, °C	t, h	3	4	5
1.4	2.0	20	17	0.1	ND[c]	0.2
1.4	3.4	20	17	0.5	0.1	2.8
1.4	4.5	20	17	0.5	0.5	2.3
1.4	7.0	20	17	0.2	0.1	0.1
5.0	3.4–4.2	90	0.3	8.0	0.7	ND
5.0	3.4–4.2	90	3.0	8.8	2.3	ND
5.0	3.4–4.2	90	6.0	8.0	1.5	ND
5.0	5.4–5.9	90	0.3	9.0	2.7	ND
5.0	5.4–5.9	90	3.0	13.5	4.3	ND
5.0	5.4–5.9	90	6.0	11.7	2.6	ND
5.0	7.0–7.3	90	0.3	1.3	0.1	ND
5.0	7.0–7.3	90	3.0	4.5	0.2	ND
5.0	7.0–7.3	90	6.0	5.5	0.2	ND

[a] Determined by GC and based on starting nicotine. [b] Buffer systems: pH 2, KCl/HCl; pH 3.4–7, citrate/phosphate. [c] ND = not detected.

nitrite.[20,21] Cleavage of the 1′–5′ bond to give **5** was favored in the pH range 3.4–4.5, as was the formation of all three nitrosamines.

Under more severe conditions (fivefold excess of nitrite, 90 °C), the yields of **3** and **4** increased, while **5** was no longer observed, as shown in Table I. The absence of **5** and the decreasing amounts of **4** at longer reaction times were due to secondary reactions, as discussed below. Under these conditions, nitrosamine formation was favored at pH 5.4–5.9. The optimum pH range for nitrosamine formation at both 20 and 90 °C is in agreement with previous studies on nitrosation of tertiary amines, as is the formation of nitrosamines under neutral conditions.[20,22,23] Since the yields of **3** were relatively high at 90 °C, isolation of this compound in gram quantities was feasible; unreacted **1** was steam-distilled and **3** was isolated by preparative high-performance liquid chromatography (HPLC) followed by distillation.

Examination of the mixtures formed in the reaction of **1** with $NaNO_2$ at 90 °C revealed, in addition to **3** and **4**, products arising from secondary reactions of **4** and **5** (**6** and **7**) and from fragmentation and oxidation of the pyrrolidine ring (**8–18**), as shown in Table II. Under these conditions, **1** was 15–25% unreacted. Yields of products reported in Table II were determined by GC or HPLC: approximately 65–70% of the mixture was characterized.

The structures of 4-(*N*-methyl-*N*-nitrosamino)-2-oximino-1-(3-pyridyl)-1-butanone (**6**) and 1-methyl-5-(3-pyridyl)pyrazole (**7**) were deduced from spectral and analytical data, as discussed below. The other major products were the *cis*- and *trans*-3-(3-pyridyl)acrylonitrile isomers **8a** and **8b** (the formation of **8a** was also reported in ref 5), *N*-methylnicotinamide (**9**), and nicotinic acid (**10**). These products and the minor components **11–18** were identified by comparison to available reference samples.

Compound **6**, isolated from the aqueous portion of the reaction mixture, had a high-resolution electron impact (EI)

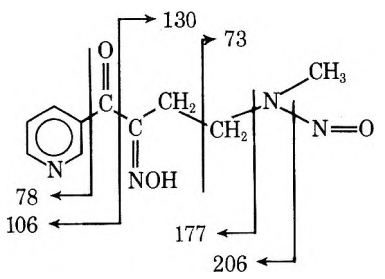
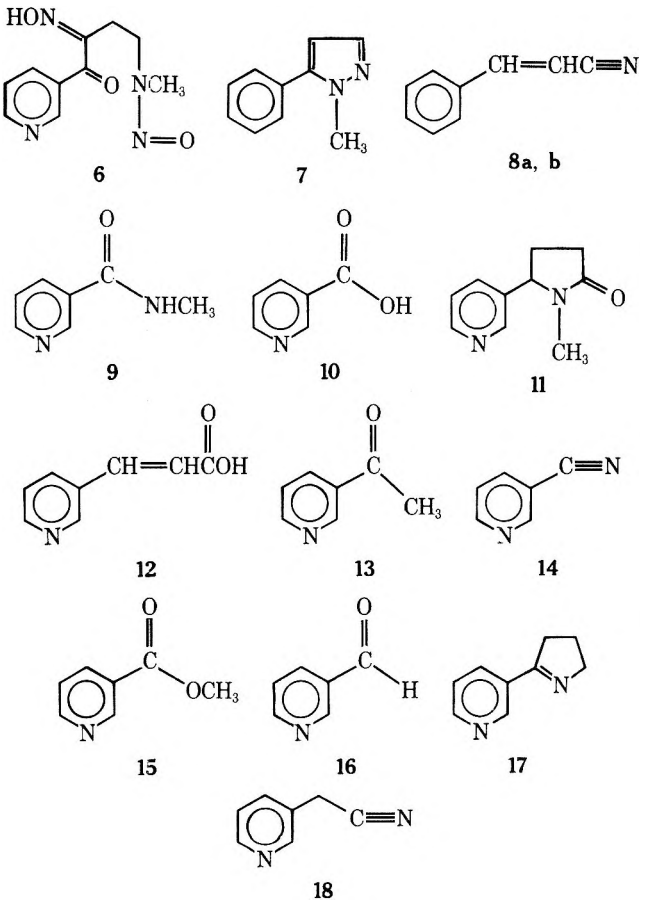


Table II. Products Formed in the Reaction of Nicotine and $NaNO_2$[a,b]

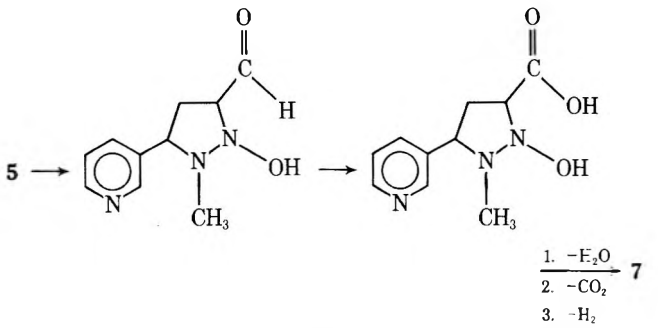
Product	% yield[c]	Method of identification[d]
3	8.8	A[e]
4	2.3	A[f]
6	4.0	C, A
7	2.1	C
8a,b	19.0	A[g]
9	6.2	B
10	4.0	B
11	0.6	A[h]
12	0.5	B
13	0.5	B
14	0.5	B
15	0.3	B
16	0.2	B
17	0.1	A[e]
18	0.1	B

[a] Reaction of 1 equiv of **1** with 5 equiv of $NaNO_2$ at 90 °C, 3 h, pH 3.4–4.2. [b] 15–25% of **1** was unreacted. [c] Based on starting **1**. [d] A, comparison of GC or HPLC retention times and mass spectra to independently synthesized standards; B, comparison to commercially available standards; C, spectral properties (see text). [e] Reference 17. [f] Reference 19. [g] Reference 24. [h] Reference 25.



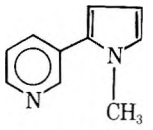
mass spectrum with fragments at 73 ($C_2H_5N_2O$), 78 (C_5H_4N), 106 (C_6H_4ON), 130 ($C_4H_8N_3O_2$), 165 ($C_8H_9O_2N_2$), 177 ($C_9H_9O_2N_2$), 206 ($C_{10}H_{12}O_2N_3$), and 219 ($C_{10}H_{11}O_2N_4$). Elemental analysis indicated an empirical formula of $C_{10}H_{12}N_4O_3$. A small (relative intensity 0.2%) peak was observed at *m/e* 237 in the low-resolution EI spectrum of **6**; the chemical ionization (CI) mass spectrum gave *m/e* 238 (100%). The fragmentation pattern can be rationalized as shown; the peaks at 237 (EI) and 238 (CI) apparently resulted from M + 1 and M + 2 ions, respectively. The structure for **6** was also

Scheme I



supported by IR and NMR data (see Experimental Section). To confirm the structural assignment, **6** was prepared in 62% yield by reaction of **4** with isopropyl nitrite. Both synthetic and isolated **6** were obtained as mixtures of *syn*- and *anti*-oxime isomers. These isomers **6a** and **6b** (mp 126–127 and 132–133 °C) could be separated after several recrystallizations. Since **6a** and **6b** each had an >NN=O group, four isomers, (*E*)-**6a**, (*Z*)-**6a**, (*E*)-**6b**, and (*Z*)-**6b**, were actually present. According to NMR, the *E* isomers predominated.

Compound **7** was isolated from the distillable portion of the reaction mixture; its volatility was similar to **8a**, **8b**, and **17**. High-resolution mass spectral data (EI) indicated a molecular ion of $C_9H_9N_3$ (rel intensity, 100%) with fragments corresponding to $C_8H_7N_2$ (50%), C_7H_6N (15%), and C_5H_4N (8%). This spectrum is similar to that of nicotyrine (**19**).[26] The CI



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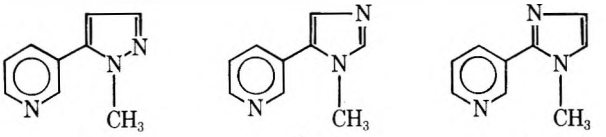
spectrum showed an M + 1 peak at *m/e* 160. The IR spectrum was similar to that of myosmine (**17**). The proton NMR spectrum of **7** showed a methyl singlet at 3.94 ppm and doublets (1 H each, J = 4 Hz) at 6.40 and 7.59 ppm, in addition to resonances for four pyridyl protons. The fully decoupled ^{13}C NMR spectrum showed resonances at 37.9 (1 C), 107.8 (2 C), 124.4 (1 C), 137.0 (1 C), 140.0 (2 C), and 150.8 (2 C) ppm.

These MS, IR, and NMR data required a pyridine ring attached to an *N*-methylated five-membered ring containing two nitrogens. Such a heterocyclic compound could be either a pyrazole or an imidazole; assuming that the *N*-methyl group remained in the same relative position as in **1**, three structures (a, b, and c) were possible. Based on the proton NMR spec-



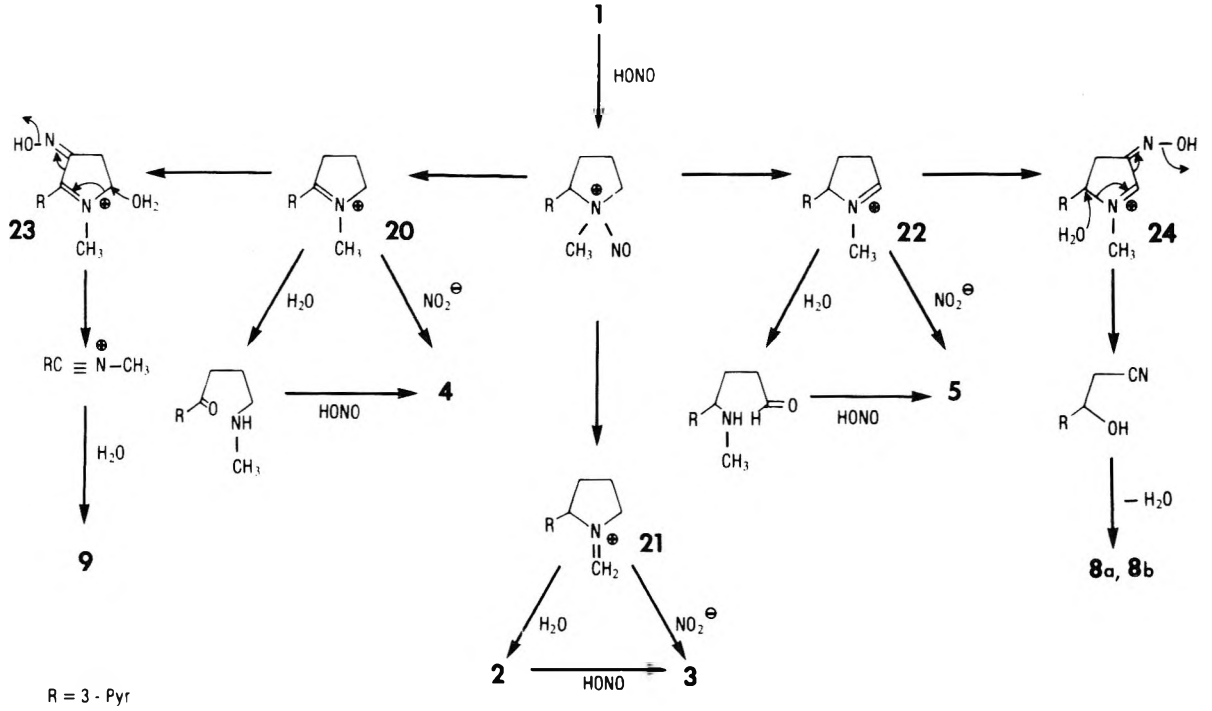
a b c

trum, the pyrazole structure a was assigned; the ring protons on C-4 and C-5 of 3-methylpyrazole resonate at 6.10 and 7.52 ppm, compared to 6.40 and 7.59 ppm in **7**; in 1-methylimidazole the ring protons are observed at 6.96, 7.10, and 7.49 ppm and in 1,2-dimethylimidazole at 6.70 and 6.80 ppm.[27]

The origin of **7** in the reaction mixture from **1** and $NaNO_2$ may be attributed, at least partially, to secondary reactions of nitrosaminoaldehyde **5**. When **5** was treated under the reaction conditions (pH 3.4, 90 °C, 3 h, fivefold excess nitrite), **7** was formed in 10% yield. Disappearance of **5** was complete under these conditions. When $NaNO_2$ was omitted from the mixture, **5** was recovered unchanged. The mechanism of this conversion is not yet known, but could proceed as shown in Scheme I. In the acidic medium, **5** could cyclize by reaction of its enol with the nitroso group. Oxidation followed by loss of H_2O, CO_2, and H_2 would give **7**. A related reaction has been observed in the HNO_3 oxidation of nicotine to nicotinic acid.[28] In this oxidation, a minor product (5%) was 3-nitro-5-(3-pyridyl)pyrazole, which may be formed by a mechanism similar to that shown in Scheme I.

The formation of nitrosamines **3–5** and the fragmentation products **8a**, **8b**, and **9** can be explained via the intermediacy of cyclic iminium salts, as shown in Scheme II. Previous studies on nitrosation of tertiary amines support an initial addition of NO^+ to the amine, followed by loss of HNO.[22] In the case of nicotine, this would give rise to three iminium species, **20–22**. Reaction of **20–22** to give nitrosamines **3–5** could proceed in either of two ways. The iminium salts could be hydrolyzed to the corresponding secondary amines, which are then nitrosated. Alternatively, **20–22** could react directly

Scheme II



with NO_2^- to give **3–5.** This pathway, which would be more important at neutral pH, has been demonstrated for the exocyclic iminium salt **25,** which gives nitrosopyrrolidine upon nitrosation.[29] To examine the formation of nitrosamines by

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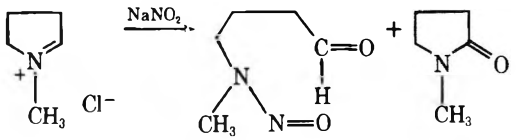
interaction of an endocyclic pyrrolinium salt with nitrite, the reaction of **26** with nitrite was investigated. When **26,** obtained by reduction of *N*-methylpyrrolidone (**28**),[30] was allowed to react with $NaNO_2$ under neutral conditions in either H_2O or 95% EtOH, the nitrosaminoaldehyde **27** was isolated in 5–10% yield.[18] The major product was *N*-methylpyrrolidone (**28**). Thus, both exocyclic and endocyclic pyrrolinium salts, such as **20–22, 25,** and **26,** can serve as precursors for nitrosamines.



26 **27** **28**

The intermediates **20** and **22** offer the simplest rationale for formation of products **8a, 8b,** and **9.** Under the reaction conditions, these salts should be in equilibrium with the corresponding enamines, which can undergo C-nitrosation to give isonitrosoiminium ions **23** and **24.** Beckmann type fragmentation reactions of **23** and **24** would then lead to **8a, 8b, 12,** and **9.** Compounds **10, 11, 13,** and **15–17** are typical oxidation products of nicotine, which have been observed under similar conditions.[31]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 267 grating infrared spectrophotometer in Nujol mull or as liquid films. NMR spectra were determined with a Hitachi Perkin-Elmer Model R-24 spectrometer in $CDCl_3$ solution and are reported as parts per million downfield from Me_4Si as internal reference. ^{13}C NMR spectra were obtained on a Varian Associates XL-100A spectrometer. Mass spectra and combined GC–MS were run with a Hewlett Packard Model 5982A dual source instrument using a membrane separator. Chemical ionization mass spectra were determined with methane as ionizing gas. High-resolution mass spectra were determined by Shrader Analytical and Consulting Laboratories, Detroit, Mich. GC analysis was done on a Hewlett Packard Model 5711 instrument equipped with a flame ionization detector and columns: A, 6 ft × ⅛ in. 10% Carbowax 20M–TPA on Gas Chrom Q; B, 6 ft × ⅛ in. 10% UCW-98 on Gas Chrom Q; C, 6 ft × ⅛ in. 10% Carbowax 20 M-2% KOH on Chromosorb W, with helium as carrier gas. HPLC was performed with a Waters Associates Model ALC/GPC–202 high-speed liquid chromatograph equipped with a Model 6000A solvent delivery system, a Model 660 solvent programmer, a Model U6K septumless injector, a Model 440 UV detector, and a 6 mm × 30 cm Microbondapak/C18 column. Preparative HPLC was done with a Waters Associates Prep LC/System 500 using Prep-Pak-500/Silica cartridges. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Reaction of Nicotine and $NaNO_2$. (A) Analytical Scale. Redistilled nicotine (Aldrich Chemical Co., Milwaukee, Wisc.) which contained <0.01% nornicotine according to GC analysis (column C, 165 °C) and was free of other impurities (1.0 g, 6.2 mmol) was added to 10 mL of the appropriate buffer and $NaNO_2$ (2.1 g, 30.4 mmol in 5 mL of H_2O) was added in one portion. The resulting solution was heated at 90 °C for the appropriate time interval, and then basified to pH 10–12 by addition of aqueous NaOH. The solution was saturated with NaCl and extracted with 3 × 40 mL of $CHCl_3$. The $CHCl_3$ extracts were dried (Na_2SO_4) and concentrated to give an oily residue, 0.4–0.5 g. Reactions under mild conditions (entries 1–4, Table I) were done similarly, except that the molar ratio of $NaNO_2$ to nicotine was 1.4 and the solutions were stirred at 20 °C for 17 h before basification.

The $CHCl_3$ extracted products were examined by GC using column A with a temperature program of 100 °C for 4 min, then 4°/min to 240 °C. The flow rate was 60 mL/min and injector and detector temperatures were 250 °C. The relative retention times of the volatile components of the mixture were as follows: **16,** 0.67; **13,** 0.72; **14,** 0.73; **15,** 0.84; **1,** 1.00; **17,** 2.05; **18,** 2.20; **8a** and/or **8b,** 2.26 and/or 2.78; **7,** 2.52; **9,** 3.70; **11,** 3.70; **3,** 4.23; **5,** 4.82; and **4,** 5.20. The absolute retention time of **1** was 12.8 min. Identity was confirmed by comparison of retention times and mass spectra to standards.

Compounds **6, 10,** and **12** were isolated from the aqueous portion of the reaction mixture. The aqueous extract was readjusted to pH 7 and freeze-dried to give a residue which was triturated with methanol. Aliquots were concentrated and silylated with bis(trimethylsilyl)trifluoroacetamide and then examined by GC using column B (flow rate 60 mL/min) and a temperature program of 100–240 °C at 4°/min. Compounds **10** and **12** were identified by comparison of mass spectra and retention times to those of silylated standards.

An aliquot of the above methanol solution was examined by HPLC for identification and quantification of **6,** using program 8 with elution by 15% CH_3OH in H_2O to 100% CH_3OH in 45 min at a flow rate of 1.5 mL/min. The retention volume of **6** was 37.5 mL. When the reaction was done on a larger scale, **6** could be isolated by column chromatography on silica gel with elution by chloroform/methanol followed by recrystallization from EtOAc.

(B) Preparative Scale. Isolation of 3. Nicotine (250 g, 1.54 mol) was brought to pH 3 by cautious addition of concentrated HCl. The resulting salt was added to 3 L of pH 3 citrate/phosphate buffer in a 12-L round bottom flask. The mixture was heated with stirring to 90 °C. The heating mantel was removed and a solution of $NaNO_2$ (525 g, 7.61 mol) in 1 L of H_2O was added dropwise over a period of 1.5 h at a rate which maintained the temperature at 90 °C. The mixture was then stirred for 5 h at 90 ° C, cooled to room temperature, saturated with NaCl, cooled to 0 °C, and brought to pH 12 by cautious addition of NaOH pellets. The resulting mixture was extracted with 4 × 3 L of $CHCl_3$ and the combined $CHCl_3$ layers were dried (Na_2SO_4) and concentrated to give a residue of 115 g. This material was steam-distilled to remove unreacted nicotine (53 g). The pH of the distillation pot was maintained at 10 by addition of NaOH. After distillation was complete, the residue was extracted with $CHCl_3$ and the $CHCl_3$ solution was dried and concentrated to give 45 g of material. This was chromatographed by preparative HPLC using two cartridges with elution by $CHCl_3$/cyclohexane/CH_3CN/MeOH (44:48:7:1) at a flow rate of 250 mL/min. Fractions containing **3,** as determined by TLC on silica gel [$CHCl_3$/MeOH (20:1)], were combined and concentrated to give a residue of 20 g. This was distilled to give 10 g (3.7%) of **3,** bp 150–160 °C (0.2 mm), identical with **3** prepared from **2.**[17] The forerun from this distillation was enriched in **7.**

4-(*N*-Methyl-*N*-nitrosamino)-2-oximino-1-(3-pyridyl)-1-butanone (6). The nitrosamino ketone **4** (100 mg, 0.48 mmol) was dissolved in dry methanol (10 mL) which had been saturated with dry HCl. Isopropyl nitrite (225 mg, 2.6 mmol) was added at 0 °C and the solution was stirred for 2 h at 0 °C and an additional 3 h at room temperature. The mixture was brought to pH 7 and extracted with 4 × 25 mL of $CHCl_3$. Drying (Na_2SO_4) and concentration gave a solid residue, which was recrystallized from EtOAc to give 80 mg (62%) of **6,** mp 127–129 °C, as a mixture of isomers. Further recrystallization from EtOAc gave the *syn- anti*-oxime isomers **6a,** mp 126–127 °C, and **6b,** mp 132–133 °C. Spectral properties: IR (**6a**) 3200–2100, 1642, 1590, 1131, 1030, 1010, 732, 712, 692, 673, 630 cm^{-1}; IR (**6b**) 3200–2100, 1659, 1590, 1510, 1418, 1340, 1265, 1131, 1027, 1008, 758, 738, 714, 691, 675, 630 cm^{-1}; MS *m/e* (rel intensity) 237 (0.2), 219 (6), 206 (29), 177 (8), 165 (7), 130 (10), 114 (4), 106 (100), 78 (97), 73 (49), 51 (40), 42 (45), identical for **6a** and **6b**; NMR (mixture of **6a** and **6b**) ($CDCl_3$) 9.42–7.25 (4 H, m, pyridyl CH), 4.48 (1.8 H, t, $CH_2NN{=}O$, **6a** + **6b** *E* isomers), 3.81 (0.5 H, m, $-CH_2N(N{=}O)CH_3$, **6a** + **6b** *Z* isomers), 3.21 (2 H, t, $HON{=}CCH_2-$), 3.15 ppm (2.7 H, s, $CH_3NN{=}O$, **6a** + **6b** *E* isomers). Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.85; H, 5.12; N, 23.72. Found: C, 50.75; H, 5.19; N, 23.66.

Formation of 1-Methyl-5-(3-pyridyl)pyrazole (7) from 5. Nitrosaminoaldehyde **5** (12.8 mg, 0.06 mmol) was dissolved in 1 mL of pH 3 buffer and $NaNO_2$ (200 mg, 2.9 mmol) was added. The solution was heated at 90 °C for 3 h, cooled, adjusted to pH 10, and extracted with 3 × 5 mL of $CHCl_3$. After drying and concentration, the residue was examined by GC using column A, programmed from 100 to 240 °C at 4°/min. The predominant volatile product (10% yield from **5**) was **7,** which was identified by comparison of its retention time and mass spectrum to **7** isolated from the reaction of **1** with $NaNO_2$. An unknown component, with a molecular ion of 192, eluted at 23.8 min.

Nitrosaminoaldehyde **5** was not detected. Spectral data for **7** are given in the text.

Reaction of *N*-Methyl-Δ^1-pyrrolinium Chloride (26) with $NaNO_2$. *N*-Methyl-Δ^1-pyrrolinium chloride (**26**) was prepared by the lithium aluminum hydride reduction of *N*-methyl-2-pyrrolidone (**28**), followed by dehydration as previously reported.[30] The NMR spectrum ($CDCl_3$) showed the following absorptions: 12.91 (br s, 1 H, $CH{=}N^+$), 3.78 (t, 2 H, CH_2N^+), 3.14 (s, 3 H, N^+CH_3), 3.02 (m, 2 H, $CH_2C{=}N^+$), and 2.31 ppm (m, 2 H, ring CCH_2C), indicating the absence of **28**. The pyrrolinium salt **26** (1.6 g, 0.023 mol) thus obtained was dissolved in 20 mL of H_2O and allowed to react with $NaNO_2$ (1.6 g, 0.023 mol) in 20 mL of H_2O at reflux for 10 min. The aqueous solution was extracted with $CHCl_3$ (3 × 20 mL), and the $CHCl_3$ extract was dried ($MgSO_4$) and concentrated to give a residue which was chromatographed on silica gel with elution by hexane/Et_2O/CH_2Cl_2 (1:2:2); 4-(*N*-methyl-*N*-nitrosamino)butanal (**27**) was obtained pure in 5% yield. The nitrosamine **27** showed spectral characteristics which were identical with those of a reference sample synthesized independently.[18] The major product (50%) was eluted from the column with acetone and identified as *N*-methyl-2-pyrrolidone (**28**). The nitrosation of pyrrolinium salt **26** was also done in refluxing 95% EtOH, in pH 6 buffer under reflux, and at 20 °C, under N_2, in 95% EtOH. Similar results were obtained.

Acknowledgments. We thank Dr. Curt R. Enzell and Dr. T. Nishida of the Swedish Tobacco Company, Stockholm, Sweden, for providing ^{13}C NMR and high-resolution data on 1-methyl-5-(3-pyridyl)pyrazole and for correctly suggesting the structure of this compound. We also thank Dr. Edward Leete of the School of Chemistry, University of Minnesota, for calling our attention to the formation of 3-nitro-5-(3-pyridyl)pyrazole from nicotine.

Registry No.—**3**, 16543-55-8; **4**, 64091-91-4; **5**, 64091-90-3; *anti*-**6**, 64091-89-0; *syn*-**6**, 64091-88-9; **7**, 64091-87-8; **26**, 18028-53-0; isopropyl nitrite, 541-42-4; nicotine, 54-11-5; $NaNO_2$, 7632-00-0.

References and Notes

(1) No. 52. Chemical Studies on Tobacco Smoke.
(2) Supported by Public Health Service Contract N01-CP55666 from the Division of Cancer Cause and Prevention, National Cancer Institute, and NCI Grant CA12376-05. S.S.H. is recipient of NCI Research Career Development Award No. 5K04CA00124.
(3) S. S. Hecht, R. M. Ornaf, and D. Hoffmann, *J. Natl. Cancer Inst.*, **59**, 1237 (1974).
(4) V. P. Bharadwaj, S. Takayama, T. Yamada, and A. Tanimura, *Gann*, **66**, 585 (1975).
(5) H. Klus and H. Kuhn, *Fachliche Mitt. Oesterr. Tabakregie*, **16**, 307 (1975).
(6) S. S. Hecht, R. M. Ornaf, and D. Hoffmann, *Anal. Chem.*, **47**, 2046 (1975).
(7) D. Hoffmann, G. Rathkamp, and Y. Y. Liu, *Int. Agency Res. Cancer Sci. Publ.*, **No. 9**, 159 (1974).
(8) H. Klus and H. Kuhn, *Fachliche Mitt. Oesterr. Tabakregie*, **14**, 251 (1973).
(9) D. Hoffmann, M. Dong, and S. S. Hecht, *J. Natl. Cancer Inst.*, **58**, 1841 (1977).
(10) D. Hoffmann, R. Raineri, S. S. Hecht, R. Maronpot, and E. L. Wynder, *J. Natl. Cancer Inst.*, **55**, 977 (1975).
(11) G. M. Singer and H. W. Taylor, *J. Natl. Cancer Inst.*, **57**, 1275 (1976).
(12) J. Hilfrich, S. S. Hecht, and D. Hoffmann, *Cancer Lett.*, **2**, 169 (1977).
(13) E. Boyland, F. J. Roe, and J. W. Gorrod, *Nature (London)*, **202** 1126 (1964).
(14) D. Hoffmann, S. S. Hecht, R. M. Ornaf, T. C. Tso, and E. L. Wynder, *Int. Agency Res. Cancer Sci. Publ.*, **14**, 307 (1976).
(15) S. S. Hecht, C. B. Chen, N. Hirota, R. M. Ornaf, T. C. Tso, and D. Hoffmann, *J. Natl. Cancer Inst.*, in press (1978).
(16) G. B. Neurath, M. Dünger, and F. G. Pein, *Int. Agency Res. Cancer Sci. Publ.*, **14**, 227 (1976).
(17) M. W. Hu, W. E. Bondinell, and D. Hoffmann, *J. Labelled Compd.*, **10**, 79 (1974).
(18) S. S. Hecht, C. B. Chen, and D. Hoffmann, *Tetrahedron Lett.*, 593 (1976).
(19) S. S. Hecht, C. B. Chen, M. Dong, R. M. Ornaf, D. Hoffmann, and T. C. Tso, *Beitr. Tabakforsch.*, **9**, 1 (1977).
(20) W. Lijinsky, L. Keefer, E. Conrad, and R. van de Bogart, *J. Natl. Cancer Inst.*, **49**, 1239 (1972).
(21) W. Lijinsky, *Cancer Res.*, **34**, 255 (1974).
(22) P. A. S. Smith and R. N. Loeppky, *J. Am. Chem. Soc.*, **89**, 1147 (1967).
(23) P. A. S. Smith and H. G. Pars, *J. Org. Chem.*, **24**, 1325 (1959).
(24) M. Strell and E. Kopp, *Chem. Ber.*, **91**, 1621 (1958).
(25) E. R. Bowman and H. McKennis, Jr., *Biochem. Prep.*, **10**, 36 (1963).
(26) A. Pilotti, C. R. Enzell, J. McKennis, Jr., and E. R. Bowman, *Beitr. Tabakforsch.*, **8**, 339 (1976).
(27) C. J. Pouchert and J. R. Campbell, "The Aldrich Library of NMR Spectra", Vol. 8, Aldrich Chemical Co., Milwaukee, Wisc., 1974, pp 22–35.
(28) H. Lund, *J. Chem. Soc.*, 686 (1933).
(29) L. K. Keefer and P. P. Roller, *Science*, **181**, 1245 (1973).
(30) E. Leete, *J. Am. Chem. Soc.*, **89**, 7081 (1967).
(31) W. G. Frankenburg, A. M. Gottscho, and A. A. Vaitekumas, *Tobacco Sci.*, **2**, 9 (1958).

Thermal Decomposition of 2-Azidoquinoxaline *N*-Oxides

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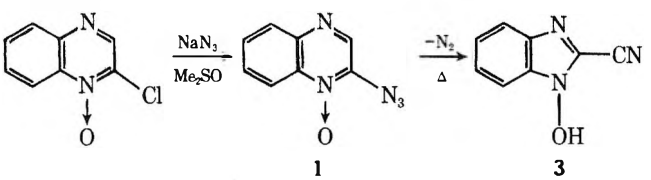
The thermolysis of some 2-azidoquinoxaline 1-oxides and 1,4-dioxides has been studied. When these are unsubstituted in the 3 position, 2-cyano-1-hydroxy-1*H*-benzimidazoles are obtained in high yield. The thermolysis of 2-azido-3-methylquinoxaline 1,4-dioxide, on the other hand, resulted in the formation of 2-cyano-2-methyl-2*H*-benzimidazole 1,3-dioxide, which underwent further intramolecular rearrangement to afford a novel 3*H*-2,1,4-benzoxadiazine 4-oxide. A mechanistic interpretation of these observations, as well as a discussion of ^{13}C NMR spectra of the thermolysis products, is presented.

In the course of work on the chemistry of quinoxalines, 2-azidoquinoxaline 1-oxide (**1**) and 2-azidoquinoxaline 1,4-dioxide (**2**) were synthesized and their thermal chemistry was studied. The thermolysis of **1** to give 2-cyano-1-hydroxy-1*H*-benzimidazole (**3**) has been described.[1] We now wish to report our observations concerning the modes of reaction of several such azides.



1 **3**

2-Azidoquinoxaline 1-oxide (**1**) was prepared by sodium azide displacement of 2-chloroquinoxaline 1-oxide[2] in Me_2SO at room temperature. Prolonging the reaction time resulted in loss of nitrogen from **1** and formation of 2-cyano-1-hydroxy-1*H*-benzimidazole (**3**). The benzimidazole **3** was more efficiently prepared by the thermolysis of **1** at 90 °C in benzene solution. The structural assignment of **3** was based on its spectral properties (NMR, IR, UV, mass spectrum), combustion analysis, and an unambiguous synthesis from 2-nitroanilinoacetonitrile according to a literature procedure.[3]

Extension of this reaction to 2-azidoquinoxaline 1,4-dioxide (**2**) was accomplished in the following manner. 2-Methylsulfonylquinoxaline 1,4-dioxide[4] (**4**) was allowed to react with

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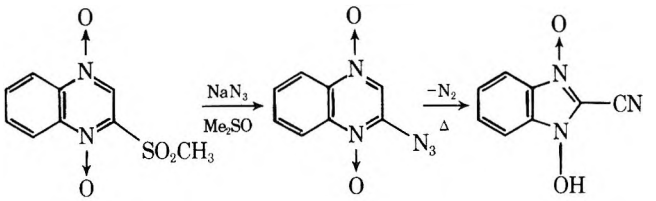
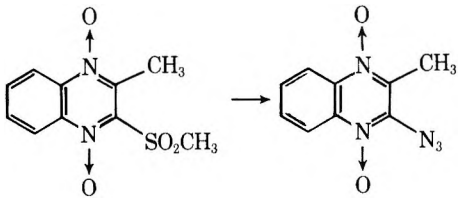


4 2 5

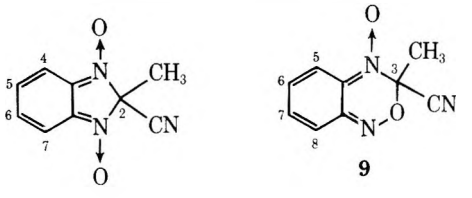
sodium azide to afford **2**. Thermolysis of **2** in refluxing benzene gave 2-cyano-1-hydroxy-1*H*-benzimidazole 3-oxide (**5**) in good yield.

We then turned our attention to a study of 2-azido-3-methylquinoxaline 1,4-dioxide (**7**), which was prepared by the reaction of 2-methylsulfonyl-3-methylquinoxaline 1,4-dioxide[5] and tetramethylguanidinium azide in methylene chloride at room temperature.[6] These are the conditions of choice for preparing such azides, owing to the absence of side products and decomposition which were noted when sodium azide in polar solvents was employed.



7

From a consideration of the behavior of 2-azido-3-methylpyridine 1-oxide on thermolysis in benzene[7] we expected the formation of 2-cyano-2-methyl-2*H*-benzimidazole 1,3-dioxide (**8**) as the major (if not exclusive) product of **7** when decomposed. Heating **7** in toluene at 90 °C for 30 min gave a 94% yield of an amber oil after column chromatography. NMR analysis of this compound revealed a complex pattern of aromatic protons which appeared at δ 6.76–7.35 in a ratio of 3:1 and a three-proton singlet at δ 2.20. The unsymmetrical nature of the aromatic proton resonances was inconsistent with the AA′BB′ pattern predicted[8,9] for **8**. The infrared spectrum of the oil showed a weak absorption at 2240 cm^{-1} (C≡N). The mass spectrum of the oil showed a molecular ion at *m/e* 189 with principal fragments at *m/e* 173 ($M^+ - O$) and 159 ($M^+ - NO$). These spectral data were consistent[10] with the novel 3*H*-2,1,4-benzoxadiazine 4-oxide **9** and not **8**.

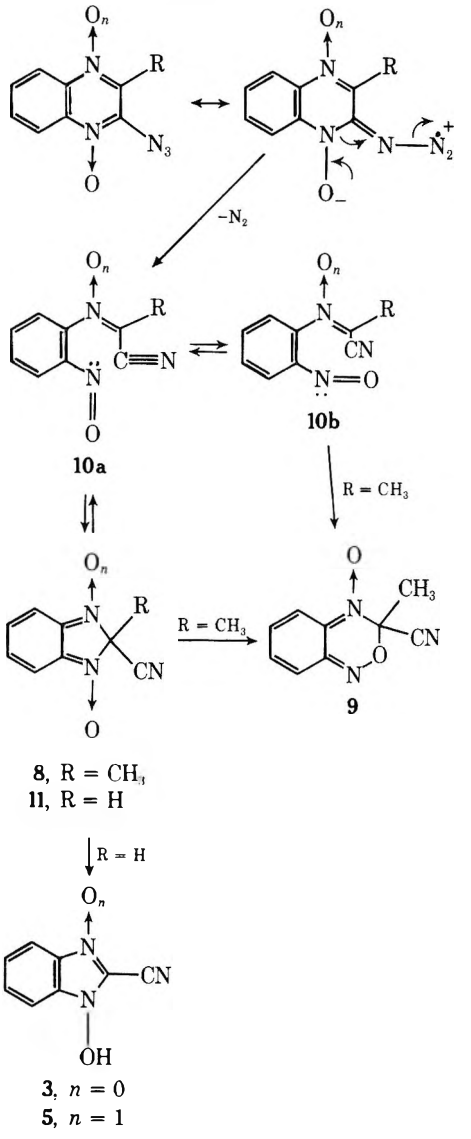


8 **9**

When the thermolysis of **7** was carried out in refluxing benzene for 10 min followed by careful column chromatography on silica gel, a violet solid (mp 111–112 °C) was obtained in 45% yield along with **9** in 41% yield. This new product was tentatively characterized as the expected 2*H*-benzimidazole 1,3-dioxide **8** based on the following spectral properties. The NMR spectrum of **8** in $CDCl_3$ exhibited an AA′BB′ pattern centered at δ 7.07 along with a singlet at δ 2.16 in the ratio of 4:3. The UV spectrum of **8** [λ_{max} (methanol) 247 (ϵ 16 550), 531 nm (4840)] compared very favorably with the reported UV spectra of similar 2*H*-benzimidazole 1,3-dioxides.[8,9]

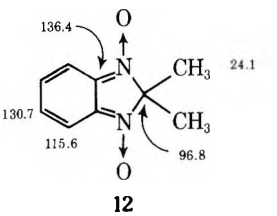
A determination of the ^{13}C NMR spectra (proton decoupled) of both products **8** and **9** enabled us to confidently characterize the amber oil as 3-cyano-3-methyl-3*H*-2,1,4-benzoxadiazine 4-oxide (**9**) and the violet crystalline solid as 2-cyano-2-methyl-2*H*-benzimidazole 1,3-dioxide (**8**). A

Scheme I



nine-line spectrum was observed for **9**. The cyano carbon resonance appeared at 113.5 ppm.[7] The spectrum also indicated the presence of six aromatic carbon atoms (four bearing a hydrogen atom, 130.6, 130.1, 123.5, and 117.3 ppm; and two that were not, 150.8 and 129.1 ppm). This further illustrates that **9** is unsymmetrical. The resonance for C-3 appeared at 86.1 ppm and the methyl carbon resonance was found at 19.1 ppm.

In contrast, the symmetrical nature of **8** was revealed by its ^{13}C spectrum. Thus two resonances were observed for the aromatic carbons bearing hydrogens at 132.1 and 115.5 ppm for C-4, C-7 and C-5, C-6, respectively. A weak signal appeared at 137.7 ppm for the ring-fused quaternary carbons. The cyano carbon resonance was found at 116.4 ppm. The resonance for C-2 appeared at 85.7 ppm, and the methyl carbon resonance was observed at 24.0 ppm. These values compare favorably with those reported in the literature[9b] for a similar 2*H*-benzimidazole 1,3-dioxide **12**.



12

A plausible mechanism which accounts for our observations is depicted in Scheme I. Loss of nitrogen from the azides accompanied by ring opening[1,7] would give the *o*-nitrosophenylnitrone **10a**, which can undergo intramolecular cyclization[1,7,8] to give **8** or **11**. If R = H, aromatization of **11** would give the observed 2-cyano-1-hydroxy-1*H*-benzimidazoles **3** and **5**.[1,8,9] Alternatively, **10b** could cyclize to a 2,1,4-benzoxadiazine 4-oxide **9**. Mechanistic analogy for this mode of cyclization exists in the chemistry of 2-azido-3-halopyridine 1-oxides, which afford 6,6-disubstituted-1,2-oxazines.[6] A more likely course of events is that **8** is formed initially, but undergoes a further rearrangement to give **9**, either via **10a** ⇌ **10b** or by a direct ring expansion. Support for this hypothesis was obtained from the following experiment. Azide **7** was heated under reflux for 5 min, which resulted in the formation of **8** and unreacted **7** in a ratio of 2:1, respectively, based on NMR analysis of the crude product mixture. When this mixture was resubjected to the reaction conditions (refluxing benzene) for 0.5 h neither **7** nor **8** could be detected, and **9** was isolated in 76% yield. The rearrangement of **8** to **9** appears to be unusual, since heating 2,2-dimethyl-2*H*-benzimidazole 1,3-dioxide (**12**) in toluene at 90 °C for 0.5 h led to no observable decomposition.[14]

Experimental Section

General. Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. Proton NMR spectra were recorded on Varian T-60 and Varian XL-100-15 spectrometers with Me_4Si as the external standard. The ^{13}C NMR were obtained in the FFT mode on a Varian XL-100-15 (25 MHz) spectrometer equipped with a Nicolet Technology 1080 data system. Complete proton decoupling was provided by square wave modulation[11] of the Varian gyrocode heteronuclear decoupler. Deuterated chloroform solvent resonance (76.9 ppm) was used as an internal standard adjusted relative to Me_4Si to provide chemical shift value. IR spectra were determined with Perkin-Elmer Model 21 and 237 B spectrophotometers. Mass spectra were obtained with Perkin-Elmer RMU-6E and AEI MS-30 mass spectrometers. Combustion analyses were performed by the Pfizer Physical Measurements Department.

2-Azidoquinoxaline 1-Oxide (1). Sodium azide (0.71 g, 11 mmol) was added to a solution of 2-chloroquinoxaline 1-oxide[2] (2.00 g, 11 mmol) in Me_2SO (25 mL) at room temperature. The solution was stirred for 6 h and then it was diluted with water (50 mL), causing a precipitate to form. The tan solid was filtered and washed with cold water to give 1.08 g (52%) of **1**: mp 81–83 °C dec; NMR (Me_2SO-d_6) δ 7.60–8.50 (4, m, H-5, H-8), 8.60 (1, s, H-3); IR (KBr) 2150 cm^{-1} (N_3); UV λ_{max} (MeOH) 225 (ϵ 18 100), 265 (29 300), 335 nm (5300); mass spectrum *m/e* 187 $[M]^+$, 159 $[M - N_2]^+$. Elemental analysis (C, H, N) of **1** was consistent with the presence of ~10% of **3**. Further purification attempts were unsuccessful due to the thermal instability of this compound.

2-Cyano-1-hydroxy-1*H*-benzimidazole (3). A suspension of 2-azidoquinoxaline 1-oxide (1.50 g, 8.1 mmol) in benzene (25 mL) was heated under reflux until the evolution of gas ceased (~0.5 h). The reaction mixture was allowed to cool to room temperature and a light brown solid was filtered and washed with benzene to afford 1.17 g (92%) of **3**: mp 249–250 °C dec; NMR (Me_2SO-d_6) δ 7.20–8.00 (m, H-4, H-7); IR (KBr) 2222 cm^{-1} (CN); UV λ_{max} (MeOH) 225 (ϵ 19 400), 286 nm (13 000); mass spectrum *m/e* 159 $[M]^+$. Anal. Calcd for $C_8H_5N_3O$: C, 60.43; H, 3.17; N, 26.43. Found: C, 60.29; H, 3.31; N, 26.69. This material was identical with **3** prepared by a literature[3] procedure via a base-catalyzed cyclization of 2-nitroanilinoacetonitrile.[12]

2-Azidoquinoxaline 1,4-Dioxide (2). To a solution of 2-methylsulfonylquinoxaline 1,4-dioxide[5] (1.00 g, 4.2 mmol) in Me_2SO (15 mL) was added sodium azide (0.27 g, 4.2 mmol). The mixture was stirred for 15 h at room temperature and then it was diluted with water (75 mL) and extracted with chloroform (3 × 20 mL). The combined chloroform extracts were dried over anhydrous magnesium sulfate and evaporated under vacuum to yield **2** as a yellow solid (0.50 g, 60%): mp 117–118 °C dec; NMR (Me_2SO-d_6) δ 8.00 (2, m, H-6, H-7), 8.50 (2, m, H-5, H-8), 8.60 (1, s, H-3); IR (KBr) 2140 cm^{-1} (N_3); UV λ_{max} (MeOH) 238 (ϵ 19 000), 283 (25 200), 395 nm (6000); mass spectrum *m/e* 203 $[M]^+$, 159 $[M - N_2O]^+$. An attempt to prepare an analytical sample of **2** was unsuccessful due to the thermal instability of this compound.

2-Cyano-1-hydroxy-1*H*-benzimidazole 3-Oxide (5). 2-Azidoquinoxaline 1,4-dioxide (200 mg, 1.0 mmol) was suspended in benzene (5 mL) and heated under reflux until the evolution of gas ceased (~0.5 h). The reaction mixture was allowed to cool to room temperature and a tan solid was filtered and washed with benzene to give 105 mg (61%) of **5**: mp 165–166 °C dec; NMR (CF_3CO_2D) δ 7.50 (m, H-4, H-7); IR (KBr) 2222 cm^{-1} (CN); UV λ_{max} (MeOH) 235 (ϵ 23 400), 303 (9200), 369 nm (4500); mass spectrum *m/e* 175 $[M]^+$, 159 $[M - O]^+$. Anal. Calcd for $C_8H_5N_3O_2$: C, 54.91; H, 2.88; N, 24.01. Found: C, 54.53; H, 2.96; N, 23.74.

2-Azido-3-methylquinoxaline 1,4-Dioxide (7). To a cooled solution of 2-methyl-3-methylsulfonylquinoxaline 1,4-dioxide[2] (4.00 g, 15.7 mmol) in chloroform (60 mL) was added dropwise tetramethylguanidinium azide (2.48 g, 15.7 mmol) in chloroform (20 mL). The solution was stirred for 1.5 h at room temperature and then it was washed with water, dried ($MgSO_4$), and evaporated to give a solid. The solid was triturated with water and then ether, which afforded a yellow solid as **7** (2.25 g, 66%): mp 106–107 °C dec; NMR (Me_2SO-d_6) δ 2.60 (s, 3, CH_3), 7.75 (m, 2, H-6, H-7), 8.41 (m, 2, H-5, H-8); IR (KBr) 2128 cm^{-1} (N_3); UV λ_{max} (MeOH) 237 (ϵ 23 340), 280 (30 200), 380 nm (7850); mass spectrum *m/e* 217.0600 (M^+; $C_9H_7N_5O_2$ requires 217.0600), 189 ($M - N_2$). An attempt to prepare an analytical sample of **7** was unsuccessful due to the thermal instability of this compound. The sample darkened at room temperature within 24 h; however, the NMR spectrum was unchanged.

2-Cyano-2-methyl-2*H*-benzimidazole 1,3-Dioxide (8). 2-Azido-3-methylquinoxaline 1,4-dioxide (200 mg, 0.92 mmol) was dissolved in benzene (7 mL) and heated under reflux for 10 min. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under vacuum to afford a purple oil, which was purified by column chromatography on silica gel. Elution with chloroform gave **9** (72 mg, 41%), which was followed by removal of **8** from the column as violet crystals (81 mg, 46%): mp 111–112 °C dec; NMR ($CDCl_3$) δ 2.16 (s, 3, CH_3), 6.90–7.24 (m, AA'BB', 4, H-4, H-7); IR ($CHCl_3$) no C≡N band observed;[13] UV λ_{max} (MeOH) 247 (ϵ 16 550), 531 nm (4840); mass spectrum *m/e* 189.0523 (M^+; $C_9H_7N_3O_2$ requires 189.0539), 173 ($M^+ - O$), 157 ($M^+ - O_2$). Attempted purification of this sample was unsuccessful owing to the thermal instability of this compound. A shorter reaction time (solution was heated for ~5 min in benzene under reflux) resulted in the formation of **8** and starting material (**7**) in a ratio of 2:1, respectively, based on NMR analysis. When this mixture was resubjected to the reaction conditions for 0.5 h neither **7** nor **8** was detected, and **9** was isolated in 76% yield.

3-Cyano-3-methyl-3*H*-2,1,4-benzoxadiazine 4-Oxide (9). 2-Azido-3-methylquinoxaline 1,4-dioxide (400 mg, 1.84 mmol) was dissolved in toluene (15 mL) and heated at 90 °C until the evolution of gas ceased (~0.5 h). The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under vacuum to afford a brown oil, which was purified by column chromatography on silica gel. Elution with chloroform gave 228 mg (94%) of **9** as an amber oil: NMR ($CDCl_3$) δ 2.20 (s, 3, CH_3), 6.76–7.16 (m, 3, H-3, H-4, H-5), 7.16–7.35 (m, 1, H-6); IR ($CHCl_3$) 2240 cm^{-1} (C≡N); UV λ_{max} (MeOH) 228 (ϵ 17 000), 405 nm (3620); mass spectrum *m/e* 189.0532 (M^+; $C_9H_7N_3O_2$ requires 189.0539), 173 ($M^+ - O$), 159 ($M^+ - NO$). Anal. Calcd for $C_9H_7N_3O_2$: C, 57.20; H, 3.73; N, 22.23. Found: C, 57.40; H, 3.79; N, 21.88. Samples of **9** darkened at room temperature within a few hours, although no change in the sample composition could be detected by NMR or UV after 24 h at room temperature. In another experiment **9** was obtained in 72% yield when benzene was used as solvent instead of toluene.

Acknowledgment. We thank Dr. G. Chmurny for determining the ^{13}C NMR spectra and for helpful discussions, and Mr. R. Ware for measuring the high-resolution mass spectra.

Registry No.—**1**, 51796-69-1; **2**, 64010-67-9; **3**, 40159-90-8; **4**, 50473-31-9; **5**, 64010-77-1; **7**, 64010-76-0; **8**, 64010-79-3; **9**, 64010-78-2; sodium azide, 26628-22-8; 2-chloroquinoxaline 1-oxide, 5227-57-6; 2-methyl-3-methylsulfonylquinoxaline 1,4-dioxide, 39576-77-7; tetramethylguanidinium azide, 56899-56-0.

References and Notes

(1) R. A. Abramovitch and B. W. Cue, Jr., *Heterocycles*, **1**, 227 (1973).
(2) A. S. Elina, *Zh. Obshch. Khim.*, **34**, 2809 (1964); *J. Gen. Chem. USSR*, **34**, 2386 (1964).
(3) D. B. Livingstone and G. Tennant, *J. Chem. Soc., Chem. Commun.*, 96 (1973).
(4) M. J. Cox and R. A. Burrell, West German Patent 2 312 730 (1973); *Chem. Abstr.*, **79**, 137194s (1973).
(5) E. Abushanab, *J. Org. Chem.*, **38**, 3105 (1973).

(6) R. A. Abramovitch, I. Shinkai, B. W. Cue, Jr., F. A. Ragan, Jr., and J. L. Atwood, *J. Heterocycl. Chem.*, **13**, 415 (1976).
(7) R. A. Abramovitch and B. W. Cue, Jr., *J. Am. Chem. Soc.*, **98**, 1478 (1976).
(8) M. J. Abu El-Haj, *J. Org. Chem.*, **37**, 2519 (1972).
(9) (a) D. W. S. Latham, O. Meth-Cohn, and H. Suschitzky, *J. Chem. Soc., Chem. Commun.*, 1040 (1972); (b) D. W. S. Latham, O. Meth-Cohn, H. Suschitzky, and J. A. L. Herbert, *J. Chem. Soc., Perkin Trans. 1*, 470 (1977).
(10) For example, loss of NO from the molecular ion is diagnostic for a 6,6-disubstituted-1,2-oxazine (ref 6).
(11) J. B. Grutzner and R. E. Santini, *J. Magn. Reson.*, **19**, 173 (1973).
(12) K. Dimroth and H. G. Aurich, *Chem. Ber.*, **98**, 3902 (1965).
(13) The cyano band for this compound was not observed. This is not unexpected for a cyano group adjacent to electron-withdrawing, oxygen-containing moieties such as the nitro and *N*-oxide groups: N. B. Colthup, H. L. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy", Academic Press, New York, N.Y., 1964, p 202.
(14) The possibility that 3,3-dialkyl-3*H*-2,1,4-benzoxadiazine 4-oxides could be formed upon reaction of benzofurazan *N*-oxide with secondary nitroalkanes has been addressed by Meth-Cohn and Suschitzky (ref 9b) and ruled out by ^{13}C NMR analysis of the products obtained.

Chlorination of the Cephem Dihydrothiazine Ring. Factors Influencing Carbon-2 Substitution vs. Degradation to Isothiazoles[1]

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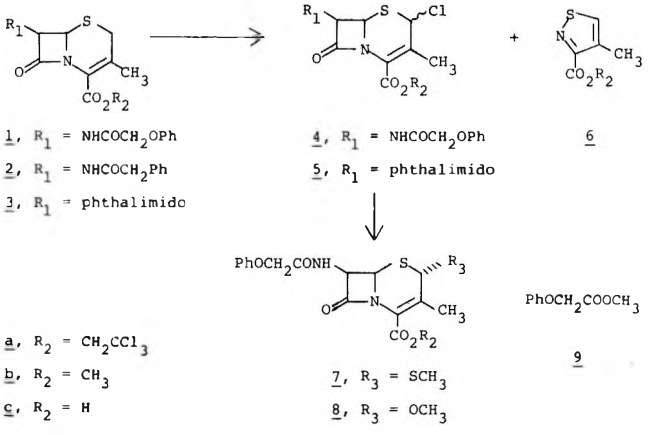
The reaction of Δ^3-cephalosporin esters with *N*-chlorosuccinimide (NCS) is described. When a 7-phenoxyacetamido- or a 7-phthalimido-Δ^3-cephem (**1a** or **3a**) is reacted with NCS, the unstable 2-chloro-Δ^3-cephem (**4a** or **5a**, respectively) can be observed in solution by NMR. Nucleophilic displacement of chloride ion in the 2-chloro derivative **4a** by methanethiol or methanol yields the 2α-methylthio- and 2α-methoxy-Δ^3-cephems **7a** and **8a**, respectively. Chlorination of 7-phenylacetamido-Δ^3-cephems **2a** and **2b** gives the isothiazoles **6a** and **6b** exclusively; **6a** is also a minor product in the chlorination of **1a**. The structure of the degradation product **6** is proven by x-ray analysis of 4-hydroxyisothiazole-3-carboxylic acid (**12**), derived from the chlorination of methyl 7-(*N*-phenylacetamido)cephalosporanate (**10**), followed by saponification.

The synthesis of 2-halo-Δ^3-cephems was undertaken to prepare a versatile intermediate for C-2 substituted cephalosporins. Methods for the introduction of alkoxy and acyloxy residues at C-2[2] involving the oxidation of sulfur in the dihydrothiazine ring cannot be used with nucleophiles susceptible to the oxidative conditions. Therefore, a substrate capable of undergoing nucleophilic substitution at C-2 was desired. Investigations by others in this area have led to the isolation and methanolysis of a 2-bromo-Δ^3-cephem and 2,3-dibromocephams, prepared by the bromination of a cephalosporin lactone[3] and Δ^2-cephems,[4] respectively. We have studied the chlorination of Δ^3-cephalosporin esters using *N*-chlorosuccinimide (NCS) and now report on the factors influencing this reaction following the initial halogenation of sulfur.

Results

A solution of **1a**, containing 1 equiv of NCS in deuteriochloroform, was monitored by NMR. Within 15 min the simultaneous disappearance of the NCS singlet (δ 2.94) and the AB quartet of the cephem C-2 protons (δ 3.43) was observed. The formation of an unstable C-2 substituted Δ^3-cephem, presumed to be the 2-chloro derivative **4a**, was indicated by the appearance of the resonances shown in Table I.[5] Simultaneously, a non-β-lactam component was formed having an aromatic methyl singlet (δ 2.63) and a low-field singlet (δ 8.42). After 1.5 h at ambient temperature the 2-chlorocephem **4a** had completely decomposed while the non-β-lactam component was stable to these conditions. To prove the intermediacy of a 2-chlorocephem, methanethiol was added to the reaction mixture after the NCS was consumed and gave the 2α-methylthio derivative **7a** in 33% yield[6] (Scheme I). The C-2 configuration was assigned based on long-range ^5J coupling (<1 Hz) between H-2β and H-7α and a nuclear Overhauser effect (15%) between H-2β and CH_3.[2b,8] Methanolysis of **4a** gave the 2α-methoxy derivative **8a** (identical with a sample prepared by a modification of Spry's procedure[2b] using NCS in methanol), plus equimolar amounts of the non-β-lactam compound and methyl phenoxyacetate (**9**). Cleavage of the trichloroethyl ester gave the free acid **8c**,[2b,4] which had less antimicrobial activity than the parent C-2 unsubstituted compound.

Scheme I



When 1 equiv of NCS was mixed with the trichloroethyl ester **2a** indeuteriochloroform, all the NCS reacted rapidly, yielding a mixture of starting material and the same non-β-lactam product observed in the reaction of **1a**. However, the desired 2-chlorocephem was not detected. The phthalimido analogue **3a** reacted slowly over a 3-h period yielding a solution of the 2-chlorocephem **5a** (Table I). None of the non-β-lactam product, formed in the chlorination of **1a** and **2a**, was observed in this reaction.

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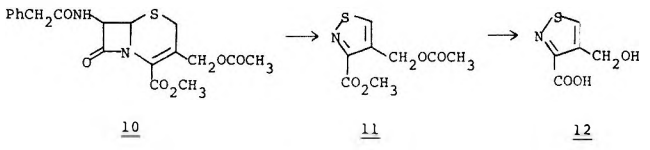
Table I. ^{1}H NMR Data of C-2 Substituted Δ^3-Cephems in $CDCl_3$

Compd	Registry no.	H-2	3-CH_3	H-6	H-7	O(S)CH_3	OCH_2CO	CH_2CCl_3
4a	64024-43-7	5.75 s	2.30 s	5.52 d (J = 5 Hz)	6.17 q (J = 5, 9 Hz)		4.67 s	5.00 m
5a	64024-44-8	5.73 s	2.28 s	5.60 d (J = 5 Hz)	6.10 d (J = 5 Hz)			5.03 AB q (J = 14 Hz)
7a	64024-45-9	4.37 s	2.28 s	5.36 d (J = 5 Hz)	6.01 m (J = <1, 5, 9 Hz)	2.28 s	4.55 s	4.88 Ab q (J = 11 Hz)
8a	64044-39-9	4.82 s	2.24 s	5.14 d (J = 4.5 Hz)	5.98 m (J = <1, 4.5, 10 Hz)	3.47 s	4.58 s	4.92 AB q (J = 12 Hz)

Scheme II



10 11 12

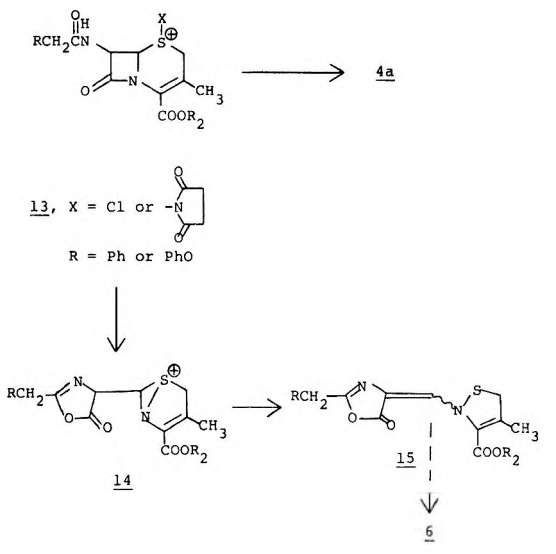
The chlorinations of **1a** and **2a** were repeated on a preparative scale giving 36 and 66% yields, respectively, of the non-β-lactam product, subsequently proven to be the isothiazole **6a.** During these reactions 2 equiv of NCS were consumed. A significant rate increase was observed when a catalytic amount of trifluoroacetic acid or sulfuric acid was added. The products **6b** and **11,** obtained from the chlorination of the methyl esters **2b** and **10,** differed only in substitution on the nuclear methyl group.

The product from **10** was a crystalline diester, which was saponified with 2 equiv of base yielding a hydroxy acid, assigned structure **12** by x-ray crystallography (Scheme II). Therefore, structures **6a, 6b,** and **11** have been assigned to the analogous non-β-lactam products. Both the ester **11** and the acid **12** exhibit two ultraviolet absorption maxima, characteristic of isothiazoles. The longer wavelength absorption of **12** (263 nm) is in agreement with the calculated value (260 nm).[10] Also, the isothiazoles exhibit coupling (0.8 Hz) between the ring proton (H-5) and the protons of the C-4 substituent.[11]

Discussion

Though all the products resulting from the acylglycyl segment of the cephem nucleus have not been identified, reasonable speculation on the origin of the isothiazole can be made (Scheme III). The reaction at sulfur by NCS would initially give a sulfonium salt **13,**[12,13] likely an intermediate

Scheme III



common to both **4a** and **6.** The electronegativity of the positively charged sulfur in **13** would facilitate the cleavage of the β-lactam ring to form the oxazolone **14,** a common occurrence in the acid-catalyzed cleavage of penicillins.[14] The formation of a 2-chloro-Δ^3-cephem with the 7β-phenoxyacetamido residue but not with the 7β-phenylacetamido residue suggests an oxazolone intermediate. An analogy can be made with the chemistry of penicillin where the phenoxyacetyl derivative is more stable than the corresponding phenylacetamido penam under conditions where oxazolone formation is implicated in their decomposition.[15] Also, kinetic evidence indicates that electron-withdrawing substituents on the C-7 side chain of various cephalosporins slow the rate of spontaneous decomposition, presumably proceeding through intramolecular attack of the amide carbonyl on the β-lactam ring.[16] Therefore, the path leading to the 2-chlorocephem **4a** can compete with the path leading to oxazolone **14** when the nucleophilicity of the amide carbonyl is inductively reduced by the phenoxymethyl residue.

The isolation of methyl phenoxyacetate (**9**) and isothiazole **6a** (1:1 ratio) after methanolysis of the reaction mixture starting with cephem **1a** is also indicative of an oxazolone intermediate. Oxazolones can behave as imino ethers and methanolysis of the imino linkage followed by hydrolysis would yield the ester **9.**[17] Further, the participation of the C-7 side chain is inferred since the phthalimido derivative **3,** which cannot form an oxazolone, does not produce the isothiazole under the reaction conditions. The mechanism of acid catalysis observed for the isothiazole formation may correspond to that proposed for the acid-catalyzed aqueous oxidation of alcohols by NCS. Presumably, NCS is protonated, which thereby increases the electrophilicity of chlorine.[18] However, in the rearrangement, acid may also catalyze the opening of the β-lactam.

The formation of the isothiazole ring may proceed by a variety of pathways. Structures **14** and **15** represent the overall result of nitrogen–sulfur bond formation and carbon–sulfur bond cleavage, respectively, leading to an isothiazoline ring.[19] From **15,** the formation of product **6** is the net result of an oxidation of the isothiazoline ring, which accounts for the second equivalent of NCS being consumed when R = phenyl, and a displacement reaction, removing the methylene oxazolone moiety. Precedent for nucleophilic displacements on 4-methylene-5-oxazolones is well documented[20] and a nucleophile present in the reaction mixture may perform the displacement on **15** or, more likely, on an oxidized form of the isothiazoline ring to give the product **6.**

In conclusion, this investigation has shown that the course of nuclear modification in cephalosporins is influenced by the nature of the C-7 amide side chain. Intervention of an oxazolone intermediate in the chlorination of cephems leads to an isothiazole and the rate of oxazolone formation is influenced by inductively changing the nucleophilicity of the amide carbonyl. When the nucleophilicity is lessened, the Pummerer-type reaction becomes competitive with S–C(6) bond cleavage and chlorination at C-2 is observed.

Experimental Section

The NMR spectra were determined on Varian nuclear magnetic resonance spectrometers (Models T-60 and XL-100-15) using tetramethylsilane as an internal standard, and chemical shifts are reported on the δ scale. Infrared spectra were recorded on Perkin-Elmer spectrometers (Models 257 and 621), and the mass spectra were obtained on an AEI-MS-902 mass spectrometer. Melting points are uncorrected.

Trichloroethyl 3-Methyl-2α-methylthio-7-(phenoxyacetamido)-3-cephem-4-carboxylate (7a) and Trichloroethyl 4-Methylisothiazole-3-carboxylate (6a). A solution of 128 mg (0.267 mmol) of cephem **1a** in 0.8 mL of deuteriochloroform was treated with 36 mg (0.267 mmol) of *N*-chlorosuccinimide (NCS). The disappearance of the NCS singlet at 2.9 ppm was monitored by NMR. After 10–15 min at ambient temperature, consumption of NCS was complete and a stream of gaseous methanethiol was bubbled through the reaction mixture for 20 min. Excess thiol was purged from the solution with nitrogen, followed by removal of solvent under reduced pressure. The mixture was separated into three bands by preparative TLC on silica gel plates developed in chloroform. Extraction yielded as oils (in order of increasing R_f) the starting cephem **1a** (28 mg), the 2α-methylthiocephem **7a** (46 mg), and the isothiazole **6a** (14 mg): IR ($CHCl_3$) 1740 (ester C=O), 1410, 1340 cm^{-1}; NMR ($CDCl_3$) δ 2.62 (doublet, J = 0.8 Hz, 3 H, CH_3), 5.07 (singlet, 2 H, CH_2CCl_3), 8.43 (multiplet, 1 H, CH); mass spectrum *m/e* 273 (molecular ion).

The 2α-methylthio cephem **7a** was precipitated as an amorphous solid (40 mg) from an ether–pentane mixture: IR ($CHCl_3$) 3410 (NH), 1790 (β-lactam C=O), 1740 (ester C=O), 1690 cm^{-1} (amide C=O); NMR (C_6D_6) δ 1.69 (singlet, 3 H, SCH_3), 2.12 (singlet, 3 H, CH_3), 3.67 (multiplet, $J_{H_2-H_7} < 1$ Hz, 1 H, H_2), 4.07 (AB quartet, J = 14 Hz, 2 H, CH_2CO), 4.70 (AB quartet, J = 12 Hz, 2 H, CH_2CCl_3), 4.93 (doublet, $J_{H_6-H_7}$ = 5 Hz, 1 H, H_6), 5.79 (multiplet, $J_{H_2-H_7}$ = <1 Hz, $J_{H_6-H_7}$ = 5 Hz, J_{NH-H_7} = 9 Hz, 1 H, H_7), 6.62–7.20 (multiplet, 6 H, aromatic and NH); mass spectrum *m/e* 524 (molecular ion). Anal. Calcd for $C_{19}H_{19}N_2O_5S_2Cl_3$: C, 43.39; H, 3.64; N, 5.33; S, 12.20. Found: C, 44.06; H, 3.59; N, 5.36; S, 12.32.

Trichloroethyl 2α-Methoxy-3-methyl-7-(phenoxyacetamido)-3-cephem-4-carboxylate (8a). Method A. A solution of 216 mg (0.450 mmol) of cephem **1a** in 1.0 mL of deuteriochloroform was treated with 60 mg (0.450 mmol) of NCS. Formation of the 2-chlorocephem **4a** was monitored by NMR. After the disappearance of the NCS singlet (~10 min), anhydrous methanol (100 μL) was added. After 8 min the solution was poured into a mixture of methylene chloride and saturated aqueous sodium bicarbonate solution and shaken. The organic layer was separated and washed with water followed by saturated sodium chloride solution. After drying (Na_2SO_4) solvent was removed in vacuo yielding an oil (215 mg). Thin-layer chromatography of the oil on silica gel plates developed in 10:1 chloroform–ethyl acetate yielded the starting cephem **1a** (36 mg), the 2α-methoxycephem **8a** [108 mg; IR ($CHCl_3$) 3380, 1785 (β-lactam C=O), 1740 (ester C=O), 1690 cm^{-1} (amide C=O); mass spectrum *m/e* 508 (molecular oin)], and an oil (32 mg) containing a 1:1 mixture of isothiazole **6a** and methyl phenoxyacetate (**9**) proven by NMR, MS, and TLC.

On standing, the 2α-methoxycephem **8a** crystallized. The colorless needle-like crystals were triturated with an ether–pentane mixture and collected: mp 115–116.5 °C. Anal. Calcd for $C_{19}H_{19}N_2O_6SCl_3$: C, 44.76; H, 3.76; N, 5.50; S, 6.29; Cl, 20.87. Found: C, 44.61; H, 3.50; N, 5.39; S, 6.36; Cl, 20.81.

Method B. To a mixture of 200 mg (0.417 mmol) of **1a** in 5 mL of anhydrous methanol was added 56 mg (0.417 mmol) of NCS. After being stirred 2 h at room temperature, the solution gave a negative starch–KI paper test. Solvent was removed in vacuo and the crude residue was purified by preparative TLC on silica gel plates developed in chloroform. Extraction yielded the starting material (35 mg) and the 2α-methoxycephem **8a** as a foam (75 mg).

2α-Methoxy-3-methyl-7-(phenoxyacetamido)-3-cephem-4-carboxylic Acid (8c). To a solution of 511 mg (1.04 mmol) of cephem trichloroethyl ester **8a** in a mixture of anhydrous dimethylformamide (15 mL) and acetic acid (3 mL) was added 980 mg (15 mmol) of zinc dust while cooling in an ice bath and stirring. After 2 h the reaction mixture was filtered to remove excess zinc. The zinc was washed with ethyl acetate and the combined filtrate and washings were diluted with ethyl acetate. After washing three times with water, the organic layer was extracted by adding water and adjusting to pH 8.8 with base. The basic solution was separated and layered with ethyl acetate. After the aqueous layer was acidified to pH 2.8, the ethyl acetate layer was separated, washed with water, and dried (Na_2SO_4). Solvent was removed under reduced pressure, and the residue (247 mg) was recrystallized twice from a 2-propanol–hexane mixture. The product crystallized with 1 molar equiv of 2-propanol: mp 150–151 °C [lit.[4] mp 141–145 °C (acetone–hexane)]; IR (KBr) 3410, 3280, 2580, 1775 (β-lactam C=O), 1720 (acid C=O), 1670 (amide C=O), 1070, 930, 755 cm^{-1}; NMR (CD_3CN) δ 1.09 (d, J = 6 Hz, 6 H, 2-propanol CH_3), 2.05 (singlet, 3 H, CH_3), 3.37 (singlet, 3 H, OCH_3), 3.86 (septet, J = 6 Hz, 1 H, 2-propanol CH), 4.53 (singlet, 1 H, H_2), 5.01 (doublet, $J_{H_6-H_7}$ = 5 Hz, 1 H, H_6), 5.82 (quartet, $J_{H_6-H_7}$ = 5 Hz, J_{H_7-NH} = 9 Hz, 1 H, H_7), 6.6–7.8 (multiplet, 6 H, aromatic and NH). Anal. Calcd for $C_{17}H_{18}N_2O_6S \cdot C_3H_8O$: C, 54.78; H, 5.98; N, 6.39. Found: C, 54.63; H, 5.64; N, 6.41.

Trichloroethyl 4-Methylisothiazole-3-carboxylate (6a). From 1a. Compound **1a** (500 mg, 1.04 mmol) was dissolved in methylene chloride (5 mL) and NCS (278 mg, 2.08 mmol) was added while stirring at room temperature. After 2 h the reaction mixture gave a negative starch–KI paper test. Dilution of the reaction mixture with methylene chloride was followed by washing with water and then pH 7.6 phosphate buffer. Drying (Na_2SO_4), decolorization with charcoal, filtration through Celite, and removal of the solvent in vacuo yielded a crude oil (464 mg). Preparative TLC on silica gel using chloroform as the developing solvent gave the isothiazole **6a** as a foam (102 mg). This material was identical with that isolated in the preparation of the 2-methylthiocephem **7a.**

From 2a. The above procedure was repeated using **2a** (500 mg, 1.08 mmol) and NCS (288 mg, 2.16 mmol). In this case the reaction was exothermic giving a negative starch–KI paper test within 3 min, but the mixture was allowed to stir 1 h. After workup and chromatography the isothiazole **6a** was isolated as a foam (195 mg).

Methyl 4-Methylisothiazole-3-carboxylate (6b). To a solution of the cephem methyl ester **2b** (1.0 g, 2.89 mmol) in methylene chloride (40 mL) was added NCS (0.771 g, 5.77 mmol) and 1 drop of trifluoroacetic acid. After 1 h the reaction mixture was worked up by washing with saturated aqueous sodium bicarbonate solution, followed by water, and drying (Na_2SO_4). Solvent was removed under reduced pressure and the residual oil was purified by dry column chromatography on silica gel (1.5 × 15 in. column developed with chloroform). The product was isolated as a reddish yellow oil (293 mg). Distillation in vacuo yielded the isothiazole **6b** as a colorless crystalline solid: mp 28–29.5 °C; IR (KBr) 1710 (ester C=O), 1430, 1250, 1080 cm^{-1}; NMR ($CDCl_3$) δ 2.59 (doublet, J_{H-CH_3} = 0.8 Hz, 3 H, CH_3), 4.02 (singlet, 3 H, OCH_3), 8.39 (multiplet, 1 H, CH); λ_{max} (95% EtOH) 227 nm (ε 4400), 268 (6000); mass spectrum *m/e* 157 (molecular ion). Anal. Calcd for $C_6H_7NO_2S$: C, 45.84; H, 4.49; N, 8.91; S, 20.40. Found: C, 45.77; H, 4.30; N, 9.13; S, 20.24

Methyl 4-Acetoxymethylisothiothiazole-3-carboxylate (11). Methyl ester **10** (2.50 g, 6.20 mmol) was dissolved in methylene chloride (80 mL) and NCS (1.66 g, 12.40 mmol) was added. The mixture was allowed to stir overnight at room temperature, then washed with water, followed by pH 7.6 buffer, and dried (Na_2SO_4). The solution was decolorized with charcoal and filtered through Celite, and solvent was removed in vacuo. A combination of column chromatography and crystallization from ethyl acetate–hexane gave 0.855 g: mp 90.5–92 °C. Recrystallization yielded analytically pure **11:** 0.620 g; mp 91.5–92.5 °C; IR (KBr) 1735 (ester C=O), 1705 (ester C=O), 1440, 1350, 1130, 1085, 1035 cm^{-1}; NMR ($CDCl_3$) δ 2.14 (singlet, 3 H, CH_3), 3.98 (singlet, 3 H, OCH_3), 5.47 (doublet, J_{H-CH_2} = 0.8 Hz, 2 H, CH_2), 8.67 (multiplet, 1 H, CH); λ_{max} (95% EtOH) 227 nm (ε 4180), 262 (6260); mass spectrum m/e 215 (molecular ion). Anal. Calcd for $C_8H_9NC_4S$: C, 44.66; H, 4.22; N, 6.51. Found: C, 44.87; H, 4.05; N, 6.51.

4-Hydroxymethylisothiazole-3-carboxylic Acid (12). The isothiazole diester **11** (0.374 g, 1.74 mmol) was dissolved in a methanol (7 mL)–0.5 N aqueous sodium hydroxide (7 mL) mixture. After stirring the solution for 1.75 h at room temperature, methanol was removed by concentration in vacuo and the pH of the residual aqueous solution was adjusted to 2.5 with 6 N hydrochloric acid while cooling in an ice bath. A colorless solid crystallized, which was collected by filtration and dried: 0.180 g; mp 183.5–185 °C dec. Concentration of the filtrate under reduced pressure yielded a second crop: 0.035 g; mp 180–182 °C dec.

The first crop was recrystallized from water yielding the analytically pure hydroxy acid **12:** 0.113 g; mp 183.5–185 °C dec; IR (KBr) 3310, 3110, 2600 (br sh), 1710 (acid C=O), 1460, 1235, 1150, 1025 cm^{-1}; NMR (Me_2SO-d_6) δ 4.80 (br s, 2 H, CH_2), 8.92 (br s, 1 H, CH); λ_{max} (95% EtOH) 225 nm (ε 4190), 263 (6110); mass spectrum *m/e* 159 (molecular ion). Anal. Calcd for $C_5H_5NO_3S$: C, 37.74; H, 3.17; N, 8.80. Found: C, 37.59; H, 3.46; N, 8.72.

X-Ray Determination of Structure 12. The monoclinic crystals of **12** ($C_5H_5NO_3S$) from aqueous solution have a = 3.952 (1), b = 11.997 (7), and c = 13.21 (1) Å, β = 90.0 (1)°, d_{calcd} = 1.69 g cm^{-3}, and

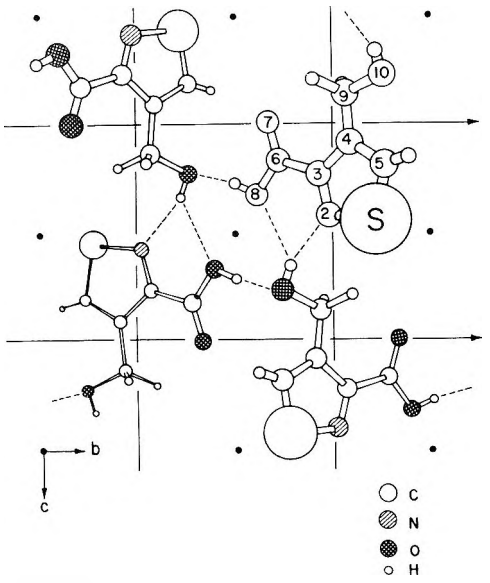


Figure 1. Crystal structure of **12**.

space group $P2_1/n$ with Z = 4; 562 "observed" intensities measured on an automatic diffractiometer (Cu Kα; λ 1.542 Å) were used for the solution and least-squares refinement of structure. Patterson and Fourier analyses revealed an atomic arrangement consistent with the 3,4-disubstituted isothiazole **12**. Refinements of the coordinates and anisotropic temperature factors, including the coordinates (but not temperature factors) of all five hydrogen atoms evident in a difference map, converged to $R = 0.06$.[21]

The heterocyclic ring is planar to within 0.004 Å and the S–N and S–C bond lengths are 1.655 (2) and 1.704 (2) Å, respectively. The carbonyl oxygen O(7) is syn to C(4) [torsional angle O(7)–C(6)–C(3)–C(4) = 1°]. There is no intramolecular hydrogen bonding; instead, O(10) adopts an anti conformation with respect to C(3) and the carboxyl group [torsional angle O(10)–C(9)–C(4)–C(3) = 179°] and is *inter*molecularly hydrogen bonded to a glide related molecule [O(8)···O(10) distance = 3.01 Å; O(10)···N(2) distance = 2.94 Å].

In addition, the carboxyl hydrogen is hydrogen bonded to O(10) of a screw-related molecule [O(8)···O(10) distance = 2.66 Å]. A drawing of this hydrogen-bonded network is shown in Figure 1.

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Registry No.—**1a,** 24647-47-0; **2a,** 28180-80-5; **2b,** 33465-36-0; **6a,** 64024-46-0; **6b,** 64024-47-1; **8c,** 58800-55-8; **10,** 3595-22-0; **11,** 64024-48-2; **12,** 64024-49-3; methanethiol, 74-93-1.

Supplementary Material Available: Tables of fractional coordinates, temperature factors, and interatomic angles and distances (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Presented in part at the β-Lactam Symposium, American Chemical Society Meeting in Miniature, Stevens Institute of Technology, Hoboken, N.J. May 14, 1975.
(2) (a) R. D. G. Cooper, P. V. Demarco, C. F. Murphy, and L. A. Spangle, *J. Chem. Soc. C*, 340 (1970); (b) D. O. Spry, *Tetrahedron Lett.*, 3717 (1972); (c) D. H. Bremner, M. M. Campbell, and G. Johnson, *ibid.*, 2909 (1976).
(3) E. H. W. Bohme and J. E. Dolfini, *Chem. Commun.*, 941 (1972).
(4) A. Balsamo, P. Crotti, B. Macchia, and F. Macchia, *J. Org. Chem.*, **41,** 2150 (1976).
(5) The synthesis of simple cyclic α-chloro sulfides using NCS has been reported by D. L. Tuleen and R. H. Bennett, *J. Heterocycl. Chem.*, **6,** 115 (1969).
(6) 2α-Methylthio-Δ^3-cephems have been prepared by methylthiolation of the allylic anion of cephalosporin sulfoxides followed by reduction to the sulfide.[1,7,8] Aromatic solvent-induced shift studies[9] have proved that the C-2 methylthio moiety introduced by this procedure also has the α configuration.[1]
(7) W. H. Koster and J. E. Dolfini, U.S. Patent 3 968 109 (1976).
(8) A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.*, **23,** 2507 (1975).
(9) P. V. Demarco and R. Nagarajan in "Cephalosporins and Penicillins: Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, N.Y., 1972, pp 353–355.
(10) (a) D. Buttimore, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J. Chem. Soc.*, 2032 (1963); (b) D. H. Jones, R. Slack, and K. R. H. Wooldridge, *ibid.*, 3114 (1964).
(11) H. A. Staab and A. Mannschreck, *Chem. Ber.*, **98,** 1111 (1965).
(12) D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, **34,** 31 (1969).
(13) (a) E. Vilsmaier and W. Sprügel, *Justus Liebigs Ann. Chem.*, **747,** 151 (1971); (b) E. Vilsmaier, K. H. Dittrich, and W. Sprügel, *Tetrahedron Lett.*, 3601 (1974).
(14) See references cited in R. J. Stoodley, *Tetrahedron*, **31,** 2321 (1975).
(15) F. P. Doyle, J. H. C. Nayler, H. Smith, and E. R. Stone, *Nature (London)*, **19,** 1091 (1961).
(16) T. Yamana and A. Tsuji, *J. Pharm. Sci.*, **65,** 1563 (1976).
(17) H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., "The Chemistry of Penicillin", Princeton University Press, Princeton, N.J., 1949, pp 734–735.
(18) N. S. Srinivasan and N. Venkatsubramanian, *Tetrahedron*, **30,** 419 (1973).
(19) A related pathway has been proposed for the rearrangement of C-2 hetero-substituted cephalosporin sulfoxides: A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.*, **23,** 2518 (1975).
(20) (a) E. Baltazzi, *Q. Rev., Chem. Soc.*, **9,** 150 (1955); (b) J. W. Cornforth in "Heterocyclic Compounds", Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1957, Chapter 5.
(21) See paragraph at end of paper regarding supplementary material.

p-Quinobis(1,3-benzodithiole) *S*-Oxide. An Unusual Vinylogous Tetrathiafulvalene Derivative

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The purple-black title compound **9** has been synthesized from *o*-benzenedithiol in several steps, the last of which involves a novel base-catalyzed vinylogous Pummerer dehydration of a sulfoxide. Some chemical and physical properties of **9**, which may be viewed as a push–pull stabilized *p*-quinodimethane, are described.

The discovery of the high solid-state electrical conductivity of the charge-transfer complex of tetrathiafulvalene (TTF, **1**) and tetracyanoquinodimethane (TCNQ, **2**)[1] has provided the impetus for the synthesis of a variety of structural modifications of both of the above-mentioned molecules.[2]

The unknown heterocycles **3** and **4** present particularly interesting structural features, since they combine in one molecule the substituted *p*-quinodimethane system of TCNQ with the two 1,3-dithiolidine moieties of TTF. This paper describes the synthesis and some chemistry of the monosul-

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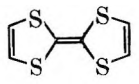
foxide of **4**, namely, *p*-quinobis(1,3-benzodithiole) *S*-oxide (**9**).



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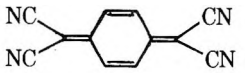

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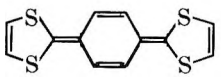

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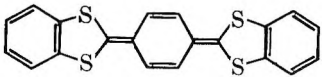

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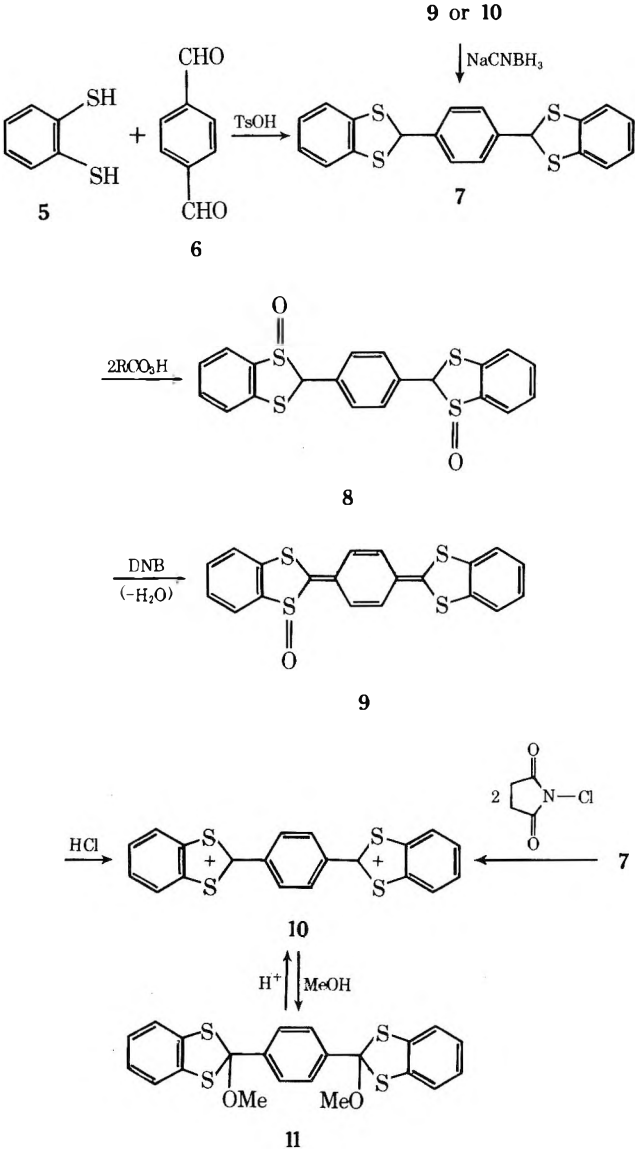
Results

Synthesis of the Quinonoid Sulfoxide 9. *o*-Benzenedithiol (**5**)[3] was reacted with terephthalaldehyde (**6**) in the presence of *p*-toluenesulfonic acid to give (73%) the bisthioketal **7**, mp 175 °C (dec). Attempts to effect a direct dehydrogenation of **7** to the quinodimethane **4** using chloranil or dichlorodicyanobenzoquinone (DDQ) lead to the disappearance of **7**, although no characterizable reaction product could be isolated. Oxidation of thioketal **7** by *m*-chloroperbenzoic acid proceeded cleanly only in the cold in the presence of the mild acid scavenger disodium hydrogen phosphate. When only 1 equiv of peracid was used, 33% of starting material could be recovered, showing the oxidized material to be a mixture of mono- and disulfoxides; these could not be separated due to their great lability on a variety of adsorbents. When a little over 2 equiv of peracid was used, NMR analysis showed the disappearance of the thioketal singlet at δ 6.12, and its replacement by a more shielded singlet at δ 5.8, attributable to the resulting stereoisomeric disulfoxides **8**. Direct warming of the latter with diazabicyclononene (DBN) and pyridine in dichloromethane led to the rapid appearance of an intense permanganate purple color and the separation, in good yield (37%), of the quinodimethane **9**.



Properties and Reactions of the Quinonoid Sulfoxide 9. Sulfoxide **9** is a purple-black, microcrystalline powder; on grinding in a mortar it acquires a striking bronze-like metallic sheen. It has no definite melting point, but turns red around 180 °C and slowly decomposes above 270 °C. It is totally insoluble in nonpolar solvents such as benzene or hexane; it is only very slightly soluble in such polar solvents as pyridine, dimethylformamide and hexamethylphosphoramide, in which it gives purple solutions due to an absorption maximum at about 530 nm. Attempted soxhlet recrystallization from the latter solvents leads to slow decomposition; however, solvent leaching of all impurities from **9** is readily carried out, the insoluble purple-black residue being directly of analytical purity.

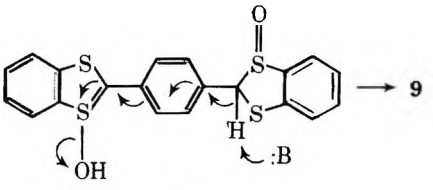
The purple sulfoxide **9** is rapidly destroyed by concentrated hydrochloric acid. The resulting yellow bisdithiolium ion **10** is formed cleanly, and may be isolated in good yield (66%) as its crystalline bisfluoborate salt. An independent synthesis of **10** was achieved by the *N*-chlorosuccinimide oxidation of thioketal **7** in hot acetonitrile.

Sulfoxide **9** was decolorized readily by sodium cyanoborohydride at pH 4 to give the starting thioketal **7**. The dication **10** was also found to be reduced to **7** by the reagent.

Finally, sulfoxide **9** was found to react with methanol in the presence of a small amount of *p*-toluenesulfonic acid to give the white crystalline dimethoxy compound **11**. The latter was quite stable under basic conditions, but was converted by strong acid to the yellow dication **10**. Again, the latter cation was the probable reaction intermediate; as expected, it reacted slowly with methanol to give the methoxy compound **11**.

Discussion

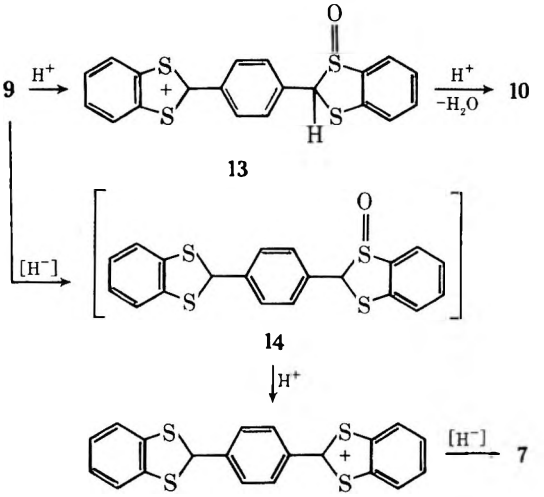
The reactions reported above include several examples of very facile Pummerer-type sulfoxide dehydrations. Thus, the dehydration of the disulfoxide **8** to the purple sulfoxide **9** is the first reported example of a *base-catalyzed vinylogous* sulfoxide dehydration.[4] It presumably involves dehydration of the "thiaenol" **12** of **8** as shown below:



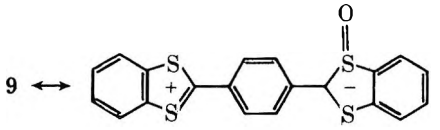
12

The conversion of **9** to dication **10** by aqueous acid must involve protonation of **9** to the cation sulfoxide **13**, followed by an unusually rapid acid-catalyzed Pummerer dehydration of **13** to **10**. A similar rapid dehydration of a 1,3-dithiole monosulfoxide **14** is probably involved in the cyanoborohydride reduction of sulfoxide **9** to thioketal **7**.

The unusual insolubility of sulfoxide **9** attests to the existence of strong forces in the crystal lattice which bind the individual molecules together. These forces are undoubtedly electrostatic in nature and result from the fact that the polar



canonical form **15** is undoubtedly a very important contributor to the structure of **9**. Sulfoxide **9** is therefore to be viewed as a new type of push–pull stabilized *p*-quinodimethane, other types of which have been previously prepared by Gompper and co-workers.[5]



Studies aimed at the conversion of sulfoxide **9** and dictation **10** into the parent *p*-quinodimethane **4** are presently under investigation in our laboratory.

Experimental Section

Melting points are uncorrected. NMR ($CDCl_3$ containing tetramethylsilane as internal standard) and ultraviolet and mass spectra were determined using Varian A-60 and Perkin-Elmer 202 and 270B spectrometers, respectively.

1,4-Phenylenebis(benzodithioketal) (7). A mixture of terephthalaldehyde (6.3 g; 0.5 equiv) and o-benzenedithiol[3] (14 g; 1 equiv) in 300 mL of benzene containing a trace (~50 mg) of *p*-toluenesulfonic acid was refluxed using a Dean–Stark trap, until no more water separated. The solid, mp 173–175 °C (dec), which crystallized upon cooling (14.3 g; 73%) was filtered. Concentration of the filtrate yielded a second crop (2.4 g) of less pure material. An analytical sample, mp 175 °C (dec), was obtained by recrystallization from absolute ethanol containing benzene: mass spectrum M^+ 382; NMR δ 6.12. Anal. Calcd for $C_{20}H_{14}S_4$: C, 62.83; H, 3.69. Found: C, 62.69; H, 3.78.

***p*-Quinobis(1,3-benzodithiole) *S*-Oxide (9).** A mixture of solutions of bisthioketal (3.82 g; 1 equiv) in 200 mL of methylene chloride and 100 mL of aqueous 5% Na_2HPO_4 was cooled to 10 °C. A cold solution of *m*-chloroperbenzoic acid (3.44 g; 2 equiv) in 200 mL of methylene chloride was added within 15 min, with good stirring. The organic layer was separated, washed once with aqueous Na_2HPO_4 solution, and filtered through phase-transfer filter paper into a flask containing a solution of 2 mL of DBN in 10 mL of CH_2Cl_2. The dark-violet solution was concentrated to half the volume, treated with 50 mL of pyridine, and warmed for 10 min on the steam bath. The black solid was filtered, washed with pyridine and methylene chloride, and dried to yield sulfoxide **9**, mp >270 °C (dec) (1.4 g; 37%). An analytical sample was obtained by boiling **9** quickly with pyridine and filtering: mp >270 °C (dec); visible spectrum λ_{max} pyridine 410 (sh), 478, 530 nm; mass spectrum *m/e* 380 (M − 16). Anal. Calcd for $C_{20}H_{12}OS_4$: C, 60.55; H, 3.05; S, 32.36. Found: C, 60.35; H, 3.07; S, 32.08.

***p*-Phenylenebis(1,3-benzodithiolium) Fluoborate (10).** (a) Finely ground **9** (1 g) was heated with a mixture of glacial acetic acid (200 mL), acetic anhydride (20 mL), and commercial fluoboric acid solution (50 mL). The yellow mixture was filtered hot, concentrated, and treated with anhydrous ether to give a yellow precipitate of crude **10** (0.93 g; 66%), decomposition above 250 °C. Recrystallization from acetonitrile containing fluoboric acid yielded pure yellow needles (0.8 g), decomposition above 280 °C. Anal. Calcd for $C_{20}H_{12}S_4B_2F_8$: C, 43.33; H, 2.18; S, 23.15. Found: C, 43.59; H, 2.12; S, 22.96.

(b) A suspension of bisketal **7** (0.191 g) and *N*-chlorosuccinimide (0.266 g) in 30 mL of acetonitrile was heated gently. Within 0.5 h the color turned green, cleared, and precipitated as an orange-brown solid. The mixture was cooled and filtered, and the precipitate was washed with acetonitrile–ether. The insoluble precipitate (0.236 g) was heated with 25 mL of fluoboric acid (50% solution) and filtered hot. The yellow crystals were filtered and washed with cold dilute fluoboric acid followed by ether to yield the fluoborate of bis(**10**) (0.136 g; 50%), mp decomposition above 280 °C, identical to the sample obtained in a (mp, IR spectrum).

Addition of Methanol to 9 (11). An intimate mixture of **9** (0.300 g) and a trace of *p*-toluenesulfonic acid in 1 mL of methanol was stirred for 2 h at room temperature. A chloroform solution of crude product (0.33 g) was filtered through basic alumina to yield **11** (0.28 g), mp 205–210 °C. Recrystallization from methanol–benzene yielded very pure **11**: mp 210–211 °C (turns pink); mass spectrum M^+ 442, *m/e* 411, 380, 335, 303, 259, 229, 228, 227, 190; NMR 8.0 (m, 12 ArH), 3.5 (s, 6 H, 2 OMe). Anal. Calcd for $C_{22}H_{18}O_2S_4$: C, 59.73; H, 4.10; S, 28.92. Found: C, 59.83; H, 4.10; S, 28.52. Compound **11** could also be made by triturating **9** with methanolic hydrogen chloride in the cold.

$NaCNBH_3$ Reduction of 9. To a mixture (10 mL) of dilute hydrochloric acid (10%) in glacial acetic acid (2 mL) was added well-powdered **9** (100 mg), followed by excess $NaCNBH_3$ (100 mg). Dilution followed by extraction with CH_2Cl_2 afforded the bisthioketal **7** (35 mg), mp 170 °C, identical in all respects (mixture mp, IR) to authentic **7**.

$NaCNBH_3$ Reduction of Bisthiolium Fluoborate of 10. To a suspension of **10** fluoborate (136 mg) in glacial acetic acid (5 mL) containing 50% HBF_4 (1 mL) and CH_2Cl_2 (~5 mL), excess $NaCNBH_3$ (100 mg) was added with swirling. Reduction was instantaneous. Dilution with water followed by separation of the organic layer and the usual workup yielded 70 mg (77.8%) of **7**, mp 170 °C, after recrystallization, identical in all respects to authentic **7**.

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Registry No.—**5**, 17534-15-5; **6**, 623-27-8; **7**, 63866-46-6; **9**, 63866-45-5; **10**, 63866-44-4; **11**, 63866-42-2.

References and Notes

(1) A. F. Garito and A. J. Heeger, *Acc. Chem. Res.*, **7**, 218 (1974), and references cited therein.
(2) M. Narita and C. U. Pittman, Jr., *Synthesis*, 489 (1976).
(3) S. Hünig and E. Fleckenstein, *Annalen*, **738**, 192 (1970).
(4) For examples of base-catalyzed sulfoxide dehydration, see: C. J. Horner, L. E. Saris, M. V. Lakshmikantham, and M. P. Cava, *Tetrahedron Lett.*, 2581 (1976).
(5) R. Gompper, H. Wagner, and E. Kutter, *Chem. Ber.*, **101**, 4123 (1968).

Effect of 2-Triphenylsilyl Substitution on the Molecular Geometry of 1,3-Dithianes.[1] Crystal Structures of 2-Methyl-2-triphenylsilyl-1,3-dithiane and *trans*-2-Triphenylsilyl-1,3-dithiane 1-Oxide

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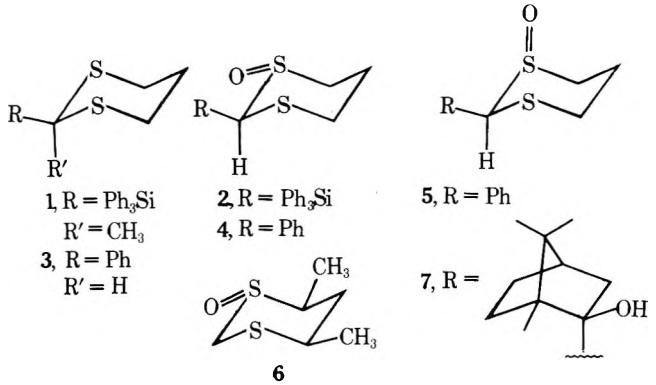
The crystal structures of 2-methyl-2-triphenylsilyl-1,3-dithiane (**1**) and *trans*-2-triphenylsilyl-1,3-dithiane 1-oxide (**2**) have been determined to establish their conformations and the effect upon ring geometry of a 2-triphenylsilyl substituent. Crystals of **1** conform to space group $C2/c$, with a = 28.780 (6), b = 11.901 (3), c = 15.909 (3) Å, β = 130.93 (3)°, and Z = 8. For **2**, the space group is $P2_1/c$, with a = 10.390 (3), b = 9.988 (3), c = 20.207 (12) Å, β = 97.61 (3)°, and Z = 4. The endocyclic C(2) valence angle in **2**, 106.0 (3)°, is 5.4° smaller than in **1**, but each of these angles is, respectively, 3.6° smaller than the corresponding angles in *trans*-2-phenyl-1,3-dithiane 1-oxide (**4**), 109.6 (2)°, and in 2-phenyl-1,3-dithiane (**3**), 115°. This additional contraction is attributed to the electron-releasing character of silicon, an effect known in phenylsilanes, but not previously noted in silyl-substituted alicyclic systems. The crystal structure of **2** contains a short intramolecular CH···O contact, which is diagnosed as a strong dipolar interaction both by virtue of the conformational change induced about the C(2)–Si bond and the valence angle distortion produced at the phenyl-ring carbon involved.

In the course of synthetic work involving dithiane oxides,[2] *trans*-2-triphenylsilyl-1,3-dithiane 1-oxide (**2**) was prepared. Its structure was determined by single-crystal x-ray analysis so as to establish the orientation of oxygen, but showed significant and interesting variations in dithiane ring geometry associated with the triphenylsilyl group, which are the subject of this paper. For purposes of comparison, and to check the validity of our conclusions, a structure determination was also carried out for 2-methyl-2-triphenylsilyl-1,3-dithiane (**1**).[3]

Our understanding of conformational effects in sulfoxides derived from 1,3-dithiane has been substantially enhanced by x-ray crystallographic structural studies. The crystal structures of a diastereomeric pair, *trans*-2-phenyl- and *cis*-2-phenyl-1,3-dithiane 1-oxide, **4** and **5**, respectively, have been described and used as models to probe the effect of equatorial vs. axial orientation of oxygen on bond distances and on valence and torsion angles.[4] The significant difference observed in the S(1)–C(2)–S(3) valence angle from one to the other has been ascribed to electrostatic interactions between the sulfoxide group and S(3).[5] The results obtained for additional examples, the equatorial oxide **6**[6] and the axial oxide **7**,[7] may be interpreted in the same way. Besides the effect upon the C(2) valence angle, oxygenation leads to different patterns of ring puckering as compared to the parent compounds, and variations in the C–S bond distances, which have been correlated to substitution patterns in the ring.[6]

Additional information on all of these effects is provided by the analyses reported here, and, in addition, evidence is presented pointing to electron transfer from silicon to the dithiane ring as a contributory factor in the changes in the C(2) valence angle. There is also evidence for the conformational importance of an intramolecular C–H···O interaction in **2**, and further examples of intermolecular C–H···O interactions are found.[4]



Results and Discussion

Atomic parameters defining the crystal structures of **1** and **2** are given in Table I, and stereoscopic ORTEP[8] drawings of the two structures are shown in Figures 1 and 2. Selected bond lengths and angles are given in Table II, and torsion angles for the dithiane rings of **1**–**4** are given in Table III.

Both rings adopt puckered chair conformations with the triphenylsilyl group equatorial at C(2), but the form of the puckering in each is different. In **1**, the presence of the axial methyl group at C(2) leads to interactions between the methyl proton H(7) and the axial hydrogen atoms on C(4) and C(6). Conformational distortion at the C(2) apex is inhibited by the quaternary substitution pattern, and these syn-axial interactions are accommodated with an increase in the torsion angles about the C(4)–C(5) and C(5)–C(6) bonds. The observed proton separations are H(7)···H(4a) 2.49 Å and H(7)···H(6a) 2.65 Å. In **2**, although the C(2) axial hydrogen atom, H(2a), is 2.66 Å from H(4a) and 2.56 Å from H(6a), these interactions are possible with a flattening of the dithiane ring at the C(5) apex relative to **1** and also to *trans*-2-phenyl-1,3-dithiane 1-oxide, **4**. Thus, although the syn-diaxial contacts between hydrogens in **2** are nearly identical to those found in **4**, 2.55 and 2.66 Å, the C(4)–C(5) and C(5)–C(6) endocyclic torsion angles are 57° and 59° in **2** compared to 64° and 67° in **4**. This difference is a direct result of the replacement of a 2-phenyl substituent by the triphenylsilyl group, which has the effect of removing a buttressing interaction in **4** between H(2a) and a phenyl-ring proton [H(2a)···H(12), 2.38 Å] that prevents movement of H(2a) in a direction away from the dithiane ring center. The combination of the buttressing interaction in **4** with the puckering induced at the C(2) apex by oxygen substitution means that syn-diaxial strain can only be relieved torsionally by increased puckering at the C(5) apex. In **2**, by contrast, with the butressing interaction removed, H(2a) is more able to move away from H(4a) and H(6a), leaving the C(5) apex comparatively unstrained. This same movement of H(2a) is presumably also responsible for the somewhat larger than usual puckering at C(2) in **2**.

The principal difference in bond angles, within the dithiane

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Table I. Atomic Parameters Defining the Crystal Structures

Atom	x/a	y/b	z/c	B	x/a	y/b	z/c	B
S(1)	4281.1 (5)	1294.4 (8)	4528.4 (8)	3.1	5138 (2)	4718 (2)	2872 (1)	5.3
S(3)	4627.4 (5)	3664.0 (8)	4487.2 (8)	3.4	4201 (2)	3170 (2)	3919 (1)	5.4
Si	3654.9 (4)	2420.8 (8)	2349.2 (8)	2.0	7163 (2)	3377 (2)	3958 (1)	3.1
C(2)	4432 (2)	2272 (3)	3857 (3)	2.7	5527 (5)	3310 (6)	3424 (3)	3.5
C(4)	5279 (2)	3351 (4)	5946 (3)	4.7	2897 (7)	2754 (8)	3292 (5)	7.5
C(5)	5133 (2)	2529 (4)	6458 (3)	4.9	2623 (8)	3748 (9)	2740 (5)	9.9
C(6)	4986 (2)	1364 (4)	5977 (3)	4.2	3730 (9)	4061 (9)	2368 (4)	7.5
C(7)	4939 (2)	1827 (4)	3864 (3)	3.9				
O					6168 (6)	4844 (6)	2437 (2)	8.2
C(11)	3564 (2)	1177 (3)	1524 (3)	2.7	8364 (5)	2400 (6)	3532 (3)	3.8
C(12)	3541 (2)	85 (3)	1804 (3)	3.2	8400 (7)	2593 (7)	2842 (3)	5.2
C(13)	3451 (2)	−823 (3)	1179 (3)	3.7	9286 (7)	1840 (8)	2524 (4)	6.7
C(14)	3389 (2)	−665 (4)	248 (3)	4.1	10 108 (7)	969 (8)	2875 (4)	7.4
C(15)	3412 (2)	395 (4)	−47 (3)	4.2	10 108 (7)	749 (8)	3554 (5)	7.3
C(16)	3496 (2)	1310 (3)	570 (3)	3.5	9214 (6)	1510 (7)	3886 (3)	5.2
C(21)	3676 (2)	3762 (3)	1758 (2)	2.7	6964 (5)	2579 (6)	4772 (3)	3.2
C(22)	4112 (2)	3935 (3)	1633 (3)	3.8	6726 (6)	1196 (6)	4801 (3)	4.4
C(23)	4131 (2)	4903 (4)	1190 (4)	4.2	6566 (7)	571 (6)	5402 (3)	5.4
C(24)	3715 (2)	5742 (4)	847 (3)	4.1	6605 (7)	1139 (7)	5975 (3)	5.4
C(25)	3277 (2)	5606 (3)	952(3)	4.1	6807 (7)	2694 (7)	5955 (3)	5.2
C(26)	3257 (2)	4632 (3)	1393 (3)	3.3	6990 (6)	3304 (6)	5356 (3)	4.3
C(31)	3002 (1)	2436 (3)	2352 (3)	2.7	7650 (5)	5156 (5)	4100 (3)	3.3
C(32)	2520 (2)	1671 (3)	1716 (3)	3.4	8920 (6)	5589 (7)	4093 (3)	4.9
C(33)	2036 (2)	1676 (4)	1726 (4)	4.4	9288 (6)	6895 (8)	4230 (4)	6.2
C(34)	2033 (2)	2442 (4)	2361 (3)	4.4	8365 (7)	7811 (7)	4392 (4)	5.9
C(35)	2502 (2)	3213 (3)	2989 (3)	4.1	7108 (6)	7424 (6)	4397 (3)	5.0
C(36)	2984 (2)	3211 (3)	2984 (3)	3.3	6757 (6)	6098 (6)	4261 (3)	4.1
H(2a)					554 (4)	252 (4)	318 (2)	1.2 (9)
H(4a)	564 (2)	303 (4)	593 (3)	5.7 (10)	303 (5)	189 (6)	309 (3)	6.2 (15)
H(4e)	538 (2)	421 (4)	626 (4)	8.4 (14)	214 (6)	279 (6)	351 (3)	7.2 (17)
H(5a)	479 (2)	286 (4)	642 (4)	7.3 (12)	217 (6)	452 (7)	300 (3)	8.9 (19)
H(5e)	549 (2)	251 (4)	727 (4)	6.6 (12)	191 (6)	352 (7)	240 (3)	8.7 (19)
H(6a)	533 (2)	97 (3)	605 (3)	4.8 (9)	406 (6)	328 (7)	214 (3)	8.5 (19)
H(6e)	487 (2)	79 (4)	634 (3)	5.3 (10)	351 (6)	470 (7)	195 (3)	9.3 (20)
H(7)	529 (2)	168 (3)	453 (3)	5.1 (10)				
H(7′)	504 (2)	248 (3)	356 (3)	5.3 (10)				
H(7″)	482 (2)	104 (3)	342 (3)	5.3 (10)				
H(12)	358 (2)	−3 (3)	246 (3)	3.3 (8)	776	331	256	*b*
H(13)	345 (2)	−159 (3)	142 (3)	8.0 (13)	931	196	199	
H(14)	334 (2)	−128 (3)	−11 (3)	6.9 (12)	1079	42	262	
H(15)	340 (2)	57 (4)	−69 (3)	4.8 (9)	1076	3	382	
H(16)	351 (2)	205 (3)	35 (3)	4.5 (9)	920	139	442	
H(22)	438 (2)	331 (4)	179 (3)	5.9 (11)	666	61	435	
H(23)	445 (2)	481 (4)	112 (4)	7.2 (13)	641	−50	542	
H(24)	374 (2)	646 (3)	57 (3)	3.6 (8)	648	87	644	
H(25)	300 (2)	628 (4)	74 (4)	6.5 (11)	682	329	640	
H(26)	295 (2)	453 (3)	148 (3)	4.8 (9)	718	431	520	
H(32)	251 (2)	110 (3)	124 (3)	3.6 (8)	964	488	398	
H(33)	170 (2)	104 (4)	131 (4)	3.5 (8)	1028	721	421	
H(34)	171 (2)	242 (4)	241 (4)	3.2 (8)	865	883	451	
H(35)	250 (2)	384 (3)	342 (3)	5.9 (11)	639	814	451	
H(36)	334 (2)	377 (3)	350 (3)	4.1 (9)	577	579	428	

[a] Positional parameters are given as fractions of the unit cell edges (C, O, and S × 10^4, H × 10^3. Equivalent isotropic *B* values (Å^2) are given for the heavy atoms and actual *B* values for H atoms whose parameters were allowed to refine in the least-squares treatment. Where applicable, estimated standard deviations are given on the same scale in parentheses. [b] In the refinement, *B* values equal to those given for the carbon atom of attachment were used for the phenyl H atoms of **2**. Positional parameters for these atoms were held fixed.

rings, between **1** and **2** is in the endocyclic C(2) valence angle which is 111.4° in **1** and 106.0° in **2**. This difference, 5.4°, is identical to that found for this same angle when 2-phenyl-1,3-dithiane, **3**, and *trans*-2-phenyl-1,3-dithiane 1-oxide, **4**, are compared,[4,9] so that it may reasonably be attributed to the effects of equatorial oxygen substitution at S(1). The same dipolar mechanism invoked to explain the difference in angles between **3** and **4** may be applied. However, there remains the observation that the differences in this C(2) angle between **1** and **3**, and between **2** and **4**, are both equal to 3.6°. This difference is attributed to the electron-releasing property of silicon with respect to carbon. Domenicano, Vaciago, and Coulson[10] have related the electronegativities of second-row elements, and the changes induced by σ-electron-density transfer, to endocyclic valence angles in phenyl rings to which these atoms are attached. In the case of silicon, the angle α, at the carbon of attachment of the phenyl ring, is decreased, and the angles β, at the flanking carbon atoms, are increased. These effects may be rationalized using arguments based on changes in orbital hybridization, or on the basis of VSEPR theory. Considering only a model involving changes in orbital hybridization, and assuming silicon to act as an electron-releasing substituent, the p character of the Si–C bond is reduced and that of the two adjacent C–C bonds is increased.

Table II. Selected Bond Lengths (Å) and Bond Angles (Deg) with Their Estimated Standard Deviations

Bond	1	2
S(1)-C(2)	1.815 (3)	1.807 (5)
S(3)-C(2)	1.824 (3)	1.811 (5)
S(1)-C(6)	1.819 (4)	1.793 (8)
S(3)-C(4)	1.828 (4)	1.778 (8)
C(4)-C(5)	1.497 (6)	1.492 (13)
C(5)-C(6)	1.505 (6)	1.488 (12)
C(2)-C(7)	1.545 (5)	
S(1)-O		1.478 (5)
Si-C(2)	1.938 (4)	1.890 (5)
Si-C(11)	1.882 (3)	1.881 (5)
Si-C(21)	1.873 (3)	1.864 (5)
Si-C(31)	1.879 (3)	1.859 (5)
Angle	**1**	**2**
S(1)-C(2)-S(3)	111.4 (2)	106.0 (3)
S(1)-C(2)-Si	105.1 (2)	115.8 (3)
S(3)-C(2)-Si	106.7 (2)	112.3 (3)
S(1)-C(2)-C(7)	111.4 (3)	
S(3)-C(2)-C(7)	111.0 (3)	
Si-C(2)-C(7)	111.0 (3)	
C(2)-S(1)-O		108.2 (3)
C(6)-S(1)-O		107.0 (4)
C(2)-S(1)-C(6)	102.6 (2)	99.5 (3)
C(2)-S(3)-C(4)	101.7 (2)	100.8 (3)
S(3)-C(4)-C(5)	113.9 (3)	115.4 (6)
S(1)-C(6)-C(5)	113.3 (3)	114.6 (6)
C(4)-C(5)-C(6)	114.3 (3)	115.7 (7)
C(2)-Si-C(11)	108.2 (3)	108.7 (3)
C(2)-Si-C(21)	108.0 (3)	107.0 (3)
C(2)-Si-C(31)	110.0 (3)	109.4 (2)
C(11)-Si-C(21)	110.8 (2)	109.9 (3)
C(11)-Si-C(31)	109.1 (2)	112.3 (3)
C(21)-Si-C(31)	110.7 (2)	109.1 (3)
C(12)-C(11)-C(16)	116.7 (3)	120.0 (6)
C(22)-C(21)-C(26)	116.0 (3)	117.6 (5)
C(32)-C(31)-C(36)	117.9 (3)	117.1 (5)
C(11)-C(12)-C(13)	122.0 (4)	118.8 (6)
C(11)-C(16)-C(15)	121.1 (4)	120.5 (7)
C(21)-C(22)-C(23)	122.3 (4)	121.2 (5)
C(21)-C(26)-C(25)	121.7 (3)	121.6 (6)
C(31)-C(32)-C(33)	120.9 (3)	122.1 (6)
C(31)-C(36)-C(35)	121.1 (4)	121.7 (6)

It has been shown[10] that, whereas, because of thermal effects, the C–C bond distances are not sensitive indicators of such effects, the angles α and β are. The mean value found for α from a survey of phenylsilanes is 116.98°, a reduction from the canonical value of 120° of just over 3°.

Given that the ipso effect[11] is dependent on σ-electron-density transfer, it seems reasonable to assume that the 3.6° diminution in each of the C(2) angles in **1** and **2**, relative to **3** and **4**, arises from similar causes consequent upon a diminution in the relative p character of the Si–C(2) bond. In the absence of a planar ring system, there is no direct need for a compensatory increase in the β angles at sulfur, but it is observed that, whereas in **3** the endocyclic valence angles at S(1) and S(3) are 99.2° and 100.9°, in **1** they are 101.7° and 102.6°. In the same way, whereas in **4** these angles are 98.2° and 100.5°, in **2** they are 99.5° and 100.8°. It seems possible that enhanced s character in the two C(2)–S bonds may also be reflected at the sulfur atoms.

Comparable ipso effects are found in five of the six phenyl rings of **1** and **2**. The mean contraction in these five angles is 2.9° and the mean expansion in β angles is 1.6°, comparable to earlier observations.[10] The exception involves the phenyl ring in **2**, one of whose β protons is involved in a short intramolecular C–H···O interaction which appears to override in importance the effect of silicon substitution. This interaction is described in more detail below.

Table III. Endocyclic Torsion Angles (Deg) in the Dithiane Rings of 1–4

Angle	Compound 1	2	3[a]	4
S(1)-C(2)	−56	−66	−57	−63
C(2)-S(3)	56	65	57	63
S(3)-C(4)	−58	−59	−56	−61
C(4)-C(5)	66	57	63	64
C(5)-C(6)	−66	−59	−61	−67
C(6)-S(1)	58	62	57	63

[a] Values of Kalff and Romers (ref 10).

Within the dithiane ring, the valence angles at C(4), C(5), and C(6) in **2** have an average value of 115.2° compared to 113.9° in **1**, an effect associated with the flattening of the C(5) apex in **2**. The remaining important difference in valence angles between **1** and **2** involves the S–C(2)–Si angles. In **1**, the presence of the sterically bulky C(2)-methyl substituent prevents any opening of these angles to minimize 1,3-interactions between sulfur and silicon, and leads to compressed values of 106.7° and 105.1° for these two angles. In **2**, by contrast, the absence of an axial substituent allows relaxation of the S···Si interactions and leads to expanded values of 115.8° and 112.3°. This opening, coupled with increased puckering at C(2) in **2**, places C(2) 0.99 Å below the least-squares mean plan through the four central atoms of the dithiane ring in **2**, compared to a displacement of 0.84 Å in **1**, but places Si 1.54 Å below that plane in **2** compared to only 0.64 Å in **1**.

McPhail[6] has suggested that differences in the C–S bond lengths in 1,3-dithianes and their oxides depend only on the pattern of substitution of the ring, shorter bonds being associated with methylene groups, and we have offered additional evidence in support of this view.[7] The observed C–S distances in **2** conform to this pattern, the longer distances involving C(2), the site of substitution, and the shorter bonds being to C(4) and C(6). This is not the case, however, in **1** where all four bonds are of equivalent length and all are longer than the distances found in **2**. Inasmuch as lengthening of these bonds is thought to depend on steric factors, it is likely that the observed lengthening and the equivalence of all four distances arise principally from the steric effects of the axial methyl group.

The mean Si–C_{sp^2} bond distance is 1.873 Å, and individual variations from this mean value probably have little significance. There is, however, a significant difference in the length of the Si–C(2) bond distance of 1.938 (4) Å in **1** and 1.890 (5) Å in **2**, which is to be correlated with the large differences in valence angles at C(2) in the two compounds.

The relative orientations of the dithiane ring and the triphenylsilyl moiety in **1** and **2** are illustrated by the Newman projections shown in Figure 3. The two conformations are markedly different, and neither is a completely staggered arrangement about C(2)–Si. The mean rotation of the two fragments in **1** is 40° and in **2** is only 25°. The diminished rotation in **2** is to be attributed to the H(12)···O interaction described below.

The dihedral angles between the three phenyl groups and the central plane of the dithiane ring are 129°, 70°, and 91° in **1** and 75°, 128°, and 90° in **2**. The 90° orientation seems to favor interaction between a β proton on the phenyl ring and the S(3) axial lone pair, whereas a 129° orientation favors an interaction between a β proton and the S(1) equatorial lone pair of **1**.

Nonbonded C–H···O interactions. In our earlier report,[4]

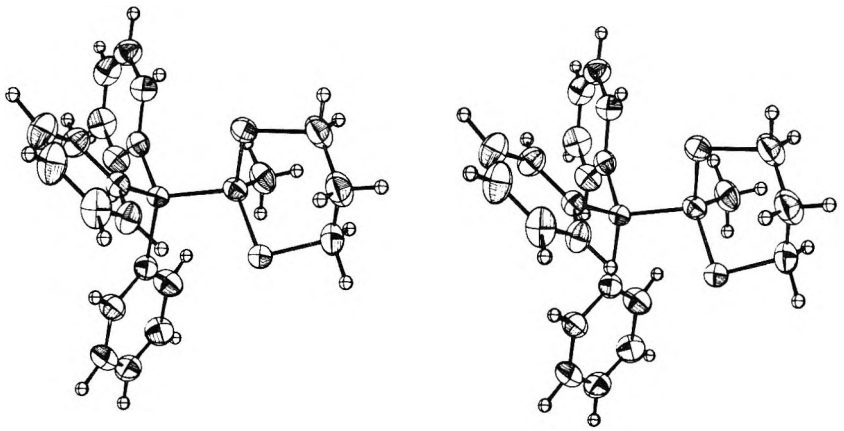

Figure 1. ORTEP stereoscopic view of the structure of **1**. Thermal ellipsoids for the nonhydrogen atoms are drawn to the 50% probability level and hydrogen atoms are represented by spheres of arbitrary radius.

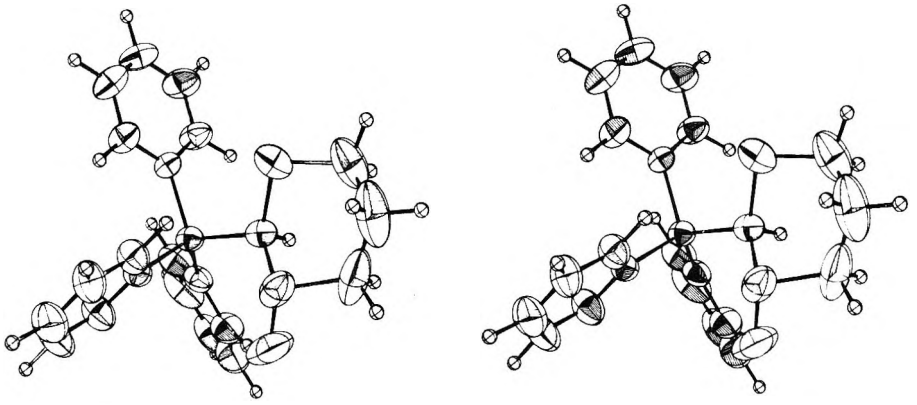

Figure 2. ORTEP stereoscopic view of **2**.

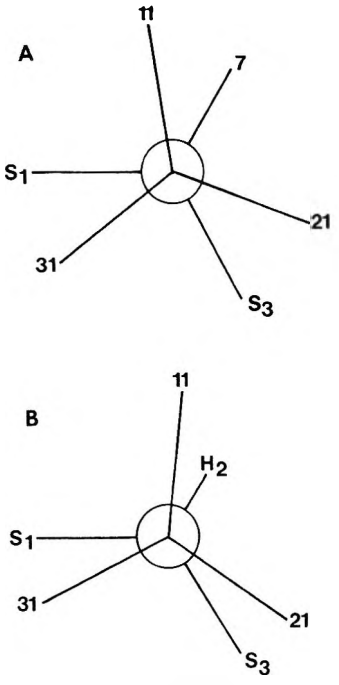

Figure 3. Newman projection down the Si–C(2) bond in **1** (A) and **2** (B). Atoms are carbon unless otherwise labeled.

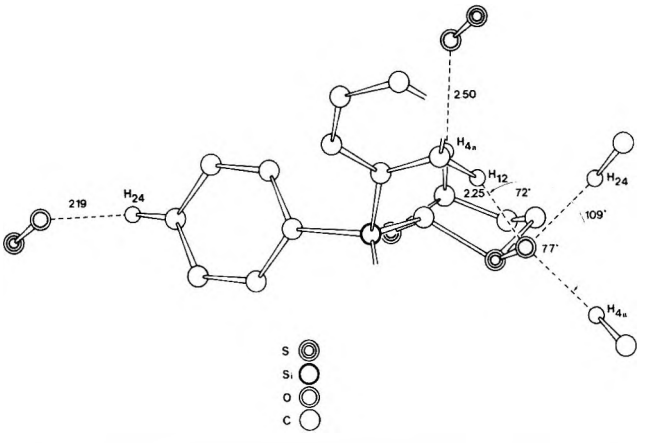

Figure 4. View of the short C–H···O interactions in the crystal structure of **2**. Distances are given in Å and angles in deg.

we noted the occurrence of striking intermolecular interactions in the crystal structures of **4** and of the two oxides *cis*-2-phenyl-1,3-dithiane 1-oxide, **5**, and 2-phenyl-1,3-dithiane *trans*-1, *trans*-3-dioxide. These involved C–H···O contacts, with potentially acidic hydrogen atoms attached to carbons adjacent to sulfur, which were markedly shorter than the sum of the accepted van der Waals radii of O and H, 2.60 Å. A similar observation has been made by McPhail for the crystal structure of the oxide **6**, and in the axial oxide **7** the oxygen atom acts as an acceptor in an O–H···O intramolecular hydrogen bond. Typically, O···H separations between 2.13 and 2.58 Å have been noted, those at the shorter end of the range being attributed to strong dipolar interactions.

In the crystal structure of **2** there are three further examples of such nonbonded interactions, two intermolecular and one intramolecular. These are illustrated in Figures 4 and 5. The intermolecular interaction involving H(4a) is of the general type previously described.[4] The other, involving H(24), the p proton of a phenyl ring, and with O···H 2.19 Å, is clearly a

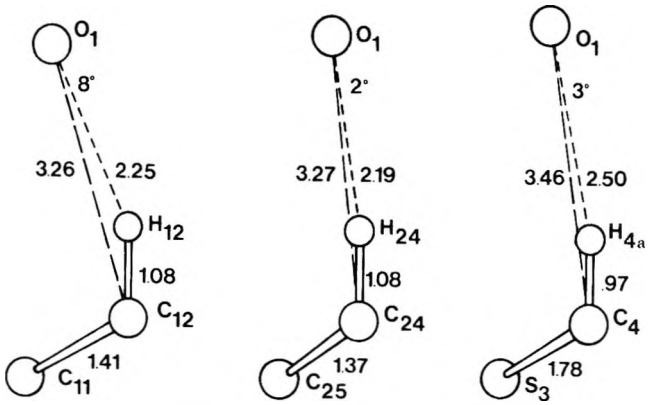

Figure 5. The individual short C–H···O interactions in 2 seen in projection onto the plane of the three atoms. The C–O–H angles are given as well as the interatomic separations (Å).

strong interaction, presumably of an induced-dipole type. The most interesting interaction, however, is the intramolecular contact between the phenyl proton H(12) and oxygen, with O···H only 2.25 Å. There seems no doubt that this contact arises from a powerful dipolar attraction between the two atoms, not only from the shortness of the interaction, but also from the effects produced on conformation about the C(2)–Si bond, described above, and on valence angle patterns in this phenyl ring. The ring involved is the only one of the six phenyl rings not to show an ipso effect of silicon substitution. Instead, the endocyclic valence angle at C(11) has a normal value of 120.0°, whereas C(12) subtends an angle of 118.8°. By the same arguments advanced to account for the angle contraction induced by silicon substitution, it seems that the interaction allows a pathway for transmission of electron density from oxygen to the phenyl ring of a magnitude comparable to that arising from silicon substitution. The widespread occurrence of such interactions in these compounds, and in other sulfoxides,[12] suggests that neutron-diffraction studies should be carried out in order to unambiguously define the exact hydrogen positions in these quasi hydrogen bonds.

Other intermolecular contacts in the crystal structures are of normal van der Waals type. Selected approach distances are listed in the Supplementary Material.

Experimental Section

NMR spectra were recorded on a Varian HA-100 spectrometer with $CDCl_3$, and chemical shifts are reported in ppm (δ) from internal tetramethylsilane. Infrared spectra were measured on a Perkin-Elmer 337 grating instrument as KBr disks. Melting points are corrected and were determined on a Thomas-Hoover apparatus. Mass spectra were obtained using a Hitachi-Perkin-Elmer RMU-6E spectrometer at an ionizing potential of 70 eV. Microanalyses were performed by Alfred Bernhardt, Engelskirchen, West Germany.

2-Triphenylsilyl-1,3-dithiane and 2-methyl-2-triphenylsilyl-1,3-dithiane were prepared as described in the literature.[13]

Preparation of *trans*-2-Triphenylsilyl-1,3-dithiane 1-Oxide (2). A solution containing 3.78 g (10 mmol) of 2-triphenylsilyl-1,3-dithiane in 50 mL of dichloromethane was cooled to −15 °C and *m*-chloroperoxybenzoic acid (2.03 g, 10 mmol) in 75 mL of dichloromethane was added dropwise. After standing overnight at −20 °C the solution was washed with 10% aqueous sodium carbonate and brine, dried (Na_2SO_4), and evaporated. The crude product (3.64 g) was a single isomer and was free of starting material, as evidenced by its NMR spectrum. Recrystallization from dichloromethane–ether gave pure **2** (2.28 g, 58%): mp 174.5–177 °C; IR (KBr) 1640, 1120, 1040 (S=O), 795, 748, 700, 630, 510, and 500; NMR ($CDCl_3$) δ 7.8–7.2 (m, 15, arom), 3.98 (s, 1, C-2 H), 3.5–3.2 (m, 1, C-6 eq H), and 2.9–2.2 (m, 5, ring H); mass spectrum (70 eV) *m/e* (rel intensity) 259 (100), 227 (30), 199 (70), 181 (30), 167 (35).

The analytical sample, mp 177.5–178.5 °C, was obtained by recrystallization from dichloromethane–ether.

Anal. Calcd for $C_{22}H_{22}OS_2Si$: C, 66.97; H, 5.62; S, 16.25. Found: C, 66.75; H, 5.53; S, 16.44.

Table IV. Crystal Data for 1 and 2

	1	2
Space group	$C2/c$	$P2_1/c$
a, Å	28.780 (6)	10.390 (3)
b, Å	11.901 (3)	9.988 (3)
c, Å	15.909 (3)	20.207 (12)
β, deg	130.93 (3)	97.61 (3)
ρ_{obsd}, g cm^{-3}	1.27	1.23
ρ_{calcd}	1.27	1.26
U, Å^3	4117	2079
Z	8	4
F (000)	1664	832
μ (Cu Kα), cm^{-1}	28	28
Crystal size, mm^3	0.3 × 0.3 × 0.4	0.4 × 0.5 × 0.2
Significant reflns	2182	2386
$2\theta_{max}$, deg	110	120

X-Ray Crystallographic Measurements. Crystal Data. Unit-cell symmetry and preliminary cell dimensions were derived from observations of systematic absences and measurements made on 25° precession photographs taken with Mo Kα radiation. For **1**, reflections occur only for hkl: $h + k = 2n$; $h0l$: $l = 2n$ ($h = 2n$); and $0k0$; ($k = 2n$); consistent with space groups Cc and $C2/c$. The distribution of intensity as a function of scattering angle indicates the presence of a center of symmetry and, hence, space group $C2/c$. With eight molecules in the unit cell, no molecular symmetry is implied. For **2**, the limiting conditions are $h0l$: $l = 2n$, and $0k0$: $k = 2n$, uniquely defining the space group as $P2_1/c$. Again, no molecular symmetry is implied. Accurate unit-cell dimensions were obtained by a least-squares fit to the diffractometer values of $\pm 2\theta$ for 20 strong general reflections from carefully centered crystals (λ = 1.5418 Å). Relevant data for the two compounds are presented in Table IV.

Intensity Data. Measurements of intensity for **1** and **2** were made using a Picker four-circle diffractometer controlled by an XDS Sigma 2 computer. Cu Kα radiation was used, made monochromatic by Bragg reflection from a highly oriented graphite crystal, with scintillation counting and pulse-height analysis. The θ–2θ scan method was used with a scan range of 2.5° and a scan speed of 2° min^{-1}. Background intensities were measured for 10 s at the beginning and end of each scan with the crystal and counter stationary. Measurements were made in each case, for a single quadrant of reciprocal space with the symmetry equivalent $0k\bar{l}$ reflections also measured to provide a check on crystal alignment. The deviation from the mean in these averaged intensities was typically <2%. Stability of the experimental conditions was monitored by measurement of three reference reflections after every 50 scans. The rms deviations about the mean intensities were 2.5%, fluctuations being random. Scattered intensity in a scan was taken as significantly above background at the 3σ level. No absorption corrections were applied, and intensities were converted to structure amplitudes in the usual way.

Structure Determination and Refinement. For **1**, the locations of the three heavy atoms (2S + Si) were determined from a sharpened three-dimensional Patterson function, and the phase problem was solved by the heavy-atom method using phases calculated for these three atoms (R = 0.54). Preliminary least-squares refinement of the parameters for Si, S, O, and C atoms (R = 0.08) enabled positions for the hydrogen atoms to be calculated [except for those of the C(7) methyl group which were located by a general-plane difference electron-density synthesis]. Continued refinement (3 × 3, 6 × 6 blocks) of all positional and anisotropic thermal parameters for all atoms other than H, for which isotropic B values were adopted, gave at convergence [$\Delta(p) < 0.2\ \sigma(p)$] conventional unweighted and weighted residuals of 0.041 and 0.048, respectively, for the observed reflections.

For **2**, the phase problem was solved using the FAME-MAGIC[14] direct-methods program. Reflections 340, 473, and 734 were given plus signs to determine the origin, and symbols were assigned to 14, 1, 4, 863, and 943. Of the top 400 $E(hkl)$, 393 were phased with $p > 0.98$, and the resulting E map correctly indicated the positions of 24 of the 26 heavy atoms in the molecule. The remaining atoms were found in the standard way from difference electron-density maps. The refinement proceeded in the same way as for **1**, save that the hydrogen atoms of the phenyl rings were included in the least-squares treatment in fixed positions with isotropic B values set equal to the equivalent isotropic B for the carbon of attachment. For the observed reflections, both the unweighted and weighted R values were 0.064. The higher

residual in this structure is probably associated with the generally higher level of thermal vibration in **2** than in **1**.

In each case, a conventional weighting scheme was used.[15] Scattering curves for the nonhydrogen atoms were taken from Hanson, Herman, Lea, and Skillman,[16] and allowance was made for the real part of the anomalous dispersion terms for Si, S, and O.[17] For hydrogen, the curve of Stewart, Davidson, and Simpson was used.[18] Programs used, other than FAME-MAGIC and ORTEP for which a CDC 6400 computer was used, were written in this laboratory for the Sigma 2 computer.

Registry No.—**1**, 13433-56-2; **2**, 63883-55-6; **4**, 60349-76-0; 2-triphenylsilyl-1,3-dithiane, 13433-53-9.

Supplementary Material Available. Anisotropic thermal parameters, selected nonbonded intramolecular contact distances, intermolecular contacts, and information on least-squares mean planes of interest (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Presented, in part, at the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1974, and at the 10th International Union of Crystallography Congress, Amsterdam, Netherlands, August 1975; see: *Acta Crystallogr., Sect. A*, **31**, S166 (1975).
(2) F. A. Carey, O. D. Dailey, Jr., O. Hernandez, and J. R. Tucker, *J. Org. Chem.*, **41**, 3975 (1976).
(3) The directly analogous 2-triphenylsilyl-1,3-dithiane was prepared for comparison with **2**, but crystal twinning prevented a successful x-ray analysis. Use of **1** allows a check on the effect of oxygenation and of triphenylsilyl substitution and throws light on the effect of additional axial substitution at C(2).
(4) F. A. Carey, P. M. Smith, R. J. Maher, and R. F. Bryan, *J. Org. Chem.*, **42**, 961 (1977).
(5) For a theoretical treatment, see: N. L. Allinger and J. Kao, *Tetrahedron*, **32**, 529 (1976).
(6) A. T. McPhail, K. D. Onan, and J. Koskimies, *J. Chem. Soc., Perkin Trans. 2*, 1004 (1976).
(7) R. F. Bryan, F. A. Carey, O. D. Dailey, Jr., R. Maher, and R. W. Miller, *J. Org. Chem.*, accompanying paper in this issue.
(8) C. K. Johnson, "ORTEP-II, A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations", ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1976.
(9) Values of geometrical parameters for 2-phenyl-1,3-dithiane are taken from H. T. Kalff and C. Romers, *Acta Crystallogr.*, 20, 490 (1966).
(10) (a) A. Domenicano, A. Vaciago, and C. A. Coulson, *Acta Crystallogr., Sect. B*, **31**, 221 (1975); (b) A. Domenicano, P. Mazzeo, and A. Vaclago, *Acta Crystallogr., Sect. A*, **31**, S117 (1976); (c) A. Domenicano, A. Vaciago, and C. A. Coulson, *Acta Crystallogr., Sect. B*, **31**, 1630 (1975).
(11) M. Colapietro, A. Domenicano, and A. Vaciago, *Acta Crystallogr., Sect. A*, **31**, S117 (1975).
(12) A comparable nonbonded interaction occurs intramolecularly in (−)-*o*-carboxyphenyl methyl sulfoxide, but excited no comment. See: B. Dahlén, *Acta Crystallogr., Sect. B*, **30**, 642, (1974).
(13) A. G. Brook, J. M. Duff, P. F. Jones, and N. R. Davis, *J. Am. Chem. Soc.*, **89**, 431 (1967).
(14) E. B. Fleischer, R. B. K. Dewar, and A. L. Stone, *Abstr. Am. Crystallogr., Assoc. Atlanta*, 20 (1967).
(15) D. F. Grant, R. C. G. Killean, and J. L. Lawrence, *Acta Crystallogr., Sect. B*, **25**, 374 (1969).
(16) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr.*, **17**, 1040 (1964).
(17) D. T. Cromer and D. Liberman, *J. Chem. Phys.*, **53**, 1891 (1970).
(18) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1969).

Optically Active 1,3-Dithiane 1-Oxide: Optical Resolution and Absolute Configuration

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1,3-Dithiane 1-oxide (**1**) has been resolved into its enantiomers by two methods, both based on separation of D(+)-camphor adducts followed by base-catalyzed cleavage back to **1** and camphor. Reaction of the lithio derivative of (±)-**1** with D(+)-camphor gives a mixture of diastereomeric adducts **2** and **3**, either of which may be isolated depending on the temperature at which the reaction is carried out and the isolation procedure adopted. Diastereomer **2** was cleaved to (−)-**1** on treatment with potassium hydroxide in *tert*-butyl alcohol, whereas similar treatment of **3** yielded (+)-**1**. Oxidation of (2*R*)-2-(1,3-dithian-2-yl)isoborneol (**4**) with *m*-chloroperoxybenzoic acid gave a mixture of diastereomeric sulfoxides from which **3** could be isolated. The absolute configuration of (−)-**1** is *S* as determined by x-ray crystallographic characterization of its precursor **2**. Crystals of **2** conform to space group $P2_12_12_1$ with a = 23.890 (7), b = 9.336 (4), c = 6.727 (3) Å, and Z = 4. The valence angle of 112.8° found for S–C–S in the dithiane moiety of **2** is identical with that found in *cis*-2-phenyl-1,3-dithiane 1-oxide.

The stereochemical properties of 1,3-dithiane 1-oxide (**1**) and its derivatives are receiving much attention. Questions of conformation have been studied experimentally[1-3] and probed by molecular mechanics.[4] These investigations, together with x-ray crystallographic studies,[5] have revealed significant structural effects associated with cross-ring electrostatic interactions. The stereoselectivity of formation of diastereomeric derivatives of **1** by oxidation of 2-substituted 1,3-dithianes[1,6] and by the reaction of the 2-lithio derivative of **1** with electrophilic reagents has been determined.[7]

Since **1** is a chiral molecule, other aspects of stereochemistry may be explored as well. Asymmetric synthesis, for example, would use optically active **1** as a chiral carbonyl equivalent group. The synthetic value of carbonyl equivalents in nucleophilic acylation reactions is well established.[8] Many useful transformations involving 1,3-dithiane[9] and methyl methylthiomethyl sulfoxide[10] have been described which embody this concept. Considerable success in asymmetric synthesis has also been achieved by Meyers using (4*S*,5*S*) 2-substituted 4-methoxymethyl-5-phenyl-2-oxazolines as chiral carbonyl equivalents.[11]

A number of techniques have been developed for the preparation of optically active sulfoxides.[12] Sulfinyl-group transfers from optically active sulfinate esters on reaction with organometallic reagents have proven particularly useful[13] but are not appropriate for **1**. Oxidations of unsymmetrical sulfides with optically active peroxy acids have been reported, but normally with low optical yields.[12] We envisioned generation of optically active **1** by base-catalyzed cleavage of a single stereoisomer of a β-hydroxyalkyl sulfoxide (eq 1). The process

(1)

is then one of resolution whereby separation of a mixture of diastereoisomers and subsequent cleavage lead to optically

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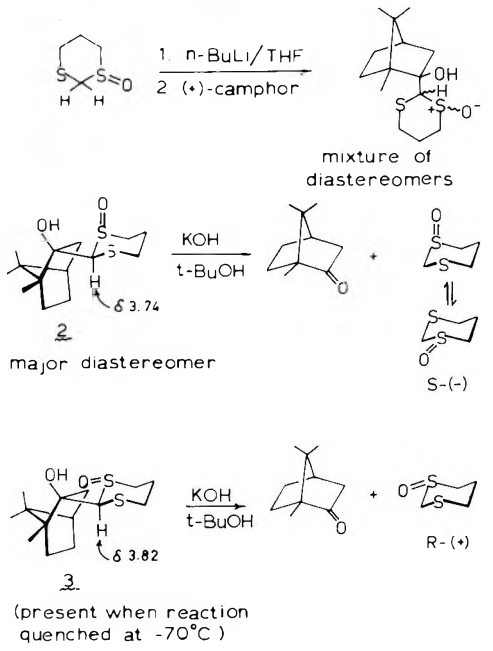
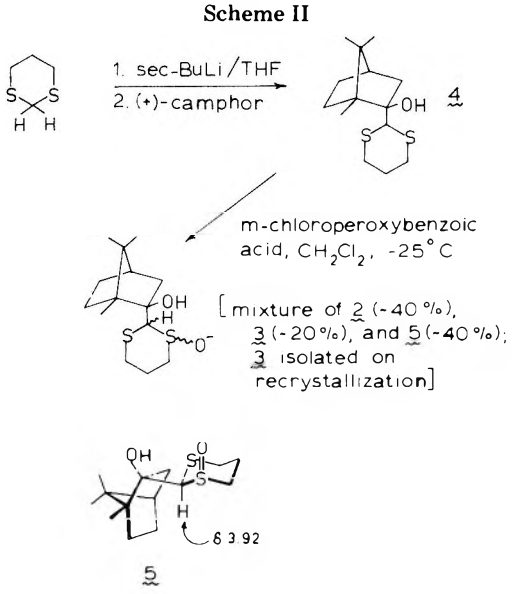
Scheme I



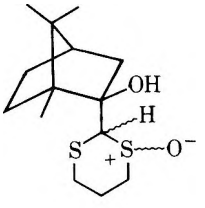
Scheme II



active sulfoxide. In principle, the technique could be extended to other systems in which the chiral atom is one which can stabilize an adjacent carbanion. This paper reports the successful optical resolution of **1** by this method and the determination of the absolute configurations of its enantiomeric forms by x-ray crystallographic methods, making use of the known absolute configuration of camphor as an internal reference center.[14]

Results and Discussion

Optical Resolution. The β-hydroxyalkyl sulfoxides chosen for study were the stereoisomeric 2-(1,3-dithian-2-yl)isoborneol 1′-oxides having the general structure A. Since these



A

adducts are formed by organometallic addition to D(+)-camphor, highly stereoselective attack from the endo face is assumed. There are then just two chiral centers of variable configuration and four diastereoisomeric forms of A to be considered. Two distinct procedures, described in Schemes I and II, were developed for formation of diastereoisomers of A. As anticipated, these adducts are labile in base and are readily cleaved to (+)-camphor and the corresponding (+)- or (−)-**1** on treatment with potassium hydroxide in refluxing *tert*-butyl alcohol.

The first route (Scheme I) involves reaction of 2-lithio-1,3-dithiane 1-oxide[7,15] with D(+)-camphor to yield a mixture of diastereomeric adducts together with unreacted (and partially resolved) **1**. The composition of the product mixture is extremely sensitive to the experimental conditions. When the reaction was carried out at − 70 °C and allowed to warm to +15 °C before quenching, the recovered unreacted **1** (19%) had a specific rotation of +75°. The NMR spectrum of the adduct mixture revealed the presence of two diastereoisomers characterized by signals for the C(2) proton of the dithiane oxide ring at δ 3.74 and 3.92 ppm, with the former present in slightly greater amount. Chromatography and recrystallization gave the δ 3.74 material as a pure diastereomer: mp 190.5–192 °C; $[\alpha]^{20}_D$ −74.4° (c 2.7, ethanol). The structure of this adduct was established as (2*R*)-2-[(1*S*,2*R*)-1,3-dithian-2-yl]isoborneol 1′-oxide (**2**) by single-crystal x-ray analysis. Base-catalyzed cleavage of **2** occurred readily to give (*S*)-(−)-**1**; $[\alpha]^{20}_D$ −223° (c 1, ethanol).

If the reaction was both carried out and quenched at −65 to −75 °C, then the **1** recovered from the reaction mixture (14%) had a rotation of −111°. The crude product contained, in addition to the two diastereoisomers observed previously, a third adduct having a signal for its C(2) proton at δ 3.82 ppm. As estimated by NMR, the ratio of the δ 3.74, 3.82, and 3.92 diastereomers was 44:37:19. The δ 3.82 diastereomer **3** is the least soluble of these and was obtained in pure form, mp 216–217.5 °C and $[\alpha]^{24}_D$ +25° (*c* 1.3, chloroform), after recrystallization. Base-catalyzed cleavage of **3** gave (+)-**1**, $[\alpha]^{20}_D$ +230° (c 1.0, ethanol), in 94% yield.

Structure **3**, (2*R*)-2-[(1*R*,2*R*)-1,3-dithian-2-yl]isoborneol 1′-oxide can be assigned to the δ 3.82 diastereomer both from its cleavage to (*R*)-(+)-**1** and from its NMR (^{13}C and ^{1}H) spectra. The ^{13}C chemical shift of C(2′) is sensitive to the orientation of the sulfoxide oxygen.[16] For six trans 2-substituted 1,3-dithiane 1-oxides (equatorial oxygen) studied, the chemical shifts of C(2) were 15.0–19.5 ppm farther downfield than for C(2) for the corresponding 2-substituted 1,3-dithianes.[17] For four cis 2-substituted 1,3-dithiane 1-oxides (axial oxygen), the C(2) chemical shifts were 9.5–12.6 ppm farther downfield than for the corresponding 2-substituted 1,3-dithianes.[17] The ^{13}C chemical shift of C(2) of the dithiane ring moiety of 2-(1,3-dithianyl)isoborneol (**4**) is 61.30 ppm. Compound **2** (axial oxygen by x-ray structure determination) has its C(2) signal at 70.38 ppm, corresponding to $\Delta\delta$ = 9.08 ppm, whereas compound **3** has its C(2) signal at 77.90 ppm, corresponding to $\Delta\delta$ = 16.60 ppm. Therefore, the sulfoxide oxygen must be equatorial in this diastereomer. An equatorial oxygen is also indicated by the proton NMR spectrum which shows a multiplet, assigned to the C(6) equatorial proton of the dithiane ring, at 3.2–3.6 ppm. Evidence has been presented previously that a signal in this region is characteristic of trans 2-monosubstituted 1,3-dithiane 1-oxides.[6,7] The stereoisomer of A which has an equatorial sulfoxide oxygen and which is related to (*R*)-(+)-**1** by cleavage can only by **3**.

The second route (Scheme II) uses the dithiane (**4**), prepared from 2-lithio-1,3-dithiane and D(+)-camphor. Oxidation of **4** with *m*-chloroperoxybenzoic acid in dichloromethane at −25 °C yields a mixture of three diastereomeric oxides in a ratio of about 2:1:2, as determined by integration of the

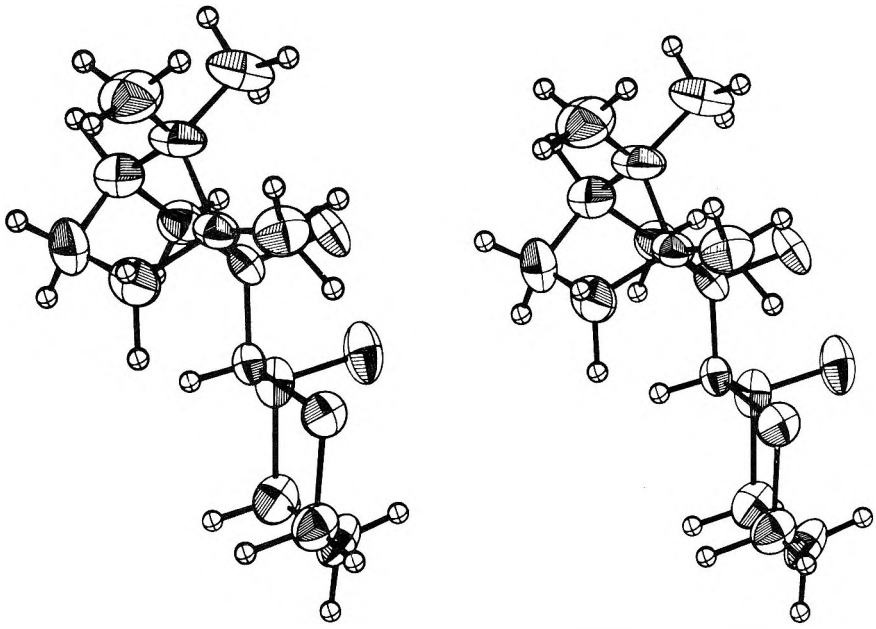


Figure 1. ORTEP drawing of the structure of **2**. Thermal ellipsoids for S, O, and C are drawn with the 50% probability level as boundary surface. Hydrogen atoms, where located, are represented by spheres of arbitrary radius.

NMR signals at δ 3.92 (**5**), 3.82 (**3**), and 3.74 (**2**), respectively. Direct base-catalyzed cleavage of this mixture yielded **1** having $[\alpha]_D$ +38°. Since **2** is related to (−)-1 and **3** to (+)-1, the δ 3.92 component must yield (+)-1 on cleavage and therefore has the *R* configuration at sulfur. Structure **5**, (*R*)-2-[(1*R*,2*S*)-1,3-dithian-2-yl]isoborneol 1′-oxide, may therefore be assigned to the δ 3.92 diastereomer.

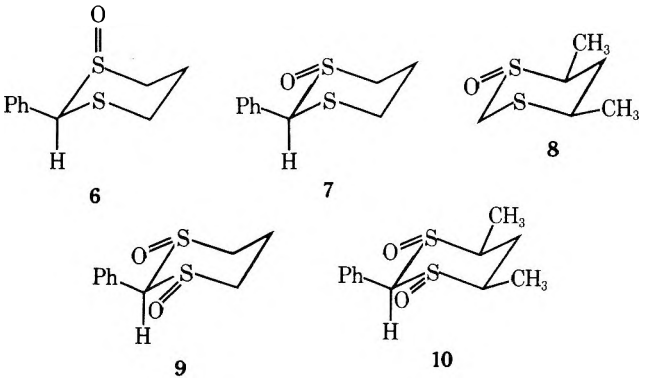
Recrystallization of the crude mixture of **2, 3,** and **5** leads to the isolation of **3** (the least soluble component), mp 215–217 °C. Base-catalyzed cleavage of **3** gave (+)-1, $[\alpha]^{21}_D$ +225° (*c* 1.3, ethanol).

The procedure in Scheme II is not as efficient as either of the modifications of Scheme I. Condensation of 2-lithio-1,3-dithiane with (+)-camphor proceeds in only 49% yield to **4**. The corresponding reaction of 2-lithio-1,3-dithiane 1-oxide with (+)-camphor gives yields of 56–83%, depending on the conditions used, along with recovered (and optically active) **1**. Moreover, the diastereoisomer which is obtained on recrystallization corresponds to only about 20% of the mixture of oxides formed by oxidation of **4**. A considerable degree of flexibility exists in that not only does Scheme I allow the isolation of either (*R*)- or (*S*)-**1**, depending on conditions, but also the commercial availability of both enantiomers of camphor permits the isolation of (*R*)- or (*S*)-**1** by proper choice of starting materials.

Absolute Configuration. Because cleavage of **2** to (−)-**1** is a process which does not involve the chiral sulfoxide group, the absolute configuration of (−)-**1** may be determined by relation to the structure of **2**. The absolute configuration of (+)-camphor is known, and its use as a potential internal reference center in the x-ray determination of absolute configuration has been explicitly mentioned.[18] The assignment of absolute configuration to **2** made in this way has also been independently confirmed by taking into account the anomalous scattering terms for sulfur in separate structure factor calculations for each of the two enantiomers of **2** where a clear preference for the enantiomer embodying the (+)-camphor structure emerged.[19]

An ORTEP[20] view of **2** is shown in Figure 1. Positional and thermal parameters are given in Table I, and the numbering scheme, bond lengths, valence angles, and torsion angles in **2** are illustrated in Figure 2.[21] The configuration of the sulfoxide group is *S*. The dithiane ring is in a chair conformation with the sulfoxide oxygen axial and the 2-hydroxyl-1,7,7-trimethylbicyclo[2.2.1]heptyl group equatorial.

It is of interest to compare certain structural features of **2** with other derivatives of **1** for which x-ray crystallographic data have been reported. These include: the axial sulfoxide, *cis*-2-phenyl-1,3-dithiane 1-oxide (**6**);[5b] two equatorial oxides, *trans*-2-phenyl-1,3-dithiane 1-oxide (**7**)[5b] and *r*-4,c-6-dimethyl-1,3-dithiane *t*-1-oxide (**8**);[5a] and two diequatorial dioxides, 2-phenyl-1,3-dithiane *trans*-1,*trans*-3-dioxide (**9**)[5b] and *r*-4, c-6-dimethyl-1,3-dithiane *t*-1,*t*-3-dioxide (**10**).[5a] The



axial oxides **2** and **6** are slightly less puckered (sum of torsion angles = 371° and 375°, respectively) than the equatorial oxides **7** (381°), **8** (382°), **9** (389°), and **10** (400°) (Table II). All of the oxides are more puckered than 2-phenyl-1,3-dithiane (**11**, 348°)[22] or *r*-4,*c*-6-dimethyl-1,3-dithiane (**12**, 366°).[5a]

Electrostatic interactions between the sulfoxide group and the cross-ring sulfur, as reflected in the S(1)–C(2)–S(3) valence angle, have been discussed previously.[5] This angle in **2** (112.8°) is identical, within the limits of error, with that found for the other axial oxide **6** (112.9°). Both are larger than the angles found in the equatorial oxides **7** (109.6°) and **8** (110.0°).

The pattern of S–C bond distances (Table III) follows that seen in **6, 7,** and **9**, where it was observed that the S(1)–C(2) distance is significantly longer than the S(1)–C(6) distance (1.842 vs. 1.803 Å in **2**). The situation is reversed in **8** and **10**, where S(1)–C(2) is shorter than S(1)–C(6) (1.805 Å vs. 1.828 Å in **8** and 1.812 Å vs. 1.821 Å in **10**). McPhail[5a] has suggested

Table I. Atomic Parameters for 2[a]

Atom	x	y	z	B
S(1′)	−138.2 (5)	2298.6 (13)	6851.4 (18)	3.46
S(3′)	182.9 (5)	3193.8 (13)	2653.3 (20)	3.68
C(2′)	382 (2)	2181 (5)	4839 (7)	2.62
C(4′)	−479 (2)	2359 (6)	2054 (8)	4.24
C(5′)	−900 (2)	2503 (6)	3704 (10)	4.58
C(6′)	−742 (2)	1643 (6)	5524 (9)	4.15
C(1)	1479 (2)	2578 (5)	4342 (8)	3.44
C(2)	940 (2)	2714 (5)	5710 (7)	2.87
C(3)	1111 (2)	1825 (6)	7545 (8)	4.00
C(4)	1688 (2)	1205 (6)	6992 (11)	5.14
C(5)	1589 (3)	80 (6)	5343 (13)	6.19
C(6)	1462 (2)	1023 (6)	3535 (10)	4.80
C(7)	1964 (2)	2452 (7)	5898 (9)	4.74
C(8)	2074 (3)	3790 (8)	7150 (11)	6.10
C(9)	2537 (3)	2073 (8)	4931 (13)	6.94
C(10)	1553 (2)	3734 (7)	2768 (9)	4.95
O(1′)	−230 (2)	3849 (4)	7252 (6)	4.95
O(2)	877 (2)	4216 (3)	6167 (6)	4.17

[a] Positional parameters (for hydrogen atoms are provided in the microfilm edition; see footnote on supplementary material) are given as fractions of the unit cell edges (×10⁴) with esd's, in parentheses on the same scale. Equivalent isotropic thermal parameters are given in Å². (Anisotropic thermal parameters for S, O, and C and isotropic *B* values for hydrogen atoms are given in the microfilm edition.)

Table II. Endocyclic Torsion Angles for 1,3-Dithiane Systems (Deg)

Central bond	Compound							
	11[a]	2	6[b]	7[b]	9[b]	12[c]	8[c]	10[c]
S(1)–C(2)	57	57	59	63	61	62	68	67
C(2)–C(3)	−57	−58	−61	−63	−60	−62	−67	−67
S(3)–C(4)	56	60	62	61	61	57	58	62
C(4)–C(5)	−63	−68	−68	−64	−72	−64	−62	−72
C(5)–C(6)	61	69	67	67	73	64	65	72
C(6)–S(1)	−54	−59	−58	−63	−62	−57	−63	−62

[a] Data of Kalff and Romers; see ref 22. [b] See ref 5b. [c] Data of McPhail et al., see ref 5a.

that the bond-length differences in 8 and 10 simply depend on the degree of substitution at the carbon atoms involved—the shorter bonds always involving the methylene carbon atom. All of the results, including those not known to McPhail at the time his suggestion was made, are consistent with this generalization; **2**, **6**, **7**, and **9** are unsubstituted at C(6), whereas **8** and **10** are unsubstituted at C(2).

Turning briefly to the bicyclo[2.2.1]heptyl moiety, the distortion which results from substitution at C(2) can be considered as a partial pseudorotation of a cyclopentane envelope. This is conveniently described in Figure 3 after the work of Altona and Sundaralingam.[23] The synchro (−,−) twist observed in **2** is also seen in (+)-10-bromo-2-*exo*-chloro-2-nitrosocamphane[24] and in (−)-2-*exo*-bromo-2-nitrocamphane,[25] the only two reported camphane structures substituted at C(2). Particularly unfavorable gauche interactions about the C(1)–C(2) bond lead to opening of the C(1)–C(2)–C(2′) and S(3′)–C(2′)–C(2) valence angles to 117.1° and 111.6°, respectively, as opposed to the corresponding C(3)–C(2)–C(2′) and S(1′)–C(2′)–C(2) angles of 111.7° and 106.6°. For the same reason the C(1)–C(2) bond is lengthened to 1.588 Å. A similar situation is found in 1,3-biapocamphane,[26] leading, in that compound, to a value of 119.6 for the corresponding C–C–C angle and to a C–C bond length of 1.584 Å. The remaining features of the camphane system in **2** are comparable to those found in related structures[27] (though our

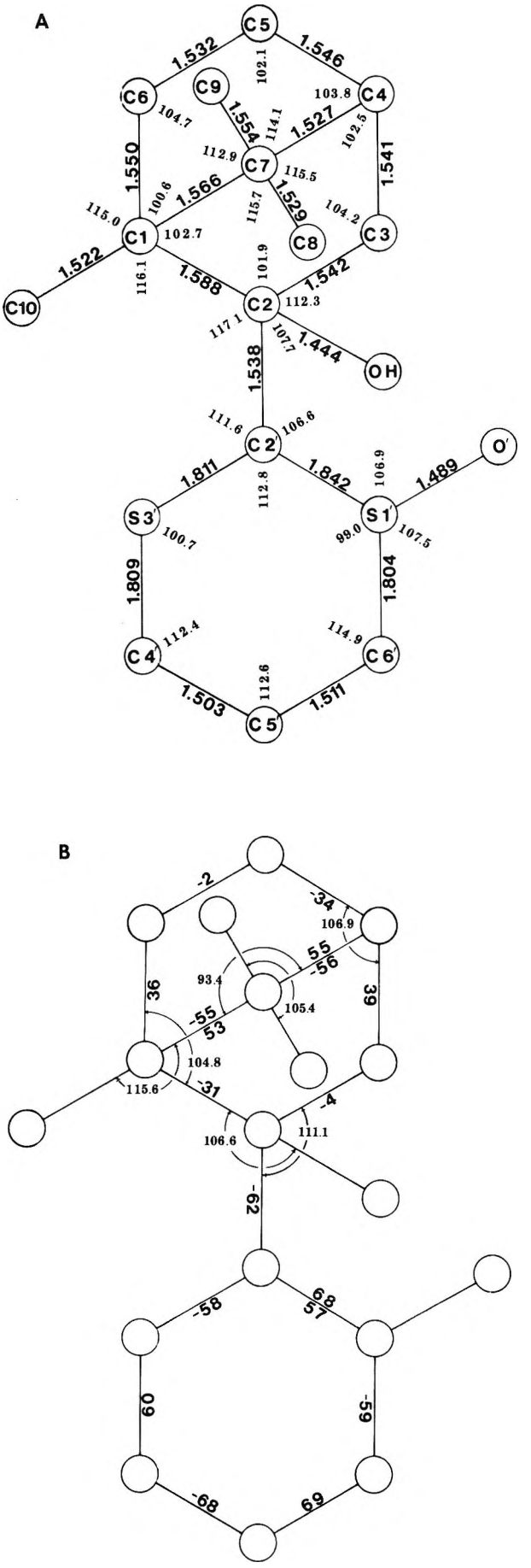


Figure 2. (a) Bond lengths (Å) and bond angles (deg) in **2**. Esd's are S–C 0.005 Å, S–O 0.003 Å, C–C 0.010 Å C–S–C 0.2°, C–S–O 0.2°, S–C–S 0.2°, S–C–C 0.4°, C–C–C 0.6°. (b) Torsion angles in **2** and remaining bond angles.

Table III. 1,3-Dithiane Ring Bond Lengths (Å)

Bond	Compound							
	11[a]	2	6[b]	7[b]	9[b]	12[c]	8[8]	10[c]
S(1)–C(2)	1.79	1.842 (4)	1.843 (3)	1.830 (2)	1.834 (5)	1.791 (5)	1.805 (3)	1.812 (5)
S(3)–C(2)	1.80	1.811 (4)	1.797 (3)	1.814 (2)	1.833 (4)	1.792 (5)	1.797 (3)	1.821 (6)
S(1)–C(6)	1.81	1.804 (5)	1.803 (3)	1.806 (2)	1.803 (5)	1.825 (4)	1.828 (2)	1.821 (5)
S(3)–C)4)	1.83	1.809 (5)	1.812 (3)	1.808 (2)	1.787 (5)	1.822 (4)	1.823 (3)	1.819 (5)
C(4)–C(5)	1.46	1.503 (7)	1.508 (4)	1.506 (3)	1.513 (8)	1.523 (5)	1.522 (3)	1.524 (7)
C(5)–C(6)	1.51	1.51[2] (8)	1.512 (4)	1.519 (2)	1.513 (6)	1.513 (6)	1.527 (4)	1.505 (8)

[a] Data from ref 22. [b] Data from ref 5b. [c] Data from ref 5a.

Table IV. Endocyclic Valence Angles (Deg) for 1,3-Dithiane Systems

Central atom	Compound							
	11[a]	2	6[b]	7[b]	9[b]	12[c]	8[c]	10[c]
S(1)	101	99.0 (2)	98.7 (2)	98.2 (2)	96.9 (2)	99.0 (2)	97.1 (1)	96.4 (2)
S(3)	99	100.7 (2)	99.2 (2)	100.5 (2)	97.0 (2)	99.4 (2)	99.7 (1)	96.7 (2)
C(2)	115	112.8 (2)	112.9 (2)	109.6 (2)	114.2 (3)	114.5 (3)	110.0 (1)	112.5 (3)
C(4)	116	112.4 (4)	112.6 (2)	113.0 (2)	113.4 (4)	112.7 (3)	112.2 (2)	109.1 (3)
C(5)	117	112.6 (4)	113.0 (3)	113.3 (2)	111.2 (4)	116.7 (3)	116.3 (2)	115.5 (4)
C(6)	115	114.9 (4)	114.6 (2)	114.0 (2)	112.0 (3)	112.9 (3)	111.9 (2)	109.8 (3)

[a] Data of ref 22. [b] Data of ref 5b. [c] Data of ref 5a.

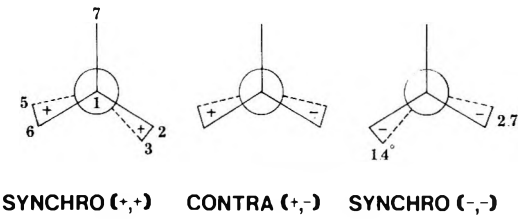


Figure 3. Projections along the C(1)···C(4) axis of the camphane moiety showing possible modes of twist and the values observed for **2**.

results appear to be the most accurate thus far obtained for this system) and are not discussed further.

All intermolecular distances correspond to normal van der Waals separations. The S–O bonds of neighboring molecules have their dipoles aligned, but the nonbonded S···O separations of 3.39 Å are greater than the sum of the van der Waals radii of the atoms involved (3.22 Å).[27] The sulfoxide oxygen atom appears to act as an acceptor in an intramolecular O–H···O hydrogen bond involving the isoborneol hydroxy group (O···O 2.77 Å) but the hydrogen atom involved has not been definitively located.

Experimental Section

Infrared spectra (IR) were obtained on a Perkin-Elmer 337 grating spectrometer as KBr disks or thin films and were calibrated with either the 1601- or 1028-cm^{-1} band of polystyrene. Melting points are corrected and were measured on a Thomas-Hoover apparatus. Optical rotations were measured at ambient temperatures on a Perkin-Elmer 141 polarimeter using a 1-dm tube. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia, and by Alfred Bernhardt, Engelskirchen, West Germany. Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6E spectrometer at 70 eV. Carbon-13 NMR spectra were recorded using a JEOL-PS 100P/EC-100 Fourier transform spectrometer. The operating conditions are described in ref 17. Proton NMR spectra were obtained at 60 MHz using a Hitachi-Perkin-Elmer R-20 instrument.

All metalation reactions were carried out under nitrogen in a three-necked flask equipped with thermometer, serum cap, nitrogen inlet, and drying tube (Drierite). Tetrahydrofuran (THF) and diisopropylamine were distilled from calcium hydride and stored over 4A molecular sieves under argon. *n*-Butyllithium in *n*-hexane and *sec*-butyllithium in *n*-hexane were supplied by Alfa Inorganics.

(2*R*)-2-[(1*S*,2*R*)-1,3-Dithian-2-yl]isoborneol 1'-Oxide (2).[28] A slurry of 6.81 g (50.0 mmol) of 1,3-dithiane 1-oxide (1) in 125 mL of THF was treated with 21 mL (50 mmol) of 2.4 M *n*-butyllithium at −70 to −60 °C. After stirring for 1 h at −70 °C, 7.61 g (50.0 mmol) of D(+)-camphor dissolved in 20 mL of THF was added rapidly via a dropping funnel. The mixture was stirred for 1 h, then allowed to warm to 15 °C, and quenched with 25 mL of saturated ammonium chloride solution. The THF was evaporated, 100 mL of saturated ammonium chloride was added to the residue, and the product was extracted in chloroform (two 100-mL portions). The combined chloroform layers were washed with 100 mL of brine and dried over sodium sulfate. After removal of solvent, the crude product was purified by column and thin-layer chromatography to give 8.134 g (56%) of a mixture of diastereomeric adducts along with 1.276 g (18.7%) of recovered **1**, mp 82–91 °C, $[\alpha]^{20}_D$ +74.8° (*c* 3.2, ethanol). Recrystallization of crude **1** from cyclohexane/dichloromethane gave material melting at 89.5–94 °C and with $[\alpha]^{20}_D$ +92.2° (*c* 1.05, ethanol). The NMR spectrum of the crude mixture of diastereomers showed singlets at δ 3.74 and 3.92, corresponding to the C(2) proton on the dithiane ring. The mixture of diastereomers was recrystallized five times from dichloromethane/ether and twice from ethanol, yielding 546 mg of pure **2**: mp 194.5–195 °C; $[\alpha]^{20}_D$ −74.4° (*c* 2.7, ethanol); IR (KBr) 3365 (OH) and 1025 cm^{-1} (S=O); NMR ($CDCl_3$) δ 0.83 (s, 3, CH_3), 1.06 (s, 3, CH_3), 1.08 (s, 3, CH_3), 1.2–2.0 (m, 7, remaining isoborneol skeletal H), 2.1–3.4 (m, 7, dithiane ring protons and OH), and 3.74 ppm [s, 1, C(2') H]; mass spectrum *m/e* (rel intensity) 288 (17), 271 (35), 166 (100), 165 (51), 151 (45), 137 (57), 123 (64), 109 (65), 95 (87), 81 (80).

Anal. Calcd for $C_{14}H_{24}O_2S_2$: C, 58.29; H, 8.39; S, 22.23. Found: C, 58.32; H, 8.39; S, 22.29.

Base-Catalyzed Cleavage of 2. A 450-mg (1.56 mmol) portion of **2** was treated with 104 mg (1.58 mmol) of 85% potassium hydroxide in refluxing *tert*-butyl alcohol under nitrogen for 3 h. After cooling, saturated ammonium chloride was added to the reaction mixture. The *tert*-butyl alcohol was removed in vacuo, and the residue was partitioned between brine and chloroform. The layers were separated, and the aqueous phase was extracted with a second portion of chloroform. The combined chloroform layers were dried over sodium sulfate. Removal of solvent provided a mixture of (−)-**1** and (+)-camphor which was washed with cyclohexane to remove the camphor. The residual (−)-**1** (201 mg, 95%) had mp 103–105 °C, $[\alpha]^{20}_D$ −192° (*c* 2.1; ethanol). Recrystallization from cyclohexane/dichloromethane gave white crystals: mp 108.2–109.4 °C, $[\alpha]^{20}_D$ −224° (*c* 0.85, ethanol).

(2*R*)-2-[(1*R*,2*R*)-1,3-Dithian-2-yl]isoborneol 1'-Oxide (3). *n*-Butyllithium (50.0 mmol) was added to a slurry of 6.81 g (50.0 mmol) of **1** in 125 mL of THF at −75 to −65 °C. After stirring at −75 °C for 1 h, a solution of D(+)-camphor (50.1 mmol) in 20 mL of THF was added dropwise over a 10-min period (temperature never exceeding −68 °C). After stirring at −75 °C for 1 h, 25 mL of saturated ammonium chloride solution was added and the mixture allowed to warm up to room temperature overnight. Workup furnished 16.36 g of creamy white solid, containing 44% **2** and 37% **3**, which was placed

on a column containing 90 g of silica gel 60. Unreacted camphor and nonpolar impurities were eluted with 300 mL of carbon tetrachloride, 550 mL of 2% 2-propanol/carbon tetrachloride, and 375 mL of 3% 2-propanol/carbon tetrachloride. Elution with 850 mL of 5% 2-propanol/carbon tetrachloride afforded 7.68 g of product. Further elution with 700 mL of 8% 2-propanol/carbon tetrachloride gave 1.53 g of diastereomers and unreacted **1**. Pure 1,3-dithiane 1-oxide (757 mg) was obtained upon elution with 250 mL of 8% 2-propanol/carbon tetrachloride, 775 mL of 10% 2-propanol/carbon tetrachloride, and 250 mL of 20% 2-propanol/carbon tetrachloride. A quantity of diastereomer **3** (1.72 g, mp 190–192 °C) failed to dissolve in the solvent used for loading the column.

Purification of fractions containing **1**, diastereomers, and impurities by TLC (silica gel; 20% 2-propanol/carbon tetrachloride) yielded an additional 225 mg of **1**, 501 mg of a mixture of diastereomers, and 726 mg of pure **3**, mp 214–217 °C. Recrystallization of the mixture of diastereomers (8.18 g) from ether/dichloromethane afforded 2.452 g of **3**, mp 216–217.5 °C. The isolated **3** (4.90 g total, 34%) was further purified by recrystallization from ethanol giving 3.53 g (24.5%) of pure material melting at 216–218 °C: $[\alpha]^{20}_D$ +25.9° (c, 1.3, $CHCl_3$); IR (KBr) 3215 (OH) and 1010 cm^{-1} (S=O); NMR ($CDCl_3$) 0.83 (s, 3, CH_3), 1.06 (s, 3, CH_3), 1.09 (s, 3, CH_3), 1.2–3.1 (m, 13), 3.1–3.6 [m, 1, C(6′) eq H], and 3.82 ppm [s, 1, C(2′) H]; mass spectrum *m/e* (rel intensity) 288 (14), 271 (23), 166 (100), 165 (50), 151 (53), 137 (56), 123 (74), 109 (58), 95 (45), 90 (52), 81 (58).

Anal. Calcd for $C_{14}H_{24}O_2S_2$: C, 58.29; H, 8.39; S, 22.23. Found: C, 58.25; H, 8.41, S, 22.29.

The unreacted 1,3-dithiane 1-oxide (982 mg) isolated had $[\alpha]^{24}_D$ −111° (c, 1.2, ethanol).

Base-Catalyzed Cleavage of 3. Using the procedure previously described for **2**, 3.14 g (10.9 mmol) of **3** gave 1.40 g (94%) of (*R*)-(+)-**1**: mp 108.4–109.3 °C, $[\alpha]^{24}_D$ +227° (*c* 1.0, ethanol). After recrystallization from cyclohexane/dichloromethane, material with mp 108–111 °C and $[\alpha]^{20}_D$ +230° (*c* 1.0, ethanol) was obtained.

(2*R*)-2-(1,3-Dithian-2-yl)isoborneol (4). To a solution of 6.01 g (50.0 mmol) of 1,3-dithiane in 75 mL of THF was added 38.5 mL (50 mmol) of 1.3 M *sec*-butyllithium at −50 to −30 °C. The reaction mixture was stirred at −30 to −20 °C for 1 h and then warmed to −10 °C. Thereupon, 7.61 g (50.0 mmol) of D(+)-camphor dissolved in 20 mL of THF was added at −10 to 0 °C. The reaction mixture was stirred at 0 to 20 °C for 12 h, and following the usual workup 13.06 g of crude product was obtained. The NMR spectrum of this material indicated that the reaction was 49% complete. A combination of recrystallization from cyclohexane and sublimation at 100 °C and 0.35 Torr afforded 5.54 g (41%) of purified **4** (mp 122 °C). Recrystallization from ether gave the analytical sample: mp 125.5–127 °C; $[\alpha]^{20}_D$ +2.9° (*c* 1.5, ethanol); IR (KBr) 3500 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 1.05 (s, 3, CH_3), 1.08 (s, 3, CH_3), 1.20–2.23 (m, 9), 2.31 (s, 1, OH), 2.7–3.1 [m, 4, C(4′) and C(6′) H], and 4.22 ppm [s, 1, C(2′) H]; mass spectrum *m/e* (rel intensity) 272 (6), 254 (6), 153 (100), 135 (65), 120 (98), 119 (90), 109 (60), 97 (69), 95 (71), 69 (67), 55 (57), 41 (86).

Anal. Calcd for $C_{14}H_{24}OS_2$: C, 61.71; H, 8.88; S, 23.54. Found: C, 61.87; H, 8.95; S, 23.37.

***m*-Chloroperoxybenzoic Acid Oxidation of 4.** A solution of 4.80 g (23.6 mmol) of 85% *m*-chloroperoxybenzoic acid in 80 mL of dichloromethane was added dropwise at −25 to −15 °C to a solution of 6.40 g (23.5 mmol) of **4** in 120 mL of dichloromethane over a 1-h period. The resultant slurry was stirred at −25 °C for 1 h and then stored at −25 ° C overnight. The reaction mixture was washed with 100 mL of 10% sodium carbonate solution and 100 mL of brine, and the organic solution was dried over sodium sulfate. Removal of solvent yielded 6.69 g (98.8%) of white solid, mp 147–159 °C. The NMR spectrum showed singlets at 3.74, 3.82 (minor constituent), and 3.91 ppm, corresponding to the C(2) proton of the dithiane ring. The crude product showed $[\alpha]^{20}_D$ −3.6° (*c* 2.6, ethanol). Successive recrystallizations from dichloromethane/ether, ethanol, dichloromethane/ether, and ethanol afforded 357 mg of **3**: mp 215–217 °C; $[\alpha]^{21}_D$ +24.4° (*c* 1.27, $CHCl_3$).

When 196.5 mg (0.68 mmol) of the crude mixture of diastereomers was subjected to base-catalyzed cleavage under the conditions previously described, 85.1 mg (92%) of 1,3-dithiane 1-oxide was obtained. After purification by preparative TLC on silica gel (15% 2-propanol in CCl_4), 57.5 mg of **1** was obtained, mp 84–88 °C, $[\alpha]^{20}_D$ +38° (*c* 2, ethanol).

Carbon-13 NMR Spectra. ^{13}C chemical shift data for **3**, **4**, and **5** are given in the microfilm edition of the Journal. (See note on Supplementary Material.)

Crystal Data. Preliminary cell dimensions were derived from 25° precession photographs taken with Mo Kα radiation. Systematic absences of axial reflections of odd order in *h*00, 0*k*0, and 00*l* define the space group for this orthorhombic crystal as $P2_12_12_1$. Accurate cell dimensions were obtained by a least-squares fit to the diffractometer values of ±2θ measured for 20 strong general reflections (λ = 1.5418 Å) and are a = 23.890 (7), b = 9.336 (4), and c = 6.727 (3) Å. The measured crystal density (flotation in $ZnCl_2$ solution) of 1.28 g cm^{-3} is identical with that calculated assuming four molecules of **2** in the unit cell. The absorption coefficient for the crystal for Cu Kα radiation is 39 cm^{-1} and the dimensions of the crystal used 0.70 × 0.17 × 0.40 mm. No absorption corrections were made, and most of the residual error is attributable to this neglect.

Intensity Data. These were measured using a Picker four-circle diffractometer controlled by an XDS Sigma 2 computer. Monochromatic Cu Kα radiation was used to survey a single octant of reciprocal space containing 1268 independent reflections (2θ < 12.0°) of which 1117 showed intensity significantly above background [$I > 3\sigma(I)$]. The θ–2θ scan method was used at a scan rate of 2° min^{-1} and scan widths 2.5–3.0°. Background measurements were made with both crystal and counter stationary for 15 s at either end of the scan ranges. Stability of the experimental conditions was monitored by measurement of a single reference reflection after every five measurement cycles, the rms deviation about the mean intensity for this reference being 1.5%. Structure amplitudes and normalized structure amplitudes were derived in the usual ways.

Structure Determination and Refinement. The structure was solved by direct methods by use of the program MULTAN[29] and refined by block-diagonal least-squares methods with a conventional weighting scheme adopted.[30] Anisotropic thermal parameters were used for S, O, and C atoms. All hydrogen atoms, except H(5b) and the hydroxy proton, were identified from difference electron-density maps and included in the refinement with isotropic B values assumed. At convergence, no calculated shift in any parameter exceeded 0.35 σ. The final conventional unweighted and weighted residuals were 0.046 and 0.057. The scattering functions used were taken from ref 31. With the exception of ORTEP and MULTAN, all programs used were written in this laboratory for the XDS Sigma 2 computer.

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Registry No.—**1**, 63903-43-5; (*R*)-(+)-**1**, 63865-79-2; (*S*)-(−)-**1**, 63865-78-1; **2**, 63903-42-4; **3**, 63865-80-5; **4**, 63865-77-0; D(+)-camphor, 464-49-3; 1,3-dithiane, 505-23-7; *sec*-butyllithium, 598-30-1.

Supplementary Material Available. Listings of complete bond length and angle calculations, information on least-squares mean planes of interest, intermolecular contact distances, and ^{13}C chemical shift data for **3**, **4**, and **5** (8 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) M. J. Cook and A. P. Tonge, *Tetrahedron Lett.*, 849 (1973); (b) M. J. Cook and A. P. Tonge, *J. Chem. Soc., Perkin Trans. 2*, 767 (1974); (c) K. Bergesen, M. J. Cook, and A. P. Tonge, *Acta Chem. Scand. Ser. A*, **30**, 574 (1976).
(2) L. Van Acker and M. Anteunis, *Tetrahedron Lett.*, 225 (1974).
(3) S. A. Khan, J. B. Lambert, O. Hernandez, and F. A. Carey, *J. Am. Chem. Soc.*, **97**, 1468 (1975).
(4) N. L. Allinger and J. Kao, *Tetrahedron*, **32**, 529 (1976).
(5) (a) A. T. McPhail, K. D. Onan, and J. Koskimies, *J. Chem. Soc., Perkin Trans. 2*, 1004 (1976); (b) F. A. Carey, P. M. Smith, R. J. Maher, and R. F. Bryan, *J. Org. Chem.*, **42**, 961 (1977).
(6) F. A. Carey, O. D. Dailey, Jr., O. Hernandez, and J. R. Tucker, *J. Org. Chem.*, **41**, 3975 (1976).
(7) F. A. Carey, O. D. Dailey, Jr., and O. Hernandez, *J. Org. Chem.*, **41**, 3979 (1976).
(8) (a) D. Seebach and M. Kolb, *Chem. Ind. (London)*, 687 (1974); (b) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969); (c) O. W. Lever, Jr., *Tetrahedron*, **32**, 1943 (1976).
(9) D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975).
(10) K. Ogura, M. Yamashita, M. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, 3653 (1974), and preceding papers in this series.
(11) (a) A. I. Meyers and C. E. Whitten, *J. Am. Chem. Soc.*, **97**, 6266 (1975); (b) A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *ibid.*, **98**, 567 (1976); (c) A. I. Meyers and E. D. Mihelic, *J. Org. Chem.*, **40**, 1186 (1975).
(12) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971, pp 335–365.
(13) (a) K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, Jr., *J. Am. Chem. Soc.*, **87**, 1958 (1965); (b) M. Axelrod, P. Bickart, J. Jacobus, M. M. Green, and K. Mislow, *ibid.*, **90**, 4835 (1968); (c) K. K. Andersen, *Tetrahedron Lett.*, 93 (1962); (d) K. K. Andersen, W. Gaffield, N. Papanikolaou, J. W. Foley, and R. I. Perkins, *J. Am. Chem. Soc.*, **86**,

5637 (1964); (e) F. Wudl and T. B. K. Lee, *ibid.*, **95**, 6349 (1973); (f) D. N. Harpp, S. M. Vines, J. P. Montillier, and T. H. Chan, *J. Org. Chem.*, **41**, 3987 (1976); (g) J. C. Martin and T. M. Balthazor, *J. Am. Chem. Soc.*, **99**, 152 (1977).
(14) A. McL. Mathieson, *Acta Crystallogr.*, **9**, 317 (1956).
(15) R. M. Carlson and P. M. Helquist, *J. Org. Chem.*, **33**, 2596 (1968).
(16) For data on the dependence of ^{13}C shifts on sulfoxide stereochemistry, see: (a) G. W. Buchanan and T. Durst, *Tetrahedron Lett.*, 1683 (1975); (b) G. Barberella, P. Dembech, A. Garbesi, and A. Fava, *Org. Magn. Reson.*, **8**, 108 (1976); (c) D. M. Frieze and S. A. Evans, *J. Org. Chem.*, **40**, 2690 (1975).
(17) F. A. Carey, O. D. Dailey, Jr., and W. C. Hutton, *J. Org. Chem.*, following paper in this issue.
(18) F. H. Allen and D. Rogers, *J. Chem. Soc. B*, 632 (1971).
(19) (a) A. F. Peerdeman, A. J. van Bommel, and J. M. Bijvoet, *Proc. K. Ned. Akad. Wet. Ser., B*, **54**, 16 (1951); W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).
(20) C. K. Johnson, "ORTEP-II. A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations, ORNL-5138," Oak Ridge National Laboratory, Oak Ridge, Tenn. (1976).
(21) See paragraph at end of paper regarding supplementary material.
(22) H. T. Kalff and C. Romers, *Acta Crystallogr.*, **20**, 490 (1966).
(23) C. Altona and M. Sundaralingam, *J. Am. Chem. Soc.*, **92**, 1995 (1970).
(24) G. Ferguson, C. J. Fritchie, J. M. Robertson, and G. A. Sim, *J. Chem. Soc.*, 1976 (1961).
(25) D. A. Breuckner, T. A. Hamor, J. M. Robertson, and G. A. Sim, *J. Chem. Soc.*, 799 (1962).
(26) R. A. Alden, J. Kraut, and T. G. Traylor, *J. Am. Chem. Soc.*, **90**, 74 (1968).
(27) A. Bondi, *J. Phys. Chem.*, **68**, 471 (1964).
(28) We have been advised by K. L. Loening, Nomenclature Director of Chemical Abstracts Service, that the naming system used in this article is acceptable. The current Chemical Abstracts name for **2** is [(1*R*)-[1α,2α,2-(1*S**,2*R**),4α]-2-(1,3-dithian-2-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol *S*-oxide.
(29) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970).
(30) P. W. R. Corfield, R. J. Doedens, and J. A. Ibers, *Inorg. Chem.*, **6**, 197 (1967).
(31) (a) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr.*, **17**, 1040 (1964); (b) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).

Structural Dependence of Carbon-13 Chemical Shifts in Oxides of 1,3-Dithiane

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A carbon-13 nuclear magnetic resonance study was carried out on a series of 2-substituted derivatives of 1,3-dithiane 1-oxide (**2a**). The series included seven trans and five cis 2-monosubstituted 1,3-dithiane 1-oxides (**2b–h** and **3b–d,f,h**) and three 2,2-disubstituted 1,3-dithiane 1-oxides. In the monosubstituted compounds C(6) experiences a larger downfield shift than C(2) on oxidation of a 1,3-dithiane. The ^{13}C shifts of C(2), C(5), and C(6) are at higher field in an axial oxide than an equatorial oxide. The results are discussed with respect to: (a) assignment of stereochemistry to 1,3-dithiane 1-oxides; (b) relation of ^{13}C shifts to structure; and (c) ring deformation in 2,2-disubstituted 1,3-dithiane 1-oxides. Assignments of sulfoxide stereochemistry can be made with confidence by ^{13}C NMR. The preferred conformation of 1,3,5-trithiane 1-oxide was determined to have oxygen equatorial. Comparison of chemical shifts with structural parameters available from x-ray crystallography allowed theories of chemical shifts to be evaluated; electric field effects may be important. Twist conformations appear to be significant in 2,2-disubstituted 1,3-dithiane 1-oxides.

Carbon-13 nuclear magnetic resonance spectroscopy has developed rapidly as a structural probe to where it has become a powerful addition to those techniques employed as a matter of routine in stereochemical studies.[1] In the course of a detailed investigation into the stereochemical features of ground-state properties and chemical reactivity of sulfoxides derived from 1,3-dithiane (**1a**),[2] many derivatives of rigorously established structure have become available, presenting an opportunity to extend and complement recent systematic ^{13}C NMR studies reported on sulfur-containing heterocycles.[3,4] It was felt that such an extension would be appropriate, since numerous examples have already appeared which relate ^{13}C chemical shifts to stereochemistry at tricoordinate sulfur.[4-12] Further, because precise structural parameters have been determined for several key compounds,[2d,13] we hoped that structural features which might be considered as potentially significant in influencing ^{13}C shieldings could be examined explicitly.

Results

Three groups of 2-substituted 1,3-dithiane 1-oxides (trans, cis, and 2,2-disubstituted) form the basis of the present study. X-ray crystallographic methods have shown that the chair conformation of the dithiane ring is adopted in the solid state for both the trans and cis series of 2-substituted derivatives.[2d,13] The sulfoxide oxygen is equatorial in the trans and axial in the cis. It will be seen from analysis of the ^{13}C NMR data that the 2,2-disubstituted 1,3-dithiane 1-oxides are subject to a distortion which causes them to be conformationally distinct from the monosubstituted series. These will be treated separately in the Discussion. The structures of four of the oxides (**2d, 2g, 3d,** and **3h**) have been rigorously established by x-ray crystallographic methods[2d,13a,b] and the others,

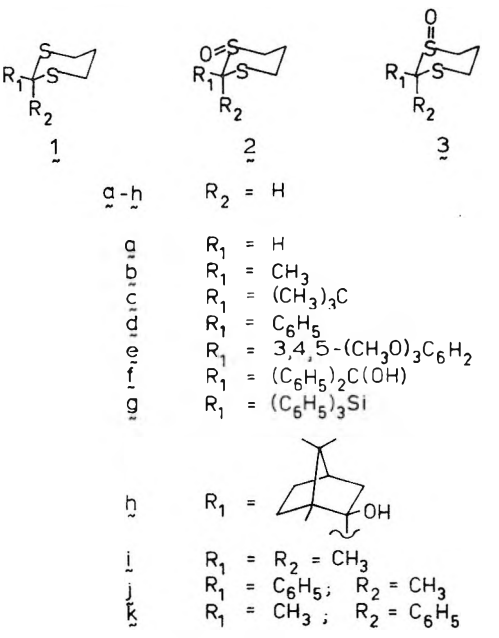

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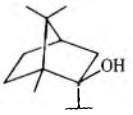
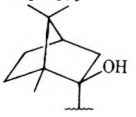
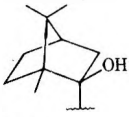
Table I. ^{13}C Chemical Shifts of 1,3-Dithianes

Compd	Registry no.	R_1	R_2	Chemical shift, δ C(2)	C(4)[a]	C(5)	Other
1a[b]		H	H	32.0	29.9	26.6	
1b[b]		CH_3	H	42.2	30.9	25.5	CH_3 21.1
1c[b]		$(CH_3)_3C$	H	61.8	31.2	26.0	4 °C 35.7 CH_3 27.8
1d[b]		C_6H_5	H	51.3	31.9	25.0	
1e	57009-70-8	$3,4,5\text{-}(CH_3O)_3C_6H_2$	H	51.4	31.8	24.7	
1f	5849-23-0	$(C_6H_5)_2C(OH)$	H	58.5	30.4	25.1	
1g	13433-53-9	$(C_6H_5)_3Si$	H	32.5	31.7	25.7	
1h	63949-54-2		H	61.3	(30.1) (30.5)	25.4	
1i	6007-22-3	CH_3	CH_3	45.0	27.0	25.2	CH_3 30.8
1j	6331-22-2	C_6H_5	CH_3	53.7	27.9	24.5	CH_3 32.6

[a] Because of symmetry, C(4) = C(6) in all cases, except 1h. The chemical shifts of C(4) and C(6) in 1h could not be uniquely assigned. [b] Data of E. L. Eliel, V. S. Rao, and F. G. Riddell, *J. Am. Chem. Soc.*, 98, 3583 (1976).

Table II. ^{13}C Chemical Shifts of 2-Substituted 1,3-Dithiane 1-Oxides

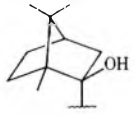
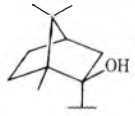
Compd	Registry no.	R_1	R_2	M[a]	Chemical shift, δ C (2)	C(4)	C(5)	C(6)	Other
2a (3a)	16487-10-8	H	H	1.00	49.9	26.6	27.8	52.3	
2a (3a)		H	H	0.10	50.3	27.1	28.2	52.8	
2a (3a)	60349-89-5	D	D	1.02		26.5	27.7	52.2	
			Trans 2-Substituted (Equatorial Oxygen)						
2b	60349-75-9	CH_3	H	1.02	59.8	29.3[b]	29.8[b]	53.2	CH_3 14.9
2c	41893-04-3	$(CH_3)_3C$	H	1.00	76.8	29.8[b]	30.2[b]	55.4	4 °C 35.9 CH_3 28.3
2d	60349-76-0	C_6H_5	H	1.00	69.2	29.2	31.0	54.4	
2e	63833-56-7	$3,4,5\text{-}(CH_3O)_3C_6H_2$	H	1.05	69.3	29.0[b]	30.9[b]	54.2	
2f	60349-77-1	$(C_6H_5)_2C(OH)$	H	0.44	74.1	29.4	31.9	54.4	
2g	63883-55-6	$(C_6H_5)_3Si$	H	0.18	52.0	29.4[b]	30.7[b]	55.4	
2h	63949-97-3		H		77.9	28.9[b]	30.4[b]	54.0	
			Cis 2-Substituted (Axial Oxygen)						
3b	60349-78-2	CH_3	H	1.05	52.3	24.6	21.2	44.9	CH_3 11.8
3c	41893-05-4	$(CH_3)_3C$	H	0.18	73.8	29.7	14.4	47.7	4 °C 36.0 CH_3 28.3
3d	60349-79-3	C_6H_5	H	1.00	63.9	29.5	13.2	46.8	
3f	60349-80-6	$(C_6H_5)_2C(OH)$	H	0.13	68.0	28.5	14.4	47.0	
3h			H		70.4	28.2	13.9	47.8[c]	
			2,2-Disubstituted						
2i (3i)	41893-06-5	CH_3	CH_3	1.00	57.0	27.8	25.1	46.1	CH_3 16.0, 25.1
2j (3k)	60349-92-0	C_6H_5	CH_3	1.01	64.3	22.6	26.2	45.0	CH_3 18.6
2k (3j)	60349-93-1	CH_3	C_6H_5	0.57	65.5	28.4	27.3	47.0	CH_3 27.8

[a] Concentration (mol/L) in $CDCl_3$. [b] Assignment of signals to C(4) and C(5) may be reversed. [c] The chemical shift of this carbon may be 47.4 ppm. There are two signals in this region one of which is due to C(6) of the dithiane ring, and the other to C(3) of the isoborneol portion of the molecule. For the ^{13}C NMR spectrum of borneol, see: J. Briggs, F. A. Hart, G. P. Moss, and E. W. Randall, *J. Chem. Soc. D.* 364 (1971).

with the exception of **2h**, assigned on the basis of analogous methods of synthesis and physical correlations described earlier.[2b] The stereochemistry of **2h** was not known independently but its ^{13}C NMR spectrum allows its assignment to be made with confidence.

The thorough study by Eliel, Rao, and Riddell[3a] has provided an extensive compilation of chemical-shift data which, taken together with relative intensities, allows peak assignments to be made for the parent 1,3-dithianes. The ^{13}C shifts for the 1,3-dithianes used in this study (**1a–l**) are presented in Table I.[14] Chemical-shift data for the trans 1-oxides, cis 1-oxides, and 2,2-disubstituted 1-oxides appear in Table II. Differential shifts ($\Delta\delta$ values)[15] relating ^{13}C shifts of the oxides to the corresponding 1,3-dithianes are collected in Table III. Peak assignments for the oxides were made on the basis of the following criteria. The two lowest field signals for sp^3 carbons were assigned to C(2) and C(6), since oxidation of sulfur to sulfoxide substantially deshields the α carbons.[4] Off-resonance decoupling served to distinguish between primary, secondary, tertiary, and quaternary carbons in questionable cases. The signal for C(2) in 1,3-dithiane 1-oxide (**2a**) was identified by comparing its ^{13}C NMR spectrum with that of

Table III. ^{13}C-Shift Effects ($\Delta\delta$) of Oxygen Orientation in 1,3-Dithiane 1-Oxides

Compd	R_1	R_2	Shift effect, $\Delta\delta$ [a] C(2)	C(4)	C(5)	C(6)
2a (3a)	H	H	17.9	−3.3	1.2	22.4
	Trans 2-Substituted (Equatorial Oxygen)					
2b	CH_3	H	17.6	−1.6	4.3	22.3
2c	$(CH_3)_3C$	H	15.0	−1.4	4.2	24.2
2d	C_6H_5	H	17.9	−2.7	6.0	22.5
2e	$(CH_3O)_3C_6H_2$	H	17.9	−2.8	6.2	22.4
2f	$(C_6H_5)_2C(OH)$	H	15.6	−1.0	6.8	24.0
2g	$(C_6H_5)_3Si$	H	19.5	−2.3	5.0	23.7
2h		H	16.6	−1.2	5.0	23.5
Average			17.2 ±1.2	−1.9 ±0.6	5.4 ±0.8	23.3 ±0.7
	Cis 2-Substituted (Axial Oxygen)					
3b	CH_3	H	10.1	−6.3	−4.3	14.0
3c	$(CH_3)_3C$	H	12.0	−1.5	−11.6	16.5
3d	C_6H_5	H	12.6	−2.4	−11.8	14.9
3f	$(C_6H_5)_2C(OH)$	H	9.5	−1.9	−10.7	16.6
3h		H	9.1	−1.9	−11.4	16.9
Average			10.7 ±1.3	−2.4 ±1.2	−10.0 ±2.2	15.8 ±1.1
	2,2-Disubstituted					
2i (3i)	CH_3	CH_3	12.0	0.8	0.1	19.1
2j	C_6H_5	CH_3	10.6	−5.3	1.7	17.1
2k	CH_3	C_6H_5	11.8	0.5	2.8	19.1

[a] $\Delta\delta = (\delta_{oxide} - \delta_{parent\ dithiane})$. A positive value indicates the carbon atom of the substituted 1,3-dithiane 1-oxide appears at lower field (deshielded) than the carbon of the corresponding 1,3-dithiane derivative. A negative sign is indicative of an upfield shift (shielding) on oxidation.

its 2,2-dideuterio analogue. The signal which was absent in the spectrum of the dideuterated compound was assigned to C(2) of **2a**. In order to distinguish between C(4) and C(5) in **2a**, the trans oxides **2d** and **2f**, and in the 2,2-disubstituted oxides **2i–k**, gated decoupling was employed. The signal with the greater multiplicity was assigned to C(5) and was the more deshielded in **2a, d,** and **f**. Accordingly, the lower field signal in the other trans 2-monosubstituted oxides **2b,c,e,g,** and **h** was also assigned to C(5). In the cis oxides the signal appearing at highest field was assigned to C(5), since an axial oxygen substituent on sulfur is known to exert a significant shielding effect on carbons oriented synclinal to it.[4–9]

The solvent was $CDCl_3$ and concentrations were 1 M in most cases. In order to ensure that concentration effects were not large, since we were sometimes sample or solubility limited, the ^{13}C NMR spectrum of **2a** was determined at 0.10 and 1.0 M. The chemical shifts differed by ca. 0.5 ppm in the two runs. As is evident from the tables, this variation is small compared with differences resulting from structural factors.

Discussion

(A) Assignment of Stereochemistry to 1,3-Dithiane 1-Oxides. We have previously described proton NMR correlations which were helpful in deducing whether a particular 2-substituted 1,3-dithiane 1-oxide diastereomer belonged to the cis or trans series.[2b] The present study supersedes that work and clearly establishes that ^{13}C NMR is the method of choice for making such assignments. The chemical shifts of

Table IV. ^{13}Chemical Shifts and $\Delta\delta$ Values of Thiane 1-Oxides [a]

Compd	C(2)	C(3)	C(4)	Ref
	Equatorial Oxides			
Unsubstituted [b]	52.1 (22.8)	23.3 (−4.9)	24.7 (−2.2)	4a
trans-4-Methyl	50.7	30.0	30.5	10a
trans-4-Isopropyl	52.3 (22.2)	26.0 (−5.8)	42.8 (−1.6)	4b
trans-4-*tert*-Butyl	52.4	24.4	48.0	7b
	Axial Oxides			
Unsubstituted [b]	45.1 (15.8)	15.5 (−12.7)	24.7 (−4.9)	4a
cis-4-Methyl	45.7	23.7	30.9	10a
cis-4-Isopropyl	46.7	19.1 (−12.7)	43.0 (−1.4)	4b
cis-4-*tert*-Butyl	46.9	16.9	47.3	7b

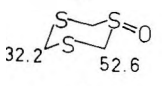
[a] $\Delta\delta$ Values are in parentheses. [b] Determined from low-temperature spectrum.

C(2), C(5), and C(6) are each sensitive to the stereochemistry of the sulfoxide group. In all of the 2-monosubstituted compounds where direct comparison of diastereomers is possible (**b,c,d,f**), C(2) and C(6) are more shielded in the cis isomer (axial oxygen) than in the trans isomer (equatorial oxygen). The ^{13}C shifts of C(6) can be used to determine stereochemistry, even if only one diastereomer is available. The seven trans oxides **2b–h** all had their C(6) signals in the range 53.2–55.4 ppm, while the corresponding signals for the five cis oxides **3b–d,f,h** were 44.9–47.8 ppm. The $\Delta\delta$ values for C(6) in each series (Table III) were also diagnostic of sulfoxide stereochemistry. The cis oxides had $\Delta\delta$ values in the range 14.0–16.9 ppm and the trans 22.3–24.2 ppm. The chemical shifts and $\Delta\delta$ values for C(6) correspond quite well to published data for the α carbon [C(2)] of thiane 1-oxide and its derivatives (Table IV). The chemical shifts and $\Delta\delta$ values for C(2) of 1,3-dithiane 1-oxides are significantly smaller than those for C(6) or for the α carbons of thiane oxides. The C(2) $\Delta\delta$ values for the cis (9.1–12.6 ppm) and trans (15.0–19.5 ppm) series are free of overlaps and are sufficiently different from each other to again permit stereochemical assignments to be made with confidence.

The carbon which is β to the sulfoxide group in dithiane oxides is C(5) and its pattern of $\Delta\delta$ values is different for the cis and trans series. The cis series, in which oxygen is axial, appears to be normal in that large upfield shifts are found relative to the parent dithianes. These $\Delta\delta$ values average −10.0 ppm and, with the exception of **3b,** are very similar to those observed for the β carbons C(3) and C(5) of thiane oxide (Table IV).[15] Interestingly, C(5) in the trans series has been shifted downfield relative to the dithianes. This effect is opposite to that which occurs in equatorial thiane oxides where $\Delta\delta$ values of ca. −5.0 ppm have been observed.

The signal for C(4) shifts upfield by about 2 ppm when either an axial or equatorial oxygen is attached to sulfur and is not useful for assigning sulfoxide stereochemistry.

Dynamic proton NMR studies have established that the equatorial oxide conformation of **2a** is 0.6 kcal/mol more stable than the axial oxide conformation.[2a,16] Qualitatively, we see from ^{13}C NMR that the chemical shifts and $\Delta\delta$ values are close to those exhibited by the trans series and indicative of an equatorial oxide. In the case of 1,3,5-trithiane 1-oxide (4), low-temperature proton NMR detected the presence of only a single conformation which was assumed to be the equatorial oxide by analogy with **2a.**[2a] The ^{13}C NMR results for **4**



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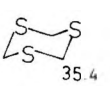

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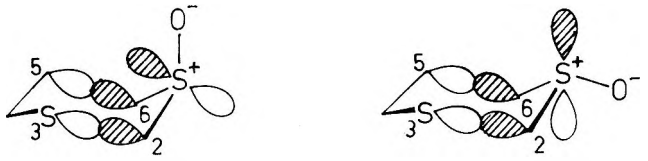


Figure 1. Proposed interaction of sulfoxide 3p orbital with σ^* orbitals of C(5)–C(6) and C(2)–S(3) fragments is better when the lone pair is equatorial and the oxygen is axial.

strongly support this assertion. The α carbons of the oxide have chemical shifts which are 17.2 ppm downfield from 1,3,5-trithiane (**5**). The environment of C(2) in **4** resembles the environment of C(2) in dithiane oxides and the $\Delta\delta$ value of 17.2 ppm is exactly the same as the average of the seven trans oxides in Table III.

(B) Relation of Chemical Shifts to Structure.[17] In attempting to understand the increased shielding of the α carbon in an axial sulfoxide compared to an equatorial one, structural relationships between the diastereomeric pair *trans*- (**2d**) and *cis*-2-phenyl-1,3-dithiane 1-oxide (**3d**) were examined. A simple explanation for decreased shielding in the equatorial oxides would be available if the electronegativity of an equatorially oriented sulfoxide group exceeded that of an axial one. Conceivably, this would be reflected in the C(2)–S(1)–C(6) valence angles and in the S(1)–O bond lengths. A larger C–S–C valence angle would indicate an increased amount of *s* character in the orbitals used by S(1) to bond to C(6) and C(2), deshielding the α carbon by shifting the center of electron density away from carbon and toward sulfur. A longer S–O distance would indicate more single bond character and more positive charge at sulfur. The anticipated greater electron-withdrawing effect of this group would lead to decreased shielding of the α carbon. Neither of these structural effects was evident. The C(2)–S(1)–C(6) valence angles are similar: 98.2° in the equatorial oxide **2d** and 98.7° in the axial oxide **3d.**[2d] The small difference is, in fact, in the wrong direction to provide an explanation for the chemical shifts. The S–O distances in **2d** and **3d,** after correcting for a pronounced thermal anisotropy, are virtually identical: 1.512 Å in **2d,** and 1.509 Å in **3d.**[2d]

A second possibility lies in an interaction of the sulfur lone-pair orbital with the σ^* orbitals associated with C(5)–C(6) and C(2)–S(3). Assuming directional properties for the sulfur 3p orbital,[18] interaction with the σ^* orbitals will be effective only when the sulfoxide oxygen is axial (lone pair equatorial) (Figure 1). Electron release from the sulfur lone pair will populate the antibonding orbitals, weaken the C(5)–C(6) and C(2)–S(3) bonds, and increase the electron density at carbons 2, 5, and 6 in the axial oxides. Again, this is not borne out by the structural evidence. The C(2)–S(3) bond in the axial oxide **3d** is shorter, not longer, than in the equatorial oxide **2d** (1.797 vs. 1.814 Å). The C(5)–C(6) distances in **2d** and **3d** (1.519 and 1.512 Å) are not significantly different from each other.[2d]

A semiquantitative rationalization of this question in terms of an electric-field effect has been presented by Buchanan and Durst.[7b] The sulfoxide oxygen is considered a point charge which polarizes the electron distribution in all the bonds to the α carbon. The shielding effect is a function of the spatial orientation (distance, angle) of these bonds with respect to the perturbing oxygen and their longitudinal polarizability. Qualitatively, the difference in shielding may be attributed to the S–O bond existing in a gauche relationship to the C_α–C_β bonds in the axial oxide (anti in the equatorial oxide) compared with a gauche relationship between S–O and the C_α–H_{ax} bond in the equatorial oxide (Figure 2). Since the longitudinal polarizability of a C–C bond is ca. 50% greater than that of a C–H bond,[19] the shift of electron density toward the α carbon is greater in the axial oxide.[20]

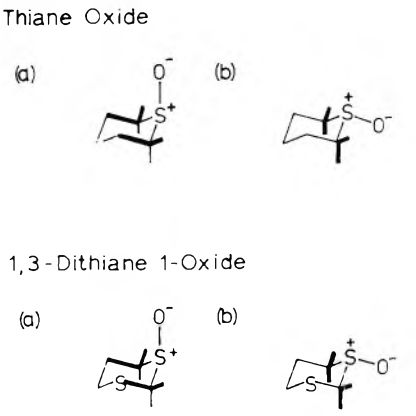


Figure 2. Bonds to α carbons subject to most pronounced polarization by electric-field associated with oxygen are thickened.

The electric-field explanation is consistent with the decreased sensitivity of the C(2) shifts to oxidation at sulfur in the 1,3-dithiane system. In the axial oxide, the most significant polarizations would involve C(5)–C(6) and C(2)–S(3). The greater polarizability of the C(2)–S(3) bond leads to increased shielding of C(2) relative to C(6) and smaller values of $\Delta\delta$. However, since the differential C(2) shifts are smaller than the C(6) shifts in the equatorial oxides as well, this cannot be the only factor. The interaction of an equatorial oxygen with the C(2)–S(3) bond must be small because of their antiperiplanar relationship.[21] What is probably a more important contributor to the decreased sensitivity of C(2) to oxidation at sulfur is its attachment to S(3). Since C(2) is already bonded to an electronegative substituent,[21] the inductive electron withdrawal by the sulfoxide group will be attenuated.

Gorenstein[22] has analyzed ^{13}C, ^{31}P, and ^{19}F chemical shifts in V–X–Y–Z systems where V, X, and Y are component atoms of a six-membered ring and Z is an axial or equatorial substituent. He notes that torsional relationships and bond angles are not independent and proposes that atoms belonging to a gauche array (Z axial) are more shielded than when part of an anti array (Z equatorial) because the ring valence angles around the atoms are larger in the gauche. Downfield shifts are associated with increases in C–X–C bond angles. The proposal apparently applies to all the atoms in the array even though presented as an alternative to the steric polarization suggested by Grant and Cheney[23] which is often used to rationalize the upfield shift of the α carbons in axially substituted six-membered rings, including C(3) of thiane oxides.[24] The ^{13}C and structural data for **2d** and **3d** provide an opportunity to test Gorenstein's proposal. Indeed, the signal for C(2) in the equatorial oxide **2d** appears at 5.3 ppm lower field than in the axial oxide **3d,** and the S(1)–C(2)–S(3) angle is smaller in the equatorial oxide (109.6°) than in the axial (112.9°).[2d] At C(6) the equatorial ^{13}C shift is 7.6 ppm to lower field than the axial, but the C(5)–C(6)–S(1) angle is now only slightly smaller in the equatorial (114.0 ± 0.2°) than in the axial oxide (114.6 ± 0.2°). The largest difference in chemical shift involves C(5) which is γ to the oxygen substituent. Here the signal for C(5) is 17.8 ppm to lower field in the equatorial than in the axial oxide, yet the C(4)–C(5)–C(6) valence angles are not significantly different, being 113.3 ± 0.2° in **2d** vs. 113.0 ± 0.3° in **3d.**

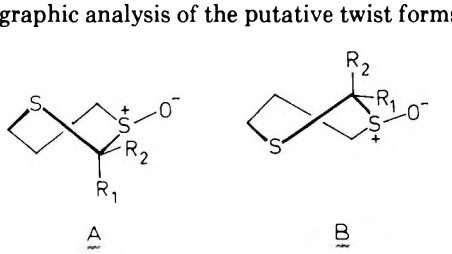
(C) Ring Deformation in 2,2-Disubstituted 1,3-Dithiane 1-Oxides. Equilibration of diastereomeric alkyl derivatives of 1,3-dithiane has provided evidence that the free-energy difference between chair and twist forms lies in the range 1.8–2.6 kcal/mol.[25] Since this is comparable to the conformational energy of a C(2)-axial methyl group (1.8 kcal/mol),[25] 2,2-disubstituted 1,3-dithianes and their oxides might be anticipated to contain significant amounts of twist confor-

mations. A proton NMR study of *trans*-2-*tert*-butyl-*cis*-2-methyl-1,3-dithiane 1-oxide in which conformational distortion in the C(4)–C(5)–C(6) portion of the ring was probed by analysis of vicinal H···H coupling constants did not provide evidence capable of distinguishing between a flattened chair form or the presence of twist forms.[26] As was noted, however, in a previous paper by the same group,[27] this method is insensitive to distortions occurring in the S(1)–C(2)–S(3) portion of the ring. The ^{13}C NMR spectra of the 2,2-disubstituted oxides **2i–k** provides complementary information and clearly indicates important contributions from twist conformations.[28]

The pattern of ^{13}C shifts and $\Delta\delta$ values in the three 2,2-disubstituted 1,3-dithiane 1-oxides **2i–k** is different from that of both the trans and cis 2-monosubstituted series. For C(2), $\Delta\delta$ values range from 10.6 to 12.0 ppm and resemble axial oxides. The $\Delta\delta$ values for C(6) are intermediate between those of axial and equatorial oxides. Since, however, the ca. 11 ppm upfield shift of C(5) characteristic of axial oxides is *not* observed in any of the three, including the diastereomeric pair **2j,k,** oxygen cannot be axial. These data point to the involvement of the twist form A in which the sulfoxide oxygen occupies an isoclinal[29] site and the substituents at C(2) are pseudoaxial or pseudoequatorial. As seen from a model, the geometric relationship of oxygen to the C(2)–S bond in A is similar to that of an axial oxide (see part B for discussion of electric-field effects on ^{13}C shifts), yet antiperiplanar rather than synclinal to C(5), consistent with the ^{13}C NMR results.

In 2,2-dimethyl-1,3-dithiane 1-oxide (**2i**) the diastereotopic methyl groups have much different chemical shifts. One is at 16.0 ppm ($\Delta\delta$ −14.8 ppm) and the other at 25.1 ppm ($\Delta\delta$ −5.7 ppm). The signal at higher field is assigned to the methyl group cis to the sulfoxide oxygen based on the premise that the torsional relationship between these groups would lead to a larger γ-gauche upfield shift than that experienced by the methyl trans to oxygen.[6a,12] The diastereomeric pair **2j,k** have similar shifts for the ring carbons but the methyl signal of **2j** which is cis to oxygen is more shielded (18.6 ppm, $\Delta\delta$ −14.0 ppm) than that of **2k** which is trans to oxygen (27.8 ppm, $\Delta\delta$ −4.8 ppm).

An alternative twist conformation **B** seems sterically as reasonable as **A** but does not fit the ^{13}C NMR results as well. A more detailed analysis of the conformations of these systems must await the results of dynamic ^{13}C NMR studies and x-ray crystallographic analysis of the putative twist forms.



A B

Experimental Section

Carbon-13 NMR spectra were recorded using a JEOL-PS100P/EC-100 Fourier transform spectrometer. Measurements were made at 25.2 MHz with a probe temperature of 23 °C using a 5-KHz rf crystal filter. Typically, a 45° pulse width was used (10 s) with a pulse repetition rate of 1 s; 8K data points were employed in the time domain. Carbon-13 chemical shifts were referenced to the center of the $CDCl_3$ multiplet using a value of $\delta_{Me_4Si} = \delta_{CDCl_3} + 76.91$ ppm.[30]

The preparation of oxides **2a,b,d,f,i–k** and **3b,d,f** have been described previously[2b,c] as have **2c** and **3c**.[31] Oxides **2g, 2h,** and **3h** were available from another study and will be reported separately.[13] 2-(3′,4′,5′-Trimethoxyphenyl)-1,3-dithiane and its oxide were obtained from Dr. O. Hernandez.[32] The parent dithianes **1f**,[2b] **1g**,[33] **1h**,[13b] and **1j**[34] have been reported. Trithiane 1-oxide was available from a previous study.[2a]

Acknowledgment. The Fourier transform NMR spectrometer was purchased with assistance from a major instrument grant from the National Science Foundation.

References and Notes

(1) (a) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972; (b) N. K. Wilson and J. B. Stothers, *Top. Stereochem.*, **8,** 1 (1974).
(2) (a) S. A. Khan, J. B. Lambert, O. Hernandez, and F. A. Carey, *J. Am. Chem. Soc.*, **97,** 1468 (1975); (b) F. A. Carey, O. D. Dailey, Jr., O. Hernandez, and J. R. Tucker, *J. Org. Chem.*, **41,** 3975 (1976); (c) F. A. Carey, O. D. Dailey, Jr., and O. Hernandez, *ibid.*, **41,** 3979 (1976); (d) F. A. Carey, P. M. Smith, R. J. Maher, and R. F. Bryan, *ibid.*, **42,** 961 (1977).
(3) (a) E. L. Eliel, V. S. Rao, and F. G. Riddell, *J. Am. Chem. Soc.*, **98,** 3583 (1976); (b) R. L. Willer and E. L. Eliel, *ibid.*, **99,** 1925 (1977).
(4) (a) J. B. Lambert, D. A. Netzel, H.-n. Sun, and K. L. Lilianstrom, *J. Am. Chem. Soc.*, **98,** 3778 (1976); (b) G. Barbarella, P. Dembeck, A. Garbesi, and A. Fava, *Org. Magn. Res.*, **8,** 108 (1976).
(5) Sulfoxides incorporated into rigid bicyclic systems: (a) H. J. Reich and J. E. Trend, *J. Org. Chem.*, **38,** 2637 (1973); (b) J. R. Wiseman, H. O. Krabbenhoft, and B. R. Anderson, *ibid.*, **41,** 1518 (1976).
(6) Penicillin sulfoxides: (a) R. A. Archer, R. D. G. Cooper, P. V. Demarco, and L. F. Johnson, *J. Chem. Soc., Chem. Commun.*, 1291 (1970); (b) K. Tori, T. Tsushima, Y. Tamura, H. Shigemoto, T. Tsuji, H. Ishitobi, and H. Tanida, *Tetrahedron Lett.*, 3307 (1975).
(7) Thiane oxides: (a) see ref 4; (b) G. W. Buchanan and T. Durst, *Tetrahedron Lett.*, 1683 (1975).
(8) Oxathiane oxides: (a) D. M. Frieze and S. A. Evans, *J. Org. Chem.*, **40,** 2690 (1975); (b) W. A. Szarek, D. M. Vyas, A.-M. Sepulchre, S. D. Gero, and G. Lukacs, *Can. J. Chem.*, **52,** 2041 (1974); (c) G. W. Buchanan, N. K. Sharma, F. de Reinack-Hirtzbach, and T. Durst, *Can. J. Chem.*, **55,** 44 (1977).
(9) Cyclic sulfites: G. W. Buchanan, J. B. Stothers, and G. Wood, *Can. J. Chem.*, **51,** 3746 (1973).
(10) Thiane and 1,3-dithiane imides: (a) P. K. Claus, W. Rieder, F. W. Vierhapper, and R. L. Wilier, *Tetrahedron Lett.*, 119 (1976); (b) P. K. Claus, F. W. Vierhapper, and R. L. Wilier, *J. Chem. Soc., Chem. Commun.*, 1002 (1976); (c) R. B. Greenwald, D. H. Evans, and J. R. De Member, *Tetrahedron Lett.*, 3885 (1975).
(11) *S*-Methylthianium salts: see ref 4 and (a) E. L. Eliel, R. L. Wilier, A. T. McPhail, and K. D. Onan, *J. Am. Chem. Soc.*, **96,** 3021 (1974); (b) E. L. Eliel and R. L. Wilier, *ibid.*, **99,** 1936 (1977).
(12) Thiolane oxides: R. T. LaLonde, C. F. Wong, A. I.-M. Tsai, J. T. Wróbel, J. Ruszkowska, K. Kabzinska, T. I. Martin, and D. B. MacLean, *Can. J. Chem.*, **54,** 3860 (1976).
(13) (a) R. F. Bryan, F. A. Carey, O. Hernandez, and I. F. Taylor, Jr., *J. Org. Chem.*, submitted; (b) R. F. Bryan, F. A. Carey, O. D. Dailey, Jr., R. J. Maher, and R. W. Miller, *J. Org. Chem.*, **42,** 961 (1977); (c) A. T. McPhail, K. D. Onan, and J. Koskimies, *J. Chem. Soc., Perkin Trans.* **2,** 1004 (1976).
(14) All chemical shifts are reported in units of ppm downfield from internal tetramethylsilane. The convention used in this paper for reporting "differential shifts" ($\Delta\delta$ values) subtracts the chemical shift of the corresponding 1,3-dithiane (**1**) from the 1,3-dithiane 1-oxide. A positive value of $\Delta\delta$ corresponds to a downfield shift in the oxide, a negative value to an upfield shift.
(15) As noted by one of the reviewers, the C(5) chemical shift of **3b** (21.2 ppm) is significantly different from that predicted on the basis of data available on the equatorial/axial preferences of various substituents on 1,3-dithiane rings. Assuming a 2-methyl substituent favors an equatorial orientation by 1.8 kcal/mol and a 1-oxide by 0.6 kcal/mol, then the equatorial CH_3-axial oxide conformation should dominate over the axial CH_3–equatorial oxide by 87:13 (1.2 kcal/mol). Based on the C(5) chemical shifts of *trans*- and *cis*-2-*tert*-butyl-1,3-dithiane 1-oxide (**2c** and **3c**) as models, C(5) in **3b** should appear at 16.5 ppm. We believe this large discrepancy results from nonadditivity of conformational energies of substituents in oxides of 1,3-dithiane and that at equilibrium much more of the axial CH_3–equatorial oxide conformer is present than predicted. The basis for the nonadditivity may lie in the comparative ease of distortion of the C(2)–S(1) bond. Structural studies[2d,13] reveal significant bond lengthening in the oxides which would have the effect of reducing the ΔG value for a C(2) methyl group owing to decreased syn-axial repulsions in the axial orientation.
(16) (a) M. J. Cook and A. P. Tonge, *Tetrahedron Lett.*, 849 (1973); (b) L. Van Acker and M. Anteunis, *ibid.*, 225 (1974); (c) M. J. Cook and A. P. Tonge, *J. Chem. Soc., Perkin Trans. 2,* 767 (1974).
(17) For critical analyses of substituent effects on ^{13}C shifts, see ref 1a and G. E. Maciel, *Top. Carbon-13 NMR Spectrosc.*, **1,** 53 (1974).
(18) J.-M. Lehn and G. Wipff, *J. Am. Chem. Soc.*, **98,** 7498 (1976).
(19) The longitudinal bond polarizabilities (in units of Å^3) are: C–H, 0.64; C–C, 0.99; and C–S, 1.88. See: R. J. W. LeFèvre, *Adv. Phys. Org. Chem.*, **3,** 1 (1965). These polarizabilities differ substantially from those cited by Buchanan and Durst in ref 7 but are of more recent origin and are similar to those cited by others (e.g., ref 18). Indeed, the C–S bond polarizability used by Buchanan and Durst does not appear to come from the reference they cite.
(20) The Buchanan–Durst analysis has been questioned (ref 4b) on the grounds that the effect is a much more general one and is observed as well when the perturbing substituent is not highly polar and even for axial vs. equatorial methyl substitution in cyclohexanes. It should be pointed out, however, that this does not invalidate their reasoning, since the physical bases for similar observable effects need not be the same for all cases.
(21) The electronegativity of sulfur has recently been estimated to be 2.52 and is therefore more electronegative than carbon which is 2.35 on this scale: G. Simons, M. E. Zandler, and E. R. Talaty, *J. Am. Chem. Soc.*, **98,** 7869 (1976).

(22) D. G. Gorenstein, *J. Am. Chem. Soc.*, **99**, 2254 (1977).
(23) D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, **89**, 5315 (1967).
(24) The physical basis of steric shifts in hydrocarbons has been recently evaluated and modified; see: K. Seidman and G. E. Maciel, *J. Am. Chem. Soc.*, **99**, 659 (1977).
(25) (a) K. Pihlaja, *J. Chem. Soc., Perkin Trans. 2*, 890 (1974); (b) E. L. Eliel and R. O. Hutchins, *J. Am. Chem. Soc.*, **91**, 2703 (1969).
(26) K. Bergesen, M. J. Cook, and A. P. Tonge, *Acta Chem. Scand., Ser. A*, **30**, 574 (1976).
(27) K. Bergesen, B. M. Carden, and M. J. Cook, *J. Chem. Soc., Perkin Trans. 2*, 345 (1976).
(28) For molecular mechanics calculations of conformations of 1,3-dithiane 1-oxides, see: N. L. Allinger and J. Kao, *Tetrahedron*, **32**, 529 (1976).
(29) For a discussion of nonchair conformations of six-membered rings and terminology, see: G. M. Kellie and F. G. Riddell, *Top. Stereochem.*, **8**, 225 (1974).
(30) G. C. Levy anc J. D. Cargioli, *J. Magn. Reson.*, **6**, 143 (1972).
(31) M. J. Cook and A. P. Tonge, *J. Chem. Soc., Perkin Trans. 2*, 767 (1974).
(32) O. Hernandez, Ph.D. Thesis, University of Virginia, 1974.
(33) (a) A. G. Brook, J. M. Duff, P. F. Jones, and M. R. Davis, *J. Am. Chem. Soc.*, **89**, 431 (1967); (b) E. J. Corey, D. Seebach, and R. Freedman, *ibid.*, **89**, 434 (1967).
(34) H. T. Kalff and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 467 (1966).

Base-Induced Rearrangements of Mesityl Thienyl Sulfones[1]

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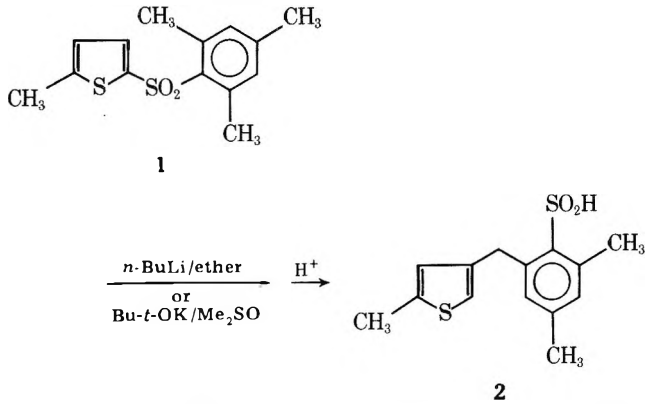
Two mesityl thienyl sulfones (5-mesitylsulfonyl-2-methylthiophene and 2-mesitylsulfonylthiophene) undergo the Truce–Smiles rearrangement. However, the thienyl unit (in contrast to the previously studied naphthyl and substituted phenyl groups) migrates with a change in orientation regardless of the base/solvent system used. The chemistry of 2-mesitylsulfonylthiophene is complicated by the acidity of the open α position, with 2 equiv of base being required for rearrangement. (The monometalated species, on the other hand, slowly decomposes to give mesitylenesulfinic acid as the only isolable product.) A modified Michael addition–β-elimination mechanism has been proposed to explain these results.

Aryl sulfones containing an ortho methyl group rearrange to *o*-benzylbenzenesulfinic acids when treated with *n*-butyllithium in ether[2] or potassium *tert*-butoxide in Me_2SO.[3] The three isomeric mesityl tolyl sulfones all give sulfinic acids with retained tolyl orientation regardless of which of these two base/solvent systems is used. In contrast to this, mesityl α-naphthyl sulfone can be caused to rearrange via two different pathways. In *n*-butyllithium/ether, rearrangement proceeds via direct displacement and retained naphthyl orientation. However, in potassium *tert*-butoxide/Me_2SO an addition–β-elimination sequence occurs, resulting in 2-(2′-naphthylmethyl)-4,6-dimethylbenzenesulfinic acid.[4]

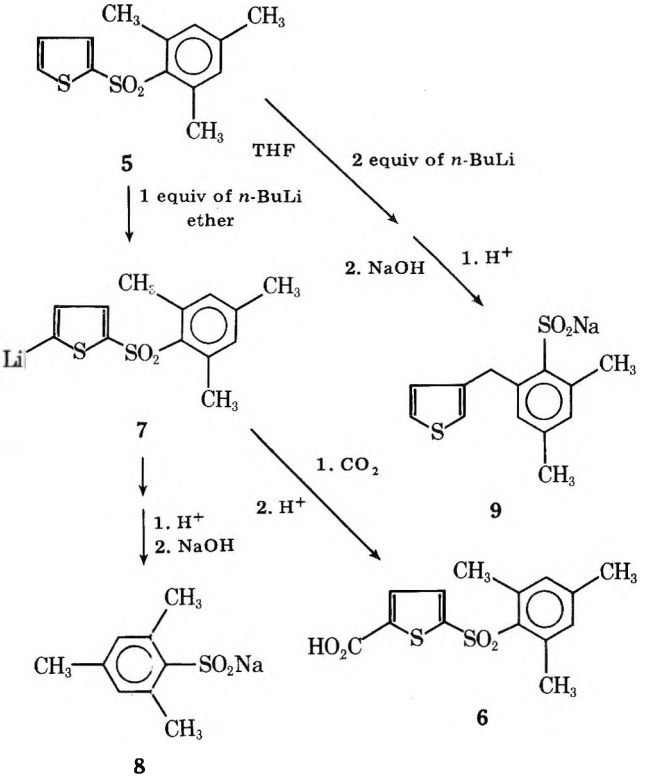
Results and Discussion

It has now been found that treatment of 5-mesitylsulfonyl-2-methylthiophene (**1**) with either *n*-butyllithium/ether or potassium *tert*-butoxide/Me_2SO yields sulfinic acid **2** via an addition–elimination sequence.



That the same sulfinic acid is produced in both base/solvent systems was shown by the identity of IR and NMR spectra as well as the melting point and mixture melting point of their 2-hydroxy-3,5-dichlorobenzyl sulfone derivative. The structure proposed for **2** is supported by the following series of reactions. Sulfinic acid **2** was treated with Raney nickel to reduce the thiophene ring to a saturated hydrocarbon unit, and to remove the sulfinate moiety. The two possible hydrocarbon products, 1-(3,5-dimethylphenyl)hexane (**3**) and 1-(3,5-dimethylphenyl)-2-methylpentane (**4**), were alternatively synthesized from 3,5-dimethylbenzyl bromide by treatment with the appropriate organometallic compounds. The Raney nickel reduction product had physical and spectral properties which matched those of hydrocarbon **4**. The spectral properties of **3** did not correlate, thus confirming **2** as the correct structure for the sulfinic acid product.

2-Mesitylsulfonylthiophene (**5**) has been found to rearrange



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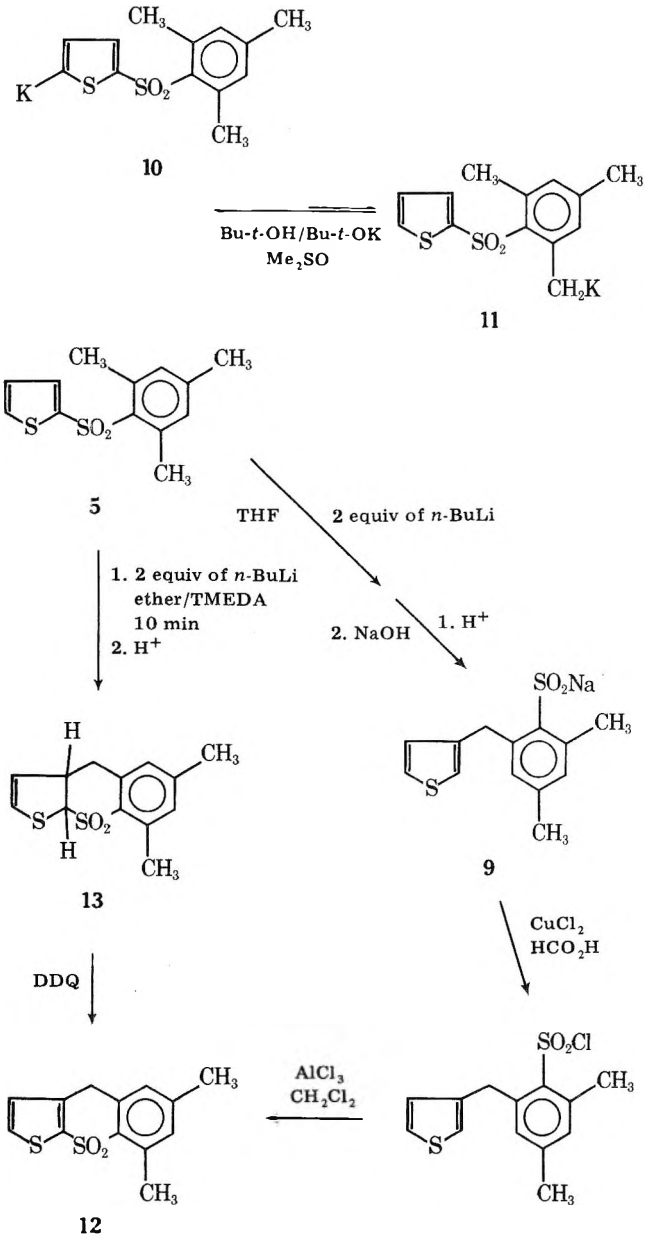
giving similar results. The chemistry of this compound, however, is more complex due to the acidity of the open α-position of the thiophene ring. A metalation study in which **5** was converted to 5-carboxy-2-mesitylsulfonylthiophene (**6**) demonstrated that this is the most acidic proton in the molecule. The lithium derivative **7** is unstable and slowly decomposes at room temperature, giving (after workup) sodium mesitylenesulfinate (**8**) as the only isolable product.

The mechanism of this cleavage reaction has not been determined, although it is possible that **7** unravels to give ethynyl sulfide (which is unstable[5]) in addition to **8**. Analogous ring-opening reactions of metalated thiophenes have previously been reported.[6]

With at least 2 equiv of *n*-butyllithium in THF, **5** rearranges to give sodium sulfinate **9**. The second equivalent of base apparently metalates on a mesityl *o*-methyl, and the dimetalated species then rearranges. Intermediate amounts of *n*-butyllithium in ether (between 1 and 2 equiv) give a mixture of **8** and **9**.

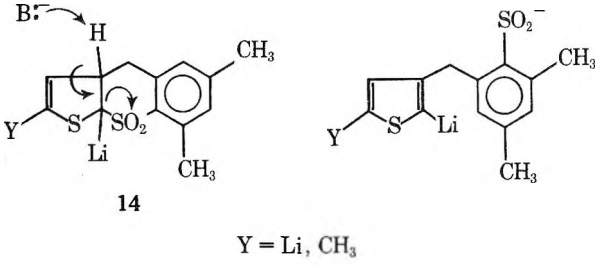
Sulfone **5** also gives sulfinic acid **9** (contaminated with a small amount of **8**) on treatment with potassium *tert*-butoxide/Me_2SO (1 or 2 equiv). In this case, rearrangement with 1 equiv of base can be explained by *tert*-butyl alcohol and potassium *tert*-butoxide aiding in a proton transfer between **10** and **11**.



The structure of sulfinic acid **9** was substantiated by the following series of reactions. The sodium sulfinate (**9**) from the *n*-butyllithium-induced rearrangement was converted to the sulfonyl chloride by reaction with cupric chloride in formic acid solution. Cyclization in a Friedel–Crafts reaction gave 4*H*-thieno[2,3-*b*][1]-6,8-dimethylbenzothiopyran 9,9-dioxide (**12**). This compound was found to be identical by IR, NMR, melting point, and mixture melting point to an authentic sample synthesized by aromatizing Michael adduct **13** with DDQ.

The reason for the occurrence of an addition–β-elimination sequence with the naphthyl mesityl sulfones in potassium *tert*-butoxide/Me_2SO is thought to be the availability of a proton source[4] (*tert*-butyl alcohol). The alcohol apparently protonates the intermediate cyclized carbanion, giving the full Michael adduct. The adduct then can undergo a β-elimination to give a sulfinic acid product with changed naphthyl orientation.

The mesitylsulfonyl-substituted thiophenes (**1** and **5**) are the first example of a system which will undergo rearrangement in aprotic media with a change in aryl orientation. One possible mechanism that would explain these results would involve a β-elimination from the cyclized intermediate **14**, rather than from the full Michael adduct. Because the reaction would be autocatalytic (**14** functioning as a proton source),



only a small percentage of the product would have to be produced via this modified mechanism. The vast majority could come from a full Michael adduct. A somewhat related ring-opening β-elimination from a dimetalated heterocyclic has been suggested to explain the products arising from 2,3-dilithiobenzo[*b*]selenophene.[7]

Experimental Section

All reactions involving *n*-butyllithium and potassium *tert*-butoxide were performed in a nitrogen atmosphere. The NMR spectra were recorded on a Varian A-60A instrument with Me_4Si used as a standard. The IR spectra were recorded on a Beckman IR-33. All melting and boiling points are uncorrected. The microanalyses were performed by Dr. C. S. Yeh and C. M. Lam of this department.

5-Mesitylsulfonyl-2-methylthiophene (1). 2-Methylthiophene was sulfonated by means of dioxane–sulfotrioxide according to the procedure of Truce and Amos[8] yielding sodium 5-methyl-2-thiophenesulfonate which was converted to the sulfonyl chloride by treatment with phosphorus pentachloride.

The sulfone was then formed by treating a well-stirred solution of 51 g (0.26 mol) of 2-methyl-5-thiophenesulfonyl chloride and 36 g (0.30 mol) of mesitylene dissolved in 200 mL of anhydrous methylene chloride with 34.5 g (0.26 mol) of aluminum chloride at −15 °C. When the addition was completed, the reaction was stirred 25 min longer at −15 °C, and hydrolyzed by pouring onto a mixture of crushed ice and 50% HCl. The layers were separated and the water layer was extracted with methylene chloride. The organic extracts were combined, dried over anhydrous $CaCl_2$, filtered, and evaporated yielding a dark solid which was recrystallized from 95% ethanol, decolorized with charcoal, and filtered, giving 36.8 g (50%) of sulfone **1**. A second recrystallization yielded pure sulfone melting at 93–94.5 °C: NMR ($CDCl_3$) δ 2.25 (s, 3), 2.44 (s, 3), 2.65 (s, 6), 6.67 (d, 1, J = 3.5 Hz), 6.92 (s, 2), 7.42 ppm (d, 1, J = 3.5 Hz).

Anal. Calcd for $C_{14}H_{16}S_2O_2$: C, 60.0; H, 5.7; S, 22.8. Found: C, 60.1; H, 5.89; S, 22.6.

2-Hydroxy-3,5-dichlorobenzyl Chloride. This preparation was adapted from the method of Buehler et al.[9] 2,4-Dichlorophenol (20 g, 0.123 mol) was dissolved in a mixture of 300 mL of concentrated

HCl and 100 mL of ethanol. The solution was warmed to 50 °C, and over a period of 30 min 20 mL of a 40% formaldehyde solution was added. HCl gas was then bubbled through the solution for 24 h. The mixture was then cooled, and the oil which had precipitated was taken up in benzene. This solution was washed with water, dried ($MgSO_4$), and stripped of solvent in vacuo. The product was purified by recrystallization from petroleum ether (90–100 °C): yield 14.0 g (54%); mp 82.5–84 °C (lit.[9] mp 81–84 °C).

General Procedure for the Preparation of 2-Hydroxy-3,5-dichlorobenzyl Sulfone Derivatives. This method was adapted from the work of Beachem et al.[10] A small amount (about 0.5 g) of the sodium salt of the sulfinic acid was dissolved in 5 to 10 mL of absolute methanol. An equimolar amount of 2-hydroxy-3,5-dichlorobenzyl chloride was dissolved in a minimal amount of absolute methanol, and the two solutions were combined. The mixture was allowed to react at room temperature in a covered flask for up to 1 day. Crystals of the sulfone often started to precipitate almost immediately and were collected by filtration when the reaction seemed complete. Generally, one recrystallization from ethanol was sufficient to obtain the derivative analytically pure.

Rearrangement of 5-Mesitylsulfonyl-2-methylthiophene. (A) *n*-Butyllithium in Ether. To 3.0 g (0.011 mol) of 5-mesitylsulfonyl-2-methylthiophene in 120 mL of anhydrous ether[11] was added dropwise a solution of 14 mL (0.018 mol) of *n*-butyllithium diluted with 30 mL of ether. The reaction mixture was stirred for 24 h at reflux in a nitrogen atmosphere, after which it was poured into ice water. The layers were separated, and the aqueous layer was extracted with ether. The aqueous layer was then cooled in an ice bath and acidified with concentrated HCl. The resulting acidic mixture was extracted with ether, and the ether extract was treated with 0.5 N aqueous NaOH. The basic solution was cooled and acidified with concentrated HCl and extracted with ether. The resulting ethereal solution was dried and evaporated, giving 2.1 g (70%) of a light-yellow oil identified as sulfinic acid **2**. One gram of this oil was dissolved in a minimum amount of methanol and neutralized to a phenolphthalein end point with 1 N methanolic KOH. To this was added 0.6 g of 2-hydroxy-3,5-dichlorobenzyl chloride in a minimum amount of methanol. The solution was allowed to stand for 12 h during which the 2-hydroxy-3,5-dichlorobenzyl derivative crystallized. Filtration followed by recrystallization from ethanol gave a 56% yield of the yellow solid: mp 188–191 °C; IR (nujol mull) 3400, 1310, and 1150 cm^{-1}.

Anal. Calcd for $C_{21}H_{20}Cl_2S_2O_3$: C, 55.5; H, 4.4; Cl, 15.4; S, 14.09; mol wt 454. Found: C, 55.50; H, 4.70; Cl, 15.64; S, 14.00; mol wt 446.2.

(B) Potassium *tert*-Butoxide in Dimethyl Sulfoxide. To 1.5 g (0.014 mol) of potassium *tert*-butoxide in 20 mL of Me_2SO was added dropwise a solution of 2.80 g (0.01 mol) of 5-mesitylsulfonyl-2-methylthiophene in 60 mL of Me_2SO. The reaction mixture was stirred in a nitrogen atmosphere at room temperature for 6 h, after which it was poured into ice water and worked up the same as the *n*-butyllithium reaction, giving a quantitative yield of a yellow tar which solidified on standing. Recrystallization from acetone–water gave mp 100–103 °C: NMR (Me_2SO-d_6) δ 2.22 (s, 3), 2.37 (s, 3), 2.63 (s, 3), 4.20 (s, 2), 6.65 (d, 1, J = 1 Hz), 6.67 (d, 1, J = 1 Hz), 6.92 (s, 2), 9.84 ppm (s, 1).

The 2-hydroxy-3,5-dichlorobenzyl derivative was prepared as above: mp 189–191 °C, mixture melting point with derivative from the *n*-butyllithium rearrangement 188–190.5 °C. The infrared spectra of these two products were identical.

Raney Nickel Reduction of the Sulfinic Acid from 5-Mesitylsulfonyl-2-methylthiophene. W-7 Raney nickel was prepared from 42 g of nickel–aluminum alloy (W. R. Grace) by the procedure of Billica and Adkins.[12] This was mixed with 5.04 g (0.018 mol) of sulfinic acid in 150 mL of absolute ethanol. The mixture was stirred at reflux for 24 h in a nitrogen atmosphere, after which it was filtered, and the nickel was washed with hot ethanol. The filtrate was evaporated, giving 3.38 g of a colorless oil. Distillation gave 1.5 g (44%) of a colorless oil boiling at 94–95 °C (3 mm): NMR ($CDCl_3$) δ 0.71–2.1 (m, 11), 2.20–2.9 (m with large s at 2.20, 8), 6.72 ppm (s, 3).

Anal. Calcd for $C_{14}H_{22}$: C, 88.4; H, 11.6; mol wt 190.3. Found: C, 88.26; H, 11.69; mol wt 196.

3,5-Dimethylbenzyl Bromide. A mixture of 30 g (0.25 mol) of mesitylene and 44.5 g (0.25 mol) of *N*-bromosuccinimide was stirred in 1500 mL of CCl_4 at reflux while being irradiated with a sunlamp. The reaction immediately turned pale green, and after 5 min the color had faded. After 2.25 h, the reaction mixture was allowed to cool to room temperature and filtered, and the precipitate was washed with CCl_4, giving 23.50 g (95%) of succinimide. Evaporation of the solvent followed by vacuum distillation gave 25.03 g (50.5%) of a colorless oil: bp 75–77 °C (1.5 mm). The NMR indicated this to be pure 3,5-dimethylbenzyl bromide. A second fraction was collected, bp 77–90 °C (1.5 mm), but an NMR spectrum indicated this is to be only 96% pure (5.50 g, 11%): NMR (neat) δ 2.10 (s, 6), 4.18 (s, 2), 6.75 and 6.83 ppm (two broad singlets, ca. 1: 2, 3).

1-(3,5-Dimethylphenyl)hexane (3). To a mixture of 0.9 g (0.13 g-atom) of Li wire cut into small pieces in 25 mL of anhydrous ether in a niyrogen atmosphere was added 7.85 g (0.052 mol) of *n*-amyl bromide dropwise with vigorous stirring. Stirring was continued for 24 h, after which the reaction mixture was filtered through a glass wool plug into a dropping funnel and slowly added to a solution of 3.98 g (0.02 mol) of 3,5-dimethylbenzyl bromide in 50 mL of ether in a nitrogen atmosphere. The reaction mixture was stirred for 5 min, after which 6 N HCl was slowly added. The layers were separated; the organic layer was washed with water and a saturated salt solution, dried, and evaporated, giving 5.52 g of a colorless oil which was vacuum distilled. Collection of the fraction boiling at 91–148 °C (1.5 mm) followed by VPC purification gave pure 1-(3,5-dimethylphenyl)-hexane (**3**), NMR ($CDCl_3$) δ 0.7–1.9 (m, 11), 2.28 (s, 6), 2.51 (t, 2, J = 7 Hz), 6.82 ppm (s, 3). NMR of the fractions boiling at 84–148 °C (1.5 mm) indicated a total of 0.39 g (10.3%) of the hydrocarbon was produced. During the distillation, 1.89 g (47.5%) of 3,5-dimethylbenzyl bromide was recovered, indicating probable incomplete formation of amyllithium

1-(3,5-Dimethylphenyl)-2-methylpentane (4). To a mixture of 4.8 g (0.2 g-atom) of Mg turnings in 200 mL of ether in a nitrogen atmosphere was slowly added 31.7 g (0.21 mol) of 2-bromopentane. The reaction mixture was stirred at reflux for 5.5 h, after which it was filtered through a glass wool plug in a dropping funnel and added dropwise to a solution of 14.2 g (0.07 mol) of 3,5-dimethylbenzyl bromide in 200 mL of ether. The reaction mixture was stirred at room temperature in a nitrogen atmosphere for 17 h, after which it was poured into 400 mL of 6 N HCl and worked up the same as the *n*-amyllithium reaction, giving 13.61 g of a slightly yellow oil. Distillation gave 2.32 g (17.2%) of a clear oil boiling at 80–90 °C (2 mm) which had IR and NMR spectra identical to the Raney nickel reduction product. A second fraction boiling at 90–125 °C (2 mm), 0.33 g, contained 90% 1-(3,5-dimethylphenyl)-2-methylpentane plus ca. 5% of a product which appears to be 1,2-bis(3,5-dimethylphenyl)ethane. When the pot was cooled, the residue solidified, giving another 3.17 g of impure symmetrical product (41% total): NMR ($CDCl_3$) δ 2.20 (s, 4), 2.75 (s, 12), 6.77 ppm (s, 6).

2-Thiophenesulfonyl Chloride. This preparation was adapted from the method of Steinkopf and Hopner.[13] Thiophene (100 g, 1.18 mol) was added dropwise to a stirred solution prepared from 230 mL (405 g, 3.14 mol) of chlorosulfonic acid and 70 mL of chloroform. The temperature was maintained at 0 °C during the 4.5-h period of addition and then allowed to warm to room temperature before quenching on a large volume of ice. The organic layer was separated, and the aqueous layer was washed three times with chloroform. The washings and the organic layer were combined, dried ($MgSO_4$), and stripped of solvent in vacuo. Vacuum distillation gave 102.2 g (47%) of the pure sulfonyl chloride: bp 82–84 °C (2 mm) [lit.[14] bp 131–132 °C (20 mm)].

2-Mesitylsulfonylthiophene. Anhydrous aluminum chloride (68 g, 0.51 mol) was added in small portions over a 30-min period to a well-stirred mixture of 2-thiophenesulfonyl chloride (91.5 g, 0.5 mol), mesitylene (72.0 g, 0.6 mol), and dichloromethane (200 mL). The temperature was maintained at −15 °C during the period of addition and for an additional 30 min before quenching on an ice/concentrated HCl mixture. The organic layer was separated, and the aqueous fraction was washed with dichloromethane. The washing and organic layer were combined, washed (aqueous $NaHCO_3$), dried ($MgSO_4$), and stripped of solvent in vacuo. The resultant dark-green solid was decolorized (Darco) and recrystallized from ethanol: yield 66.5 g (50%). A second recrystallization from ethanol was required to give pure sulfone (**5**): mp 114–115.5 °C (lit.[15] mp 115–115.5 °C); NMR ($CDCl_3$) δ 2.3 (s, 3), 2.7 (s, 6), 6.95–7.6 ppm (m, 5).

Cleavage of 2-Mesitylsulfonylthiophene. 2-Mesitylsulfonylthiophene (2.0 g, 7.5 mmol) was dissolved in 75 mL of anhydrous ether and stirred under nitrogen in an oven-dried three-necked flask. Over a period of 5 min, 4 mL of 1.9 N *n*-butyllithium was added via syringe while maintaining the reaction temperature at 0 °C. On completion of addition, the mixture was stirred at 0 °C for 5 h and then allowed to slowly warm to room temperature. After a total of 24 h, the reaction was quenched by pouring into 100 mL of water. The layers were separated, and the aqueous layer was washed once with ether. 2-Mesitylsulfonylthiophene (0.4 g, 20%) was recovered from the combined ether layer and washing. The aqueous fraction was heated on a steam bath with Darco, filtered, and chilled to 0 °C. The solution was then acidified with cold dilute HCl and extracted three times with ether. The combined extracts were dried ($MgSO_4$) and stripped of

solvent in vacuo. The crude sulfinic acid was dissolved in 10 mL of methanol and converted to its sodium salt by the addition of 1.0 N NaOH in methanol to a phenolphthalein end point. Removal of the solvent in vacuo gave a dark oil This was taken up in 25 mL of dry benzene and the benzene removed in vacuo. Two more treatments with dry benzene gave 0.5 g of a white powder identified as sodium mesitylenesulfinate (8) (24% yield): NMR (D_2O) δ 2.35 (s, 3), 2.7 (s, 6), 4.8 (s, HOD), 7.0 ppm (s, 2).

The 2-hydroxy-3,5-dichlorobenzyl sulfone derivative was prepared by reacting the sodium sulfinate with an equimolar portion of 2-hydroxy-3,5-dichlorobenzyl chloride. After 1 day, the crystalline product was isolated by filtration and recrystallized from an ethanol/water mixture: mp 171–172 °C (lit.[15] mp 170.5–171 °C); NMR ($CDCl_3$) δ 2.3 (s, 3), 2.55 (s, 6), 4.4 (s, 2), 6.1 (s, 1), 6.9–7.3 ppm (m, 4).

5-Carboxy-2-mesitylsulfonylthiophene (6). 2-Mesitylsulfonylthiophene (5.32 g, 20 mmol) was dissolved in 100 mL of anhydrous ether and stirred under nitrogen in an oven-dried three-necked flask. Over a period of 30 min, 10 mL of 2.2 N *n*-butyllithium was added via syringe while maintaining the reaction temperature at −5 °C. On completion of addition the mixture was stirred an additional 5 min and then poured onto dry ice. The dry ice was allowed to evaporate and then 100 mL of water was added. The layers were separated, and the ethereal fraction was washed once with a saturated aqueous $NaHCO_3$ solution. The washing was combined with the aqueous layer, and the solution was acidified with concentrated HCl. The crude product **6** was filtered, washed with water, and recrystallized from aqueous ethanol: yield 2.5 g (41%); mp 205–207 °C; IR (KBr) 1740 (C=O), 1310 and 1140 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 2.3 (s, 3), 2.6 (s, 6), 6.95 (s, 2), 7.5 (s, 2), 8.85 ppm (s, 1, COOH).

Anal. Calcd for $C_{14}H_{14}O_4S_2$: C, 54.17; H, 4.55; S, 20.66. Found: C, 54.07; H, 4.62; S, 20.70.

Rearrangement of 2-Mesitylsulfonylthiophene. (A) *n*-Butyllithium in Tetrahydrofuran. 2-Mesitylsulfonylthiophene (2.0 g, 7.5 mmol) was dissolved in 40 mL of dry THF (distilled from LAH) and stirred under nitrogen in an oven-dried three-necked flask. Over a period of 4 min, 13 mL of 1.0 N *n*-butyllithium was added via syringe while maintaining the temperature at −72 °C. On completion of addition, the mixture was stirred at −72 °C for an additional 15 min. The dry ice-acetone bath was then removed, and the reaction was allowed to warm to room temperature. After a total of 4 h, the reaction was quenched by pouring into 100 mL of water. The layers were separated, and the aqueous layer was washed with ether. Combination of the ether layer and washing, followed by drying ($MgSO_4$), and removal of the solvent in vacuo yielded only traces of neutral material. Workup of the aqueous layer as previously described for the isolation of sodium mesitylenesulfinate gave 1.9 g (88%) of sodium 2,4-dimethyl-6-(3′-thenyl)benzenesulfinate (9): NMR (D_2O) δ 1.95 (s, 3), 2.6 (s, 3), 4.1 (s, 2), 4.6 (s, HOD), 6.5–7.1 ppm (m, 5).

The 2-hydroxy-3,5-dichlorobenzyl sulfone derivative was prepared by reacting the sodium sulfinate with an equimolar portion of 2-hydroxy-3,5-dichlorobenzyl chloride. After 1 day, the crystalline product was isolated by filtration and recrystallized from ethanol: mp 142–144 °C (with decomposition); IR (KBr) 3450 (OH), 1305, and 1130 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 2.3 (s, 3), 2.55 (s, 3), 4.0 (s, 2), 4.35 (s, 2), 6.3 (br s, 1), 6.8–7.3 ppm (m, 7).

Anal. Calcd for $C_{20}H_{18}Cl_2S_2O_3$: C, 54.43; H, 4.11; Cl, 16.06. Found: C, 54.50; H, 4.06; Cl, 16.00.

(B) *n*-Butyllithium in Diethyl Ether. 2-Mesitylsulfonylthiophene (2.0 g, 7.5 mmol) was dissolved in 75 mL of dry diethyl ether and stirred under nitrogen in an oven-dried three-necked flask. *n*-Butyllithium (1.25 to 3 equiv) was then added via syringe while maintaining the reaction temperature at 0 °C. The reaction and workup were carried out as previously described for the isolation of sodium mesitylenesulfinate. The NMR spectra of the crude base-soluble acidic fractions showed them to contain mixtures of sodium mesitylenesulfinate and sodium 2,4-dimethyl-6-(3′-thenyl)benzenesulfinate (**9**). With 3 equiv of base, the ratio of cleavage product to rearrangement product was approximately 1 to 10. As the amount of base approached 1 equiv, sodium mesitylenesulfinate became the major product.

(C) Potassium *tert*-Butoxide in Dimethyl Sulfoxide. Potassium *tert*-butoxide (1 or 2 equiv) was suspended in 30 mL of dry Me_2SO (distilled from calcium hydride) and stirred under nitrogen in an oven-dried three-necked flask. A stopple was momentarily removed, and 2-mesitylsulfonylthiophene (4.0 g, 15 mmol) was quickly added in 1 portion. The reaction flask was cooled to maintain the temperature near 20 °C during the first few minutes of reaction. After 6 h of reaction at room temperature, the mixture was quenched by pouring into 200 mL of water. The solution was chilled in an ice bath, acidified with cold dilute HCl, and then extracted three times with ether. The ether fractions were combined and extracted two times with dilute aqueous NaOH. The aqueous extracts were worked up as previously described for the isolation of sodium mesitylenesulfinate. In both cases, mixtures of sodium mesitylenesulfinate and sodium 2,4-dimethyl-6-(3′-thenyl)benzenesulfinate (**9**) were obtained in an overall yield of approximately 60%. About 90% of these mixtures was rearrangement product (as determined from the NMR spectra). The 2-hydroxy-3,5-dichlorobenzyl sulfone derivative of the rearranged sodium sulfinate, once purified, had physical and spectral properties identical to the sulfone prepared in section A.

4*H*-Thieno[2,3-*b*][1]-6,8-dimethylbenzothiopyran 9,9-Dioxide (12). The rearranged sodium sulfinate **9** from the *n*-butyllithium/THF reaction was converted to the corresponding sulfonyl chloride by the method of Pfeil and Velten.[16] Sodium 2,4-dimethyl-6-(3′-thenyl) benzenesulfinate (1.85 g, 6.5 mmol) was dissolved in 20 mL of 88% formic acid. In a separate container, 12 g of cupic chloride dihydrate was dissolved in 12 mL of water and 12 mL of 88% formic acid. The two solutions were combined and stirred for 5 min before pouring onto an ice/concentrated HCl mixture. The pasty solid which precipitated was washed with cold concentrated HCl until the washings were clear. The solid was then taken up in dichloromethane, washed once with concentrated HCl, twice with water, dried ($MgSO_4$), and stripped of solvent in vacuo. The resulting crude sulfonyl chloride (1.6 g, 83%) was not further purified but was dissolved in 40 mL of dichloromethane and treated with 2.5 g of anhydrous aluminum chloride over a 15-min period. The reaction was maintained at 0 °C during the addition and was stirred an additional 45 min at room temperature before quenching in water. The organic layer was separated, and the aqueous layer was washed with dichloromethane. The washing and organic fraction were combined, washed with water, dried ($MgSO_4$), and stripped of solvent in vacuo. The resulting paste was cooled, and, on the addition of 5 mL of carbon tetrachloride, crystallized, giving 0.7 g (41% from **9**) of sulfone **12.** Two recrystallizations from carbon tetrachloride gave pure **12:** mp 160–162 °C; IR (KBr) 1280 and 1140 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 2.3 (s, 3), 2.8 (s, 3), 4.1 (s, 2), 7.0 (s, 2), 6.95 and 7.55 ppm (d, 1 J = 5 Hz).

Anal. Calcd for $C_{13}H_{12}O_2S_2$: C, 59.06; H, 4.58; S, 24.26. Found: C, 59.20; H, 4.69; S, 24.29.

3a*H*,8a*H*,4*H*-Thieno[2,3-*b*][1]-6,8-dimethylbenzothipyran 9,9-Dioxide (13). 2-Mesitylsulfonylthiophene (4.0 g, 15 mmol) was dissolved in 40 mL of dry diethyl ether and 40 mL of tetramethylethylenediamine (distilled from calcium hydride) and stirred under nitrogen in an oven-dried three-necked flask. Over a period of 10 min, 13.5 mL of 2.2 N *n*-butyllithium was added via syringe while maintaining the reaction temperature at 0 °C. The solution was stirred an additional 10 min at 0 °C and then quenced by pouring onto an ice/concentrated HCl mixture. Ether was removed from the acidic heterogeneous solution in vacuo. The crude sulfone was filtered, washed with an aqueous $NaHCO_3$ solution, and suction dried. Recrystallization from ethanol gave 1.3 g (33%) of the product (**13**): mp 138–141 °C; IR (KBr) 1295 and 1135 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 2.3 (s, 3), 2.65 (s, 3 , 2.9 and 3.5 (d of d, 1 proton each, J = 6, 14 Hz), 3.9–4.4 (m, 1), 5.1 (d, 1 J = 11 Hz), 5.3 and 5.85 (d of d, 1 proton each, J = 2, 6 Hz). 6.9 ppm (s, 2). Two additional recrystallizations from ethanol gave an analytically pure sample, mp 140.5–142 °C.

Anal. Calcd for $C_{13}H_{14}O_2S_2$: C, 58.62; H, 5.30; S, 24.07. Found: C, 58.35; H, 5.56; S, 23.97.

Alternate Synthesis of 12 from 13. Sulfone **13** (1.3 g, 4.9 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.5 g, 11.0 mmol), and picric acid (0.2 g) were dissolved in 30 mL of dry benzene. The stirred solution was refluxed for 6 h under nitrogen, during which time a precipitate formed. This was filtered and the filtrate was washed with a saturated $NaHCO_3$ solution until no more color was extracted. The organic phase was then washed successively with 10% aqueous NaOH, water, dilute aqueous HCl, and finally with water again. The benzene solution was then dried ($MgSO_4$), and stripped of solvent in vacuo to yield 1.2 g of a yellow oil. This was placed on an alumina column and eluted with a 1 to 1 mixture of chloroform and benzene. The first fractions contained 0.7 g (54%) of sulfone **12.** Two recrystallizations from carbon tetrachloride gave pure material, mp 161–162 °C. The IR and NMR spectra were identical to those from the sample prepared from sodium sulfinate **9.** A mixture melting point was undepressed.

Registry No.—**1,** 21991-09-3; **2,** 63988-85-2; **2** 2-hydroxy-3,5-dichlorobenzyl sulfone derivative, 63988-86-3; **3,** 63988-87-4; **4,** 63988-88-5; **5,** 21991-08-2; **6,** 63988-89-6; **8,** 50827-54-8; **8** 2-hydroxy-3,5-dichlorobenzyl sulfone derivative, 63988-90-9; **9,** 63988-91-0; **9** 2-hydroxy-3,5-dichlorobenzyl sulfone derivative, 63988-92-1;

12, 63988-93-2; 13, 63988-94-3; sodium 5-methyl-2-thiophenesulfonate, 63988-95-4; 2-methyl-5-thiophenesulfonyl, 55854-45-0; mesitylene, 108-67-8; 2-hydroxy-3,5-dichlorobenzyl chloride, 6333-33-1; 2,4-dichlorophenol, 120-83-2; formaldehyde, 50-00-0; 3,5-dimethylbenzyl bromide, 27129-86-8; amyl bromide, 110-53-2; 2-bromopentane, 107-81-3; 2-thiophenesulfonyl chloride, 16629-19-9; thiophene, 110-02-1; chlorosulfonic acid, 7790-94-5.

Notes and References

(1) Based on the Ph.D. Theses of B. VanGemert, Purdue University, 1976, and W. W. Brand, Purdue University, 1970.
(2) W. E. Truce, W. J. Ray, Jr., O. L. Norman, and D. B. Eickemeyer, *J. Am. Chem. Soc.*, **80**, 3625 (1958).
(3) W. E. Truce, C. R. Robbins, and E. M. Kreider, *J. Am. Chem. Soc.*, **88**, 4027 (1966).
(4) W. E. Truce and W. W. Brand, *J. Org. Chem.*, **35**, 1828 (1970).
(5) L. Brandsma and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **81**, 510 (1962).
(6) S. Gronowitz and T. Frejd, *Acta Chem. Scand.*, **24**, 2656 (1970).
(7) T. Q. Minh, L. Christiaens, and M. Renson, *Bull. Soc. Chim. Fr., Part 2*, 2244 (1974).
(8) W. E. Truce and M. F. Amos, *J. Am. Chem. Soc.*, **73**, 3013 (1951).
(9) C. A. Buehler, R. L. Brown, J. M. Holbert, J. G. Fulmer, and G. W. Parker, *J. Org. Chem.*, **6**, 903 (1941).
(10) M. T. Beachem, J. T. Shaw, G. D. Sargent, R. B. Fortenbaugh, and J. M. Salsbury, *J. Am. Chem. Soc.*, **81**, 5430 (1959).
(11) Mallinckrodt anhydrous ether was further dried over sodium before use.
(12) H. R. Billica and H. Adkins, "Organic Syntheses", Collect. Vol. 3, Wiley, New York, N.Y., 176 (1955).
(13) W. Steinkopf and T. Hopner, *Justus Liebigs Ann. Chem.*, **501**, 1 (1933).
(14) H. Burton and W. A. Davy, *J. Chem. Soc.*, 525 (1948).
(15) D. C. Hampton, Ph.D. Thesis, Purdue University, W. Lafayette, Indiana, 1963.
(16) E. Pfeil and O. Velten, *Justus Liebigs Ann. Chem.*, **565**, 183 (1949).

Proaporphine–Aporphine Dimers and a Bisaporphine Derived from the Tumor-Inhibitory Alkaloid Thalicarpine[1a]

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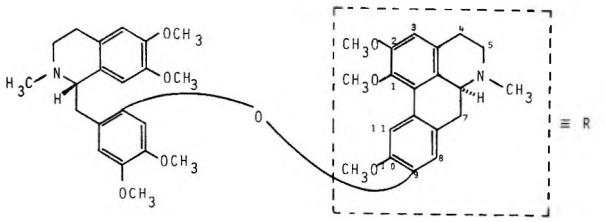
Oxidation of the tumor inhibitory alkaloid thalicarpine (1), a benzylisoquinoline–aporphine dimer, with VOF_3 in TFA gave a mixture of diastereoisomeric dienones 2 and 3, a new type of proaporphine–aporphine alkaloid. The major isomer 2 was converted to the epimeric dienols 6a and 6b which, upon treatment with BF_3–Et_2O in CH_2Cl_2, gave another new type of alkaloid, bisaporphine 8. Preliminary testing results indicate that bisaporphine 8 is active in vitro against cells derived from the human carcinoma of the nasopharynx (KB).

The alkaloid thalicarpine,[2] which has the aporphine–benzylisoquinoline structure 1,[3] exhibits a significant inhibitory activity against the Walker 256 intramuscular carcinosarcoma in rats over a wide dosage range.[4]

In order to gain some insight into the structure–tumor inhibitory activity relationship in this alkaloid series, we have undertaken studies directed toward structural modifications of thalicarpine. We report herewith the conversion of thalicarpine (1) to a new type of alkaloid, proaporphine–aporphine dimers 2 and 3, and thence to another new type of alkaloid, bisaporphine 8. Both 2 and 8 serve as models for types of alkaloids which have not been isolated from natural sources to date.



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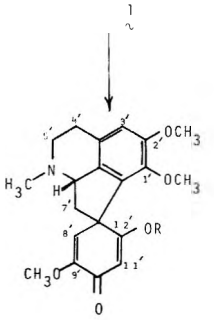
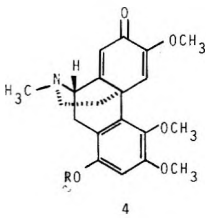


2, 3

Recently, a number of nonphenol oxidative coupling reactions which yield spirodienone intermediates and products have been reported.[5-10] Thus, morphinandienones (e.g., 4) have been recognized as the primary products of chemical[5,6] as well as electrooxidative coupling of nonphenolic tetrahydrobenzylisoquinoline precursors. On the other hand, chemical[6] and electrochemical[9] oxidative coupling of tetramethoxylated bibenzyls gave dihydrophenanthrone derivatives via five-membered ring spirodienone intermediates, similar to the proerythrinadienone-type systems (e.g., 5). Oxidation



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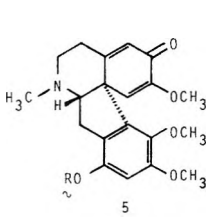

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of nonphenolic phenethyltetrahydroisoquinolines using vanadium oxytrifluoride (VOF_3) in trifluoroacetic acid (TFA) to homoaporphines via homoproerythrinadienone intermediates[10] was also reported.

Thalicarpine (1), a nonphenolic alkaloid, was thus subjected to chemical as well as anodic oxidative coupling reactions to elaborate the benzyltetrahydroisoquinoline part of the molecule. The oxidation of thalicarpine (1) was best performed by treating 0.4 mmol of the alkaloid in CH_2Cl_2, TFA,[11] and FSO_3H with 2.5 molar equiv of VOF_3 in TFA and ethyl acetate at −10 °C for 10 min. The product was a mixture of dienones 2 and 3, diastereomers at the spiro ring junction. The two isomers were separated by preparative thin layer chroma-

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Table I. NMR Resonances of Dienones and Dienols [a]

		2	3	6a	6b	7a	7b
N-Methyl	N-6	2.44	2.43	2.42	2.42	2.44	2.40
	N-6′	2.58	2.49	2.57	2.55	2.48	2.49
Methoxyl	C-1	3.68	3.65	3.61	3.59	3.64	3.64
	C-2[b]	*3.84*	*3.85*	*3.88*	*3.82*	*3.78*	*3.82*
	C-10	*3.88*	*3.89*	*3.94*	*3.88*	*3.85*	*3.88*
	C-1′[b]	3.71	3.71	3.73	3.74	3.73	3.73
	C-2′[b]	3.74	3.75	3.85	3.79	3.78	3.75
	C-9′	3.59	3.65	3.58	3.59	3.61	3.59
Aromatic	C-3[c]	6.67	6.68	6.62	6.60	6.63	6.60
	C-8	6.94	6.80	6.88	6.95	6.76	6.82
	C-11	8.09	8.14	8.10	8.08	8.08	8.09
	C-3′[c]	6.63	6.64	6.62	6.60	6.63	6.60
Olefinic	C-8′	5.63	5.59	4.91	4.96	4.83[d]	4.84[d]
	C-11′	5.81	5.46	5.02[d]	4.88[d]	4.72	4.70

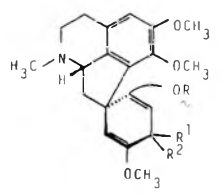
[a] Values are given in δ units relative to tetramethylsilane as internal standard. All spectra were recorded in $CDCl_3$. [b] The values are interchangeable for these methoxyl signals. [c] The values are interchangeable for these aromatic protons. [d] Doublet (J = 4–5 Hz).

tography (PTLC) and isolated in crystalline form in 72% and 5% yield, respectively. In contrast to VOF_3–(TFA–TFAA) oxidation, anodic oxidation of thalicarpine (**1**) in TFA–TFAA using tetraethylammonium tetrafluoroborate as supporting electrolyte gave the dienones **2** and **3** in yields of 40 and 5%, respectively.

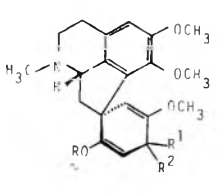
The infrared spectra of both isomers showed typical dienone absorptions at 1655, 1635, and 1605 cm^{-1}. The UV spectra of both **2** and **3** exhibited λ_{max}(EtOH) 232 (sh), 258, 263, 275, and 304 nm. The mass spectra showed a molecular ion peak at m/e 680 for both isomers and a base peak at m/e 324 (R^+) for the major isomer (**2**) and 340 (OR^+ or $M^+ - OR$) for the minor isomer (**3**). The NMR signals (Table I) were assigned by comparison to those of similar systems.[12-14]

The possibility of a morphinandienone-type (**4**) or a proerythrinadienone-type (**5**) structure for the oxidation products was excluded by the formation of a mixture of diastereoisomeric dienones and further modifications of the dienones and further modifications of the dienones as described below.

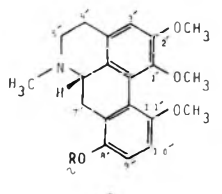
Dienones **2** and **3** were subjected to the acid-catalyzed dienone–phenol rearrangement under a variety of conditions (i.e., concentrated HCl in glacial acetic acid, BF_3–Et_2O in CH_2Cl_2, TFA) but unchanged starting material was recovered in each case. In contrast, the epimeric dienols, represented as **6a** and **6b**,[15] obtained by sodium borohydride reduction of the major dienone **2** in 75 and 15% yield, underwent smooth dienol–benzene rearrangement upon treatment with boron trifluoride etherate in CH_2Cl_2 at 0 °C for 10 min. Thus, dienol



6a, R′=OH; R²=H
b, R′=H; R²=OH



7a, R′=OH; R²=H
b, R′=H; R²=OH



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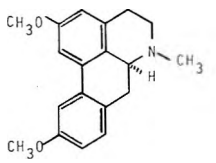
6a was converted to a bisaporphine (**8**) in 80% yield as the dihydrobromide salt. The structure of bisaporphine **8** was confirmed by sodium in liquid ammonia cleavage[16] of the bisaporphine. The nonphenolic product was indistinguishable in terms of melting point, TLC, UV, NMR, mass spectra, and specific rotation from an authentic sample of L(+)-2,10-dimethoxyaporphine (**9**) derived from sodium in liquid ammonia cleavage of thalicarpine.[17] From the physical data obtained, the phenolic product could have been either **10a** or **10b**. However, inspection of the NMR spectrum of the acetate **10c**, prepared by treatment of the phenolic product with acetic



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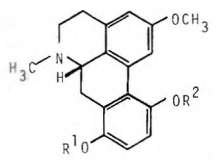

10a, R′=H; R²=CH₃
b, R′=CH₃; R²=H
c, R′=COCH₃; R²=CH₃

anhydride–pyridine, revealed that there was no change in the chemical shift of the C-1 proton at δ 7.75 (1 H, d, $J_{1,3}$ = 2.4 Hz). This suggested that the structure of the phenolic product was **10a**. Had the structure been **10b**, the C-1 H signal should have been shifted farther downfield. Further support for the structure of the phenolic product came from the study of the effect of alkali on the NMR spectrum of the phenolic product (**10a**) in Me_2SO-d_6, which showed a signal at δ 5.59 (2 H, s) for the C-9 and C-10 protons. Upon addition of a drop of alkali (sodium hydroxide in CD_3OD), the signal at δ 5.59 was shifted to δ 5.32 and appeared as an AB quartet ($J_{9,10}$ = 6 Hz, $\Delta\nu_{AB}$ = 8 Hz), whereas there was no change in the chemical shift of the C-1 proton, again confirming the structure of the phenolic product as **10a**.

In contrast to the acid-catalyzed rearrangement of the dienols **6a** and **6b** to bisaporphine **8**, the dienols, represented as **7a** and **7b**, obtained by borohydride reduction of the minor dienone **3**, gave only cleavage products upon treatment with boron trifluoride etherate in CH_2Cl_2. Further investigation of these cleavage products was not pursued.

The bisaporphine (**8**) is active (ED_{50} = 1.85 μg/mL) in vitro against cells derived from the human carcinoma of the nasopharynx (KB) and is now undergoing preliminary testing under the auspices of the National Cancer Institute.

Experimental Section

Melting points were determined on a Mettler FP2 melting point apparatus and are uncorrected. Ultraviolet spectra were determined

on a Beckman DK-2A recording spectrophotometer. NMR spectra were recorded on a JEOL PFT-100P pulse Fourier transform NMR spectrometer, using tetramethylsilane as internal standard. Infrared spectra were determined on a Perkin-Elmer 337 recording spectrophotometer. Mass spectra were obtained on Hitachi Perkin-Elmer RMU-6E and Atlas MS-902 spectrometers. Thin-layer chromatography was carried out on commercially prepared TLC plates (E. M. Reagents). Preparative TLC was carried out with silica gel (F-254 2 × 200 × 200, or 0.5 × 200 × 200, or 0.25 × 200 × 200 mm) plates. Visualization of the alkaloids was performed by spraying the entire analytical plate, or the edges of the preparative plate, with an aqueous solution of iodoplatinic acid reagent (1.0 g in 250 mL of water containing 15 g of potassium iodide) and/or ultraviolet light. Microanalyses were carried out by Atlantic Microlab, Inc., Atlanta, Ga. Column chromatography was carried out on Silica Gel 60 (70–230 mesh ASTM) obtained from E. M. Reagents. Anhydrous sodium sulfate was used as the drying agent, exclusively.

Proaporphine–Aporphine Dimers (2 and 3). (A) By Chemical Oxidation. A solution of 280 mg (0.4 mmol) of thalicarpine in 2 mL of dichloromethane and 1 mL of TFA–TFAA (20:1 by weight) was cooled to −10 °C (ice–salt bath). Following the addition of 0.1 mL of fluorosulfonic acid, a solution of 240 mg (1.9 mmol) of vanadium oxytrifluoride in 1 mL of ethyl acetate and 2 mL of TFA–TFAA (20:1 by weight) was added and the resulting dark brown solution was stirred for 10 min. The reaction was quenched with 15 mL of 10% aqueous citric acid solution, made alkaline with 58% ammonium hydroxide, and extracted with dichloromethane. The dichloromethane solution was washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated to leave 305 mg of a yellow foam, which was applied to nine 0.5-mm preparative silica gel plates and eluted with 10% methanol in chloroform. Two bands with R_f 0.55 and 0.35 were obtained. The higher R_f band after extraction with 20% methanol in chloroform and crystallization from methanol–ether–hexane (1:10:1) gave 204 mg (72%) of the proaporphine–aporphine dimer **2** as dirty white crystals: mp 178.5–180 °C; UV λ_{max}(EtOH) (log ϵ) 232 (sh, 4.63), 258 (4.39), 263 (4.40), 275 (4.32), 304 (4.18) nm; IR ($CHCl_3$) 2790, 2815, 1650, 1633, 1603 cm^{-1}; mass spectrum *m/e* 680 (M^+), 679, 678, 665, 637, 622, 340, and 324; $[\alpha]^{29}_D$ −17° (0.32, $CHCl_3$).

Anal. Calcd for $C_{40}H_{44}O_8N_2 \cdot CH_3OH$: C, 69.08; H, 6.78; N, 3.92. Found: C, 68.80; H, 6.78; N, 3.92.

The lower R_f band after extraction with 20% methanol in chloroform and crystallization from methanol–ether–hexane (1:10:1) gave 13 mg (5%) of the proaporphine–aporphine dimer **3** as dirty white crystals: mp 175.5–177.3 °C; UV λ_{max}(EtOH) (log ϵ) 232 (sh 4.67), 258 (4.42), 263 (4.41), 275 (4.30), 304 (4.2) nm; IR ($CHCl_3$) 2793, 2818, 1658, 1635, 1605 cm^{-1}; mass spectrum *m/e* 680 (M^+), 679, 678, 665, 637, 622, 340, and 324; $[\alpha]_D$ +61.2° (0.32, $CHCl_3$).

Anal. Calcd for $C_{40}H_{44}O_8N_2 \cdot CH_3OH$: C, 69.08; H, 6.78; N, 3.92. Found: C, 69.07; H, 6.91; N, 3.94.

(B) By Anodic Oxidation. The oxidation was conducted in a three-compartment cell (which separated the anode, cathode, and reference electrode solutions by glass frits) in conjunction with a Princeton Applied Research Model 376 potentiostat. The anode was a platinum mesh and a stainless steel spatula served as the cathode. The anode compartment had an approximate 120 mL volume in which the solution was agitated by means of a magnetic stir bar. A 0.1 N $AgNO_3$ solution in acetonitrile in contact with an Ag wire served as the reference.

Thalicarpine (208 mg; 0.3 mmol) was added to the anode compartment containing 120 mL of a mixture of TFA–TFAA (20:1 by weight). Tetraethylammonium tetrafluoroborate (3.0 g) was added as a background electrolyte to the anode and 1.0 g to the cathode compartments. The electrolysis was carried out at a constant potential of 1.4 V at room temperature. The initial current was 35 mA; it dropped as the reaction proceeded. The electrolysis was stopped when the current attained a constant minimum value (3 mA after 70 min). The anolyte was evaporated under reduced pressure and the residue was taken up in water and made alkaline with 58% NH_4OH. The organic material was extracted with chloroform. The chloroform solution was dried and evaporated to give a dark brown gum which was quickly passed through a short column of silica gel using 2% methanol in chloroform. The product obtained was purified by preparative layer chromatography as described in section A to give 82 mg (40%) of **2** and 11 mg (5%) of **3**.

Sodium Borohydride Reduction of Dienones 2 and 3. To a stirred solution of 200 mg (0.29 mmol) of **2** in 5 mL of ethanol was added 100 mg of sodium borohydride portionwise over 10 min under cooling, and the reaction mixture was allowed to stir for 5 h at room temperature. After removal of the solvent, the residue was suspended in water and extracted with dichloromethane. The dichloromethane extract was washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated to give 210 mg of a colorless glass which was applied to five 0.5-mm preparative silica gel plates and eluted with 10% methanol in chloroform. Two bands with R_f 0.6 and 0.35 were obtained. The higher R_f band after extraction with 20% methanol in chloroform and crystallization from ether gave 140 mg (70%) of the dienol **6a** as slightly yellow crystals: mp 171–173 °C; UV λ_{max}(EtOH) (log ϵ) 268 (sh, 4.20), 278 (4.30), 302 (4.15), 312 (sh, 4.03); IR ($CHCl_3$) 3475, 2780, 2820, 1600, 1658 cm^{-1}; mass spectrum *m/e* 682 (M^+, very weak), 664 (M^+ − 18, base peak).

Anal. Calcd for $C_{40}H_{46}O_8N_2$: C, 70.36; H, 6.80; N, 4.10. Found: C, 70.31; H, 6.84; N, 4.10.

The lower R_f band after extraction with 20% methanol in chloroform and crystallization from ether gave 30 mg (15%) of the dienol **6b** as slightly yellow crystals: mp 185–187 °C; UV λ_{max}(EtOH) (log ϵ) 268 (sh, 4.22), 278 (4.32), 302 (4.17), 312 (sh, 4.05) nm; IR ($CHCl_3$) 3480, 2780, 2825, 1600, 1658 cm^{-1}.

Anal. Calcd for $C_{20}H_{46}N_2O_8 \cdot {}^3/_4H_2O$: C, 69.06; H, 6.87; N, 4.02. Found: C, 69.06; H, 7.08; N, 4.01.

Similarly, dienone **3** (100 mg) was reduced to give **7a:** 63 mg (62%); mp 139–142 °C; UV λ_{max}(EtOH) 268, 278, 302, 314 (sh) nm; IR ($CHCl_3$) 3470, 1655, 1601 cm^{-1}; mass spectrum *m/e* 682 (M^+), 664 (M^+ − 18, base peak), and **7b:** 15 mg (15%); mp 193.5–194 °C; UV λ_{max}(EtOH) 268, 278, 304, 319 nm; IR ($CHCl_3$) 3975, 1650, 1605 cm^{-1}; mass spectrum *m/e* 682 (M^+), 664 (M^+ − 18, base peak).

Bisaporphine (8). A solution of 100 mg (0.15 mmol) of dienol **6a** in 4 mL of dichloromethane was cooled to 0 °C and treated with 0.1 mL of boron trifluoride etherate, drop by drop, with stirring and the resulting yellow solution was stirred for an additional 10 min. The reaction mixture was diluted with water, made alkaline with 58% ammonium hydroxide, and extracted with dichloromethane. The dichloromethane extract was washed with saturated brine, dried, and evaporated to leave a yellow glass which was applied to three 0.5-mm preparative silica gel plates and eluted with 10% methanol in chloroform. The major band was collected and extracted with 20% methanol in chloroform. Evaporation of the solvent and crystallization of the residue as the hydrobromide salt from methanol–ether gave 96 mg (80%) of bisaporphine **8** as an amorphous powder: mp 216–218 °C; UV λ_{max}(EtOH) (log ϵ) 278 (4.51), 304 (4.47) nm; NMR ($CDCl_3$) δ 8.17 (s, 1 H, C-11 H), 7.11–6.86 (AB quartet, C-9′ and C-10′ H, J_{AB} = 9 Hz), 6.66, 6.59, and 6.47 (each s, 3H, Ar H), 3.95, 3.89, 3.58, 3.87 (each s, 12 H, OCH_3), 3.70 (s, 6 H, OCH_3), 2.46 and 2.36 (each s, 6 H, NCH_3); mass spectrum *m/e* 664 (M^+), 649 ($M^+ - CH_3$), 633 ($M^+ - OCH_3$).

Anal. Calcd for $C_{40}H_{44}O_7N_2 \cdot 2HBr \cdot 2H_2O$: C, 55.69; H, 5.84; N, 3.25. Found: C, 55.71; H, 5.68; N, 3.33.

By following the above procedure, dienol **6b** was also converted to the bisaporphine **8** in 74% yield. However, similar treatment of dienols **7a** and **7b** yielded only a mixture of cleavage products. Further investigation of these products was not pursued.

Sodium–Liquid Ammonia Cleavage of Bisaporphine 8. A solution of 80 mg of **8** in 5 mL of dry THF was added dropwise to a stirred solution of 0.08 g of sodium metal in 60 mL of ammonia at −75 °C under a nitrogen atmosphere. A blue color persisted for 2 h, at which time the mixture was allowed to stand overnight. The residue was treated with 5% hydrochloric acid to pH 7.5 and extracted with dichloromethane. The dichloromethane solution was washed with saturated brine, dried, and evaporated to leave a brown residue which was applied to four 0.25-mm preparative silica gel plates and eluted with 10% methanol in chloroform. Two major alkaloid bands with R_f 0.4 and 0.15 were obtained.

L(+)-2,10-Dimethoxyaporphine (9). The high R_f band was isolated to yield 10 mg of **9** as a light yellow oil which was crystallized from methanol as the hydriodide salt to give 5 mg of product: mp 237–239 °C; mmp; UV λ_{max}(EtOH) (log ϵ) 266 (4.10), 272 (4.12), 298 (3.68), 310 (3.75), and 318 (3.76); mass spectrum *m/e* 295 (M^+), 294, 280, 274, 251, and 97; NMR ($CDCl_3$) δ 7.23 (d, 1 H, C-1 H, $J_{1,3}$ = 2.4 Hz), 7.16 (d, 1 H, C-8 H, $J_{8,9}$ = 8.0 Hz), 7.10 (d, 1 H, C-11 H, $J_{9,11}$ = 2.5 Hz), 6.85, 6.83, 6.77, and 6.61 (d, 1 H, C-3 H, $J_{3,1}$ = 2.4 Hz), 3.85 and 3.84 (each s, 6 H, OCH_3), 2.55 (s, 3 H, NCH_3); infrared spectrum in chloroform, as well as $[\alpha]^{24}_D$ = 111.8°, were identical with those of an authentic sample obtained by sodium–liquid ammonia cleavage of thalicarpine.

8-Hydroxy-2,11-dimethoxyaporphine (10a). The low R_f band was isolated to yield 10 mg of **10a** as a slightly yellow oil: $[\alpha]^{24}_D$ +133° (c 0.70, chloroform); mass spectrum *m/e* 311 (M^+); UV λ_{max}(EtOH) 266, 276, 300, 310, and 318 nm; NMR ($CDCl_3$) δ 7.75 (d, 1 H, C-1 H, $J_{1,3}$ = 2.7 Hz), 6.65 (s, 2 H, C-9 and C-10 H), 6.58 (d, 1 H, C-3 H, $J_{3,1}$ = 2.7 Hz), 5.44 (s, 1 H, OH), 3.80 and 3.77 (each s, 6 H, OCH_3), 2.58 (s, 3 H, NCH_3).

8-*O*-Acetyl-2,11-dimethoxyaporphine (10c). A mixture of 4 mg of **10a**, 0.1 mL of pyridine, and 0.5 mL of acetic anhydride was allowed to stand overnight. Workup and purification by preparative layer chromatography using 10% methanol in chloroform afforded 4 mg of a yellow oil: IR ($CHCl_3$) 1770, 2790; UV λ_{max}(EtOH) 266, 272, 298, 310, and 318 nm; mass spectrum *m/e* 353 (M^+), 352, 338, 322, 310; NMR ($CDCl_3$) δ 7.75 (d, 1 H, C-1 H, $J_{1,3}$ = 2.4 Hz), 7.04, 6.95, 6.93, 6.84 (AB quartet, 2 H, C-10 and C-11 H, J = 9 Hz, $\Delta\nu_{AB}$ = 6 Hz), 6.62 (d, 1 H, C-3 H, J = 2.4 Hz), 3.88 and 3.82 (each s, 6 H, OCH_3), 2.60 (s, 3 H, NCH_3), 2.35 (s, 3 H, CH_3CO).

Registry No.—**1**, 5373-42-2; **2**, 64056-78-6; **3**, 64129-87-9; **6a**, 64129-86-8; **6b**, 64129-85-7; **7a**, 64056-79-7; **7b**, 64129-78-8; **8**, 64056-80-0; **9**, 64056-81-1; **10a**, 64056-82-2; **10c**, 64056-62-8.

References and Notes

(1) (a) This investigation was supported by grants from the National Cancer Institute (CA-12059) and the American Cancer Society (CI-102K); (b) Deceased Oct 19, 1976; (c) to whom correspondence should be addressed at the Department of Chemistry, Oregon State University, Corvallis, Ore. 97331.
(2) S. M. Kupchan, K. K. Chakravarti, and N. Yokoyama, *J. Pharm. Sci.*, **52**, 985 (1963).
(3) M. Tomita, H. Furukawa, S.-T. Lu, and S. M. Kupchan, *Tetrahedron Lett.*, 4309 (1965); *Chem. Pharm. Bull.*, **15**, 959 (1967).
(4) (a) S. M. Kupchan, 7th Pan American Congress of Pharmacy and Biochemistry, Buenos Aires, Dec 1966; *Chem. Eng. News*, **44**, 64 (1966); (b) J. L. Hartwell and B. J. Abbott, *Adv. Pharmacol. Chemother.*, **7**, 117 (1969).
(5) S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *J. Am. Chem. Soc.*, **95**, 6861 (1973).
(6) S. M. Kupchan, V. Kameswaran, J. T. Lynn, D. K. Williams, and A. J. Liepa, *J. Am. Chem. Soc.*, **97**, 5622 (1975).
(7) L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Am. Chem. Soc.*, **95**, 2651 (1973).
(8) E. Kotani and S. Tobinaga, *Tetrahedron Lett.*, 4759 (1973).
(9) J. R. Falck, L. L. Miller, and F. R. Stermitz, *J. Am. Chem. Soc.*, **96**, 2981 (1974).
(10) S. M. Kupchan, O. P. Dhingra, C.-K. Kim, and V. Kameswaran, *J. Org. Chem.*, **41**, 4047 (1976).
(11) A mixture of TFA–TFAA (20:1 by weight) was used in all oxidations to make sure that the medium was anhydrous.
(12) M.Shamma, "The Isoquinoline Alkaloids, Chemistry and Pharmacology," Academic Press, New York, N.Y., 1972, p 119
(13) M. Shamma, J. L. Moniot, S. Y. Yao, G. A. Miana, and M. Ikram, *J. Am. Chem. Soc.*, **95**, 5742 (1973).
(14) M. Shamma, S. S. Salgar, and J. L. Moniot, *Tetrahedron Lett.*, 1859 (1973).
(15) Inspection of molecular models suggested that the transition state for the formation of the ring junction represented by **6a** and **6b** might be of lower energy than for the formation of that represented by **7a** and **7b** due to the steric interaction between the C-6′ proton and the aporphine ring in **7a** and **7b**. Consequently, the major dienone (**2**) is thought to have a spiro ring junction as represented in **8a** and **6b**, and the minor dienone (**3**) as represented in **7a** and **7b**.
(16) M. Shamma in ref 12, pp 233–238.
(17) S. M. Kupchan and N. Yokoyama, *J. Am. Chem. Soc.*, **86**, 2177 (1964).

Synthesis and Carbon-13 Nuclear Magnetic Resonance Spectral Properties of Two New Enamine Systems: 3-Amino-2-phospholene Sulfides and Their *S*-Methyl Salts[1]

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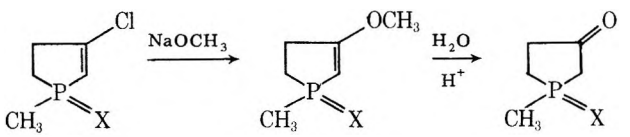
Enamines are formed in high yield by the displacement of chlorine from 1-methyl-3-chloro-2-phospholene sulfides with pyrrolidine, piperidine, morpholine, and cyclohexylamine. Alkylation fails to occur at C-2, the β carbon of the enamine system, but does occur readily on sulfur, making available a family of enamine derivatives bearing alkylthiophosphonio groups. These compounds have remarkably high field (δ 62–66) ^{13}C NMR signals for C-2 and are characterized also by a barrier to rotation about C–N that is greater even than that found in related enamino ketones. This barrier leads to separate ^{13}C signals for the α and for the β carbons of the amine moiety in the pyrrolidine derivative (coalescence temperature about 97 °C; $\Delta G^{\ddagger}$ about 18.7 kcal/mol). These effects are attributable to a substantial degree of sharing of the negative charge on C-2 of the iminium ion form with d orbitals of phosphorus; resonance forms expressing this delocalization resemble those of the ylide system. Acid hydrolysis of the methylthiophospholenium structure leads to ring opening, producing methyl methyl(3-oxobutyl)phosphinothiolate; basic hydrolysis effects only the displacement of the methylthio group, giving the corresponding phospholene oxide.

In previous work with the phospholene system, we have shown that a halogen atom separated by a double bond from a phosphoryl[2] (**1**) or thiophosphoryl[3] (**2**) group is activated



1, X = O; **2**, X = S — **3**, X = O; **4**, X = S — **5**, X = O; **6**, X = S

toward nucleophilic displacement by methoxide ion, and we have used the resulting enol ethers **3** and **4** to advantage in synthesizing keto derivatives **5** and **6**. We have now found that primary and secondary amines are also sufficiently nucleophilic to effect the halogen displacement, and we have obtained stable enamines in good yield by this process. The 3-chloro-2-phospholene sulfide system (as in **2**) is especially useful in this reaction since the starting material can be obtained in good purity, free of the isomeric 3-phospholene compound, by reacting the chloroprene–methylphosphonous dichloride cycloadduct with hydrogen sulfide.[3] The synthesis, properties, and spectra of this new family of thiophosphoryl enamines are the basis for the research discussed in this paper.

Synthesis and Structure of 3-Amino-2-phospholene Sulfides. The enamines **7–10** were prepared in 72–82% yield by refluxing a mixture of the amine and 1-methyl-3-chloro-2-phospholene sulfide (**2**). The products were nonhygroscopic solids, easily recrystallized from common solvents. Their enamine character came out clearly in their proton NMR spectra; acting in opposition to the deshielding effect of thiophosphoryl on the 2-position (cf.[3] δ 6.15 for **2**), shielding by electron release from nitrogen shifted the signal for the proton at this position to the range δ 4.1–4.5. The usual strong coupling (24 Hz) with ^{31}P was present. The proton NMR data

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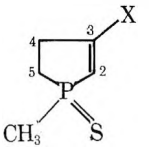
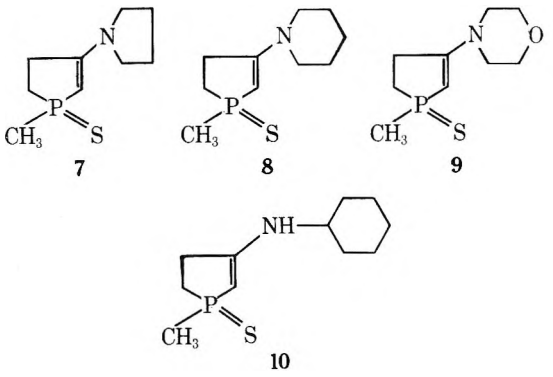
Table I. ^{13}C NMR Spectral Data for 3-X-2-Phospholene Sulfides[a]

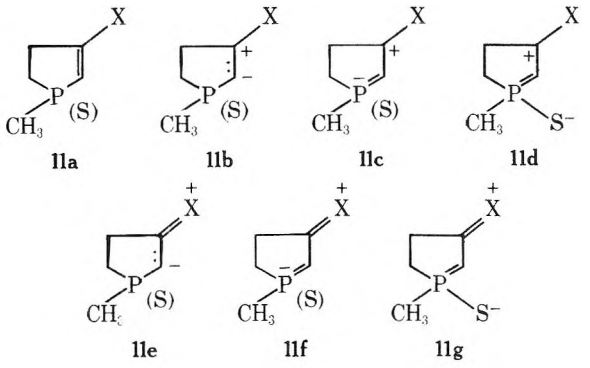


Registry no.	X	C-2	C-3	C-4[b]	C-5	PCH_3	C-1′	C-2′	C-3′	C-4′
				A. Enamines[c]						
64010-83-9	 N (7)[d]	81.4(100)	159.1(47)	30.3(3)	30.7(53)	26.1(56)	48.1	25.2		
64010-84-0	 N (8)[e]	85.1(101)	161.7(34)	30.1(2)	30.3(53)	*f*	48.1	25.4	24.0	
64010-85-1	 O N (9)[e]	87.3(98)	161.6(34)	29.6(2)	30.1(53)	25.6(56)	47.1	66.3		
64010-86-2	 NH (10)[e]	82.4(99)	158.7(35)	31.5	30.4(53)	25.7(56)	53.4	32.6	24.9	25.7
				B. Other Derivatives[g]						
	Cl (2)[d]	123.4(75)	150.0(40)	36.8	3[illegible].9(55)	23.7(50)				
	CH_3O (4)[d]	91.2(92)	171.6(40)	30.4	29.9(60)	25.0(50)				
	H (11)[d]	127.9(75)	147.3(20)	31.6(13)	30.3(45)	22.8(50)				

[a] Chemical shifts in $CDCl_3$ downfield from Me_4Si. Values in parentheses are coupling constants to ^{31}P, in Hz. [b] Unless otherwise noted, no coupling to ^{31}P was observed under conditions used. [c] Carbons of the amino fragment are numbered N-(C-1′)-(C-2′)-(C-3′)-(C-4′). [d] Taken on a Bruker HFX-10 spectrometer. [e] Taken on a JEOL FX-60 spectrometer with digital resolution to two decimals. [f] Overlapped with C-2′ signal. [g] Reported in ref 3.



7 8 9 10



11a 11b 11c 11d 11e 11f 11g

rule out the possibility that any substantial amount of imine tautomer is present in the cyclohexylamine derivative **10**.

Carbon-13 NMR Spectra of the Enamines. The ^{13}C NMR spectra were fully consistent with the assigned structures and are valuable additions to the compilation of ^{13}C data for the 2-phospholene sulfide system (data for **2, 4,** and the unsubstituted parent **11**, X = H, have been reported[3]). Data for the entire family are given in Table I to facilitate discussion of trends in the series. These trends are best examined in terms of the possible interaction of the π electrons with the thiophosphoryl group. The matter of conjugative interaction of π electrons with phosphorus functions remains unsettled.[4] Certainly there are cases which speak in favor of some degree of interaction, and indeed the activation of 3-chloro in 2-phospholene oxides and sulfides is among them. Two very recent studies on vinyl phosphonium salts, one on ^{13}C NMR effects,[5] the other on electrochemical properties,[6] speak especially strongly for a substantial degree of conjugative interaction in these charged species.

In the parent 2-phospholene sulfide (**11**, X = H), considerable polarization of the double bond is evident from the large difference in chemical shifts of C-2 (δ 127.9) and C-3 (δ 147.3). The structure of the parent may then be expressed as a resonance hybrid of forms **11a, 11b,** and **11c,** assuming in the latter form that some electron density developing on C-2 is shared with d orbitals of phosphorus. Increased electron density on sulfur is also a possibility as is expressed by **11d.** With electron releasing groups at the 3-position, as in the enol ether and enamines, significant contributions are also made by forms **11e–11g.**

Relative to the parent, very large upfield shifts occur at C-2 in the enamines **7–10** (δ 81–87) and the enol ether **4** (δ 91.2). This is quite the expected situation, as it has been seen in carbocyclic enamines[7] and enol ethers.[8] The shift is clearly the result of the large contribution to the hybrid of forms **11e–11f.** The coupling of ^{31}P with C-2 is also of interest; it is largest (99–101 Hz) in the enamines, having progressed from 75 Hz in the parent and 3-chloro derivative (**2**) through 92 Hz for the enol ether **4.** This one-bond coupling is thus directly related to the electron releasing ability of the 3-substituent. This effect has been observed in another family of vinylphosphorus compounds where the unit $XC{=}CP^+(C_6H_5)_3$ is present;[9] $^1J_{PC}$ is larger when X is an amino group than an alkoxy or alkyl group. These authors relate the effect to the sharing of the electron density at C-2 with the phosphorus d orbitals (as seen in **11f**), and not just to buildup of electron density on C-2, which in fact should cause a decrease in one-bond coupling.

In the enamines, the chemical shift of C-3 is brought to lower field (δ 159–162) from that in the parent, due to the electron-attracting effect of nitrogen and possibly to the β effect of the carbons attached to nitrogen. Another unusual coupling effect occurs at C-3; the magnitude of the two-bond coupling to ^{31}P is greatly increased on replacement of H by an atom of high electronegativity. In the parent, $^2J_{PC}$ is 20 Hz; for the enamines, values are in the range 34–47 Hz, as they are also for the 3-chloro and 3-methoxy derivatives. We have also

Table II. ^{13}C NMR Spectral Data for Methiodides of 3-Amino-2-phospholene Sulfides[a]

3-Amino	C-2	C-3	C-4[b]	C-4	PCH_3	C-1′	C-2′	C-3′	C-4′	SCH_3
N (12)[c]	62.3(107)	166.5(42)	30.6	22.3(55)	16.8(59)	48.23,49.34	23.72,24.77			12.2[d]
N (13)[c]	64.1(108)	148.3(42)	31.4	22.5(48)	17.3(60)	49.8[f]	25.23,25.91	23.7		12.7(3)
O N (14)[c]	66.5(107)	147.6(42)	31.4	22.2(48)	17.0(59)	48.3	66.1			12.8(3)
NH (15)[c]	61.5(108)	148.6(42)	30.5	22.7(49)	17.1(60)	55.0	31.7	24.9	25.3	12.4(3)

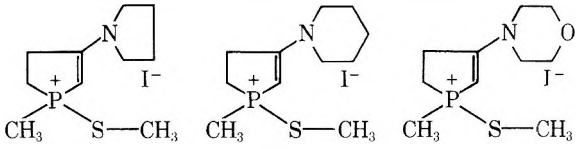
[a] Chemical shifts in $CDCl_3$ downfield from Me_4Si. Values in parentheses are coupling constants to ^{31}P, in Hz. [b] Coupling to ^{31}P is small (0–3 Hz) and not readily observed. [c] Taken on a Bruker HFX-10 spectrometer. [d] No coupling to ^{31}P observed. [e] Taken on a JEOL FX-60 spectrometer with digital resolution to two decimals. [f] Signal is distinctly broadened.

observed this effect among a similar series of 2-phospholene oxides.[10]

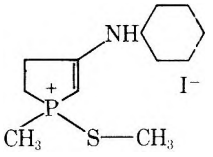
Chemical shifts for C-4 and C-5 in the enamines were readily distinguishable by their substantially different coupling to ^{31}P (nil and 53 Hz, respectively). The P-methyl signal is at slightly lower field in the enamines (δ 26) and in the enol ether **4** (δ 25) than in the 3-chloro derivative (δ 23.7) and the parent **11**, X = H (δ 22.8), but this relation is not seen for C-5 in the series even though its attachment is also to the thiophosphoryl group. A similar slight deshielding at C-1 of P-phenyl groups was seen in β-alkoxy and β-amino vinyltriphenylphosphonium salts relative to the β-methyl derivative.[9]

Carbon shifts in the amine fragment of **7–10** resembled those reported for comparable carbocyclic enamines,[7] and are not influenced by the presence of the thiophosphoryl group.

Formation and ^{13}C NMR Spectra of Methylthiophosphonium Salts. While simple enamines are readily alkylated on the β-carbon with alkyl halides, enamines bearing carbonyl or phosphoryl[2] groups on this carbon do not participate in this reaction and are usually recovered in unchanged form after product workup. Enamines with β-thiocarbonyl groups undergo alkylation on sulfur.[11] We have found that the thiophosphoryl enamines also fail to undergo C-alkylation, but they do react readily at sulfur to form isolatable quasi-phosphonium salts. S-Alkylation is a known property of phosphine sulfides,[12] but the reaction with methyl iodide occurs particularly easily with the enamines. This is consistent with the concept of sulfur assisting in the sharing of electron density, as expressed by resonance form **11g**. From enamines **7**, **8**, **9**, and **10** were obtained salts **12**, **13**, **14**, and **15**, respectively. Each is a crystallizable solid, showing good stability at room temperature if protected from water and light.



12 **13** **14**



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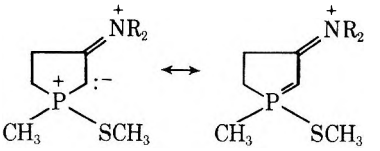
That methyl has indeed attacked on sulfur is readily apparent from spectral properties. In their ^1H NMR spectra, the salts still have a signal for an olefinic proton in the well-upfield enamine position (for **12**, overlapped by CH_2 signals), and a new methyl signal having the chemical shift and coupling to ^{31}P expected for the P^+SCH_3 function is present.

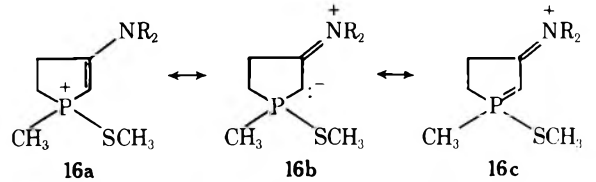


The ^{13}C NMR spectra of the salts show effects which are clear indicators of even greater electron release from nitrogen than is seen in the original enamine sulfides. All of the salts have their C-2 signals at remarkably high field (δ 62–66), having experienced upfield shifts of 20–22 ppm from the sulfides. This upfield shift is far beyond that to be expected simply from the conversion to positive phosphorus; this effect is observable at C-5 and is of the magnitude 7–8 ppm. A pronounced downfield shift occurs at C-3, which can be viewed as a consequence of greater positive character developing on nitrogen, or of increased polarization of the π-system by positive phosphorus. The most striking effect, however, is the development of a substantial barrier to rotation about the C–N bond. The barrier is revealed especially by the pyrrolidine derivative **12**, which shows separate signals for the α-carbons, as well as the β-carbons, of the amine fragment. In $CDCl_3$, the α-carbon signals are separated by 25.1 Hz, the β-carbons by 23.8 Hz. Proof that the signal splitting came from a rotational effect, and not from an extraordinary long-range coupling to ^{31}P or from the chirality of phosphorus, was obtained by observing the ^{13}C spectrum at elevated temperatures. Each of the two sets of signals exhibited coalescence phenomena, and both were reduced to sharp singlets above 100 °C. On cooling, the original doubling reappeared. No other spectral changes occurred in the heating–cooling cycle. The magnitude of the barrier to rotation can be calculated approximately from these observations. Using the α-carbon signals, which are in a clear region of the spectrum, we determined the coalescence temperature (T_c) to be 97 °C in $(CD_3)_2SO$; in this solvent, peak separation ($\Delta\nu$) was 30 Hz at 30 °C. From conventional equations,[13] $\Delta G^{\ddagger}$ was found to be 18.7 kcal/mol. The value is subject to refinement, especially if determined by full line shape analysis, but it is of use in giving an indication of the considerable magnitude of the barrier to rotation resulting from interaction with the phosphorus moiety. A β-carbonyl group also increases the barrier in enamines, but not to this extent; barriers for 4-dimethylamino-3-buten-2-one[14] and related compounds[15] are in the 13–14 kcal/mol range, with some enhancement (about 2 kcal/mol) when oxygen is replaced by sulfur.[16] There appears to be no prior record of the observation at room temperature of different ^{13}C NMR signals for the α-carbons on nitrogen, although separate $N–CH_3$ signals have been seen at low temperatures in β-acyl enamines.[17] The amine carbons of 1-pyrrolidinocyclohexen-3-one do not show nonequivalence at room temperature.[7]

The piperidino derivative **13** also showed manifestations of restricted rotation (distinct broadening of the α-carbon

signal at probe temperature; splitting of the β-carbon signal by 10 Hz) but to a smaller extent than seen for the pyrrolidino compound. No indications of restricted rotation were present in the spectrum of the morpholino compound **14**. The rotational barriers thus provide a sequence of relative electron releasing power of the amines: pyrrolidino > piperidino > morpholino. This is the same series proposed by others[7] in a ^{13}C NMR study of 1-amino-cyclohexen-3-ones, where the chemical shifts of the carbonyl carbon were used as a measure of relative electron release.

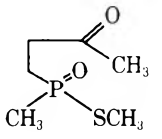
It is therefore concluded that the methylthiophosphonio enamines must have extensive electron delocalization which includes involvement of the phosphorus atom. This delocalization is expressed through resonance forms **16a–16c**. Forms



16a **16b** **16c**

16b and **16c** are seen to be those which describe ylides, an analogy drawn also by others for the similarly delocalized triphenylphosphonio enamines.[9]

Another unique property was observed in the hydrolytic behavior of the salts; on stirring at room temperature with aqueous HCl, salt **12** underwent ring opening as well as loss of the nitrogen fragment to produce the novel thiophosphinate **17**. The structure of this unexpected product, a distillable



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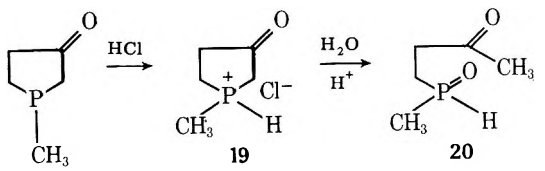
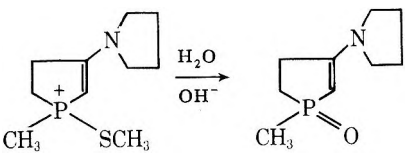
liquid, was clearly established by spectral examination. The keto group was evident from the infrared absorption at 1700 cm^{-1} and ^{13}C NMR signal at δ 205 ($^3J_{PC}$ = 15 Hz). Methyl on carbonyl was indicated by the ^1H NMR singlet at δ 2.24 and ^{13}C NMR singlet at δ 29.7, and methyl on sulfur by the doublet in the ^1H NMR at δ 2.35 ($^3J_{PH}$ = 11 Hz) and in the ^{13}C NMR at δ 10.0 (^2J = 5 Hz). The latter signal was especially helpful in eliminating the possibility of the methyl being on oxygen; in this case, the methyl signal would have been much farther downfield. The reaction is not unlike another we have recently encountered:[18] aqueous HCl opens the ring of β-ketophosphine **18** to give the quite analogous product (**20**). If the hydrolysis of the enamino salts is viewed as proceeding with initial attack at the enamine function, the product would be a ketone having a formal resemblance to salt **19**.



18 **19** **20**

With aqueous base, the hydrolysis takes an entirely different pathway. As has been reported for methiodides of tertiary phosphine sulfides,[12] nucleophilic attack results in displacement of the methylthio group with formation of the tertiary phosphine oxide retaining the cyclic structure (**21**). Structure **21** was confirmed by synthesis of the same compound from the 3-chloro-2-phospholene oxide (**1**) with pyrrolidine. Enamines in the 2-phospholene oxide series have previously been prepared from the 3-keto derivative and the secondary amine;[2] this process provides a product containing



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some of the 3-phospholene oxide isomer, however, and the chloride displacement process, which is reported here for the first time, is clearly preferable in giving an isomer-free product.

^{31}P NMR Spectra of the Enamines. The chemical shifts for the four thiophosphoryl enamines **7–10** all fall in the narrow range of +57.8 to +60.1 ppm (downfield relative to 85% H_3PO_4), which also includes values for the 3-chloro (+58.5) and 3-methoxy (+58.7) derivatives. The range is markedly upfield from the parent (**11**, X = H, +65.5). Were it not for the 3-chloro value, it might be possible to attribute this upfield shift to increased occupation of the phosphorus d orbitals (form **11e**), an effect known to cause shielding of ^{31}P.[5] But since there is evidence from both ^{13}C and ^1H NMR spectra for C-2 to suggest that the contribution of forms **11d** and **11e** must be quite small for the chloro compound, the degree of d-orbital occupation cannot be the only factor causing the upfield ^{31}P NMR shift, although it may have greater importance for the enamines and enol ether. It may be significant in this context that the ^{31}P shifts of the enamines, although quite similar, do show a trend of increased shielding with greater electron releasing ability of the amine (pyrrolidino, +57.8; piperidino, +58.1; morpholino, +58.7).

Alkylation on sulfur causes a downfield shift in the enamine. While the range of values is again small, the same trend of increased shielding with amine electron-releasing ability is present (pyrrolidino, +69.8; piperidino, +70.96; morpholino, +72.2).

Experimental Section

General. Proton noise-decoupled ^{13}C NMR spectra were obtained at 22.62 MHz on a Bruker HFX-10 spectrometer, or at 15.0 MHz with a JEOL FX-60 spectrometer, both using the Fourier transform technique. Samples were run in $CDCl_3$ solution with internal Me_4Si. Proton-decoupled ^{31}P NMR spectra were obtained with the Bruker instrument at 36.43 MHz and are referenced to external 85% H_3PO_4. ^1H NMR spectra were obtained on a JEOL MH-100 spectrometer using $CDCl_3$ as solvent with internal TMS. The sign convention used is the same for all nuclei (+ if downfield from the reference, − if upfield). Melting points are corrected. Elemental analyses were performed by MHW Laboratories, Garden City, Mich.

1-Methyl-3-pyrrolidino-2-phospholene 1-Sulfide (7). To a stirred, nitrogen-blanketed solution of 28.3 g (0.17 mol) of 1-methyl-3-chloro-2-phospholene-1-sulfide[3] in 175 mL of dry benzene was added dropwise a solution of 24.1 g (0.34 mol) of pyrrolidine in 50 mL of dry benzene. The mixture was refluxed for 46 h. It was then cooled and the precipitated pyrrolidine hydrochloride was removed by filtration. The filtrate was washed with water (2 × 20 mL); the organic layer was dried (Na_2SO_4) and most of the solvent was then removed on a rotary evaporator. The residual liquid was triturated with petroleum ether and yielded 28 g (82%) of solid enamine (**7**). This was recrystallized from a mixture of benzene and hexane: mp 71–72 °C; ^1H NMR ($CDCl_3$) δ 1.8–2 (m, NCH_2CH_2), 2.12–3.04 (m, PCH_2CH_2), 1.9 (d, $^2J_{PH}$ = 12 Hz, PCH_3), 3.16–3.44 (m, CH_2NCH_2), 4.12 ppm (d, $^2J_{PH}$ = 24 Hz, PCH = C); ^{31}P NMR ($CDCl_3$) δ +57.8; IR (Nujol) 1550 cm^{-1} (C=C); ^{13}C NMR (Table I).

Anal. Calcd for $C_9H_{16}NPS$: C, 53.73; H, 7.96; N, 6.96; P, 15.42; S, 15.92. Found: C, 53.65; H, 8.05; N, 6.75; P, 15.63; S, 16.15.

1-Methyl-3-piperidino-2-phospholene 1-Sulfide (8). A mixture of 3.5 g (0.021 mol) of 1-methyl-3-chloro-2-phospholene 1-sulfide and 8.9 g (0.05 mol) of freshly distilled piperidine was refluxed under nitrogen for 10 h. The excess amine was stripped off on a rotary evaporator; remaining traces were removed by high-vacuum evacuation. The residue was taken up in hot benzene and the amine salt was removed by filtration. Solvent was stripped from the filtrate and the residual oil was triturated with petroleum ether to give 4.5 g (75%) of

solid **8**. An analytical sample was purified by sublimation; mp 59–60 °C; ^{1}H NMR ($CDCl_3$); δ 1.56 (broad singlet, $-(CH_2)_3-$), 1.86 (d, $^2J_{PH}$ = 13 Hz, PCH_3), 2.1–3.0 (m, PCH_2CH_2), 3.16 (broad singlet, CH_2NCH_2) and 4.36 ppm (d, $^2J_{PH}$ = 24 Hz, PCH=C); ^{31}P NMR ($CDCl_3$) +58.1; IR (Nujol) 1550 cm^{-1} (C=C); ^{13}C NMR (Table I).

Anal. Calcd for $C_{10}H_{18}NPS$: C, 55.81; H, 8.37; N, 6.51; P, 14.42; S, 14.80. Found: C, 55.98; H, 8.50; N, 6.51; P, 14.65; S, 14.77.

1-Methyl-3-morpholino-2-phospholene 1-Sulfide (9). A mixture of 6 g (0.036 mol) of 1-methyl-3-chloro-2-phospholene 1-sulfide and 15.6 g (0.18 mol) of morpholine was refluxed under nitrogen for 10 h. The mixture was worked up as for **8**, yielding 5.6 g (72%) of desired product (**9**): mp 183–184 °C. A second crop (1.0 g) was obtained from the mother liquor. The total yield was 6.6 g (85%): ^{1}H NMR ($CHCl_3$) δ 1.91 (d, $^2J_{PH}$ = 14 Hz, PCH_3), 2.0–3.0 (m, PCH_2CH_2), 3.04–3.24 (m, CH_2NCH_2), 3.64–3.8 (m, CH_2OCH_2), 4.47 ppm (d, $^2J_{PH}$ = 24 Hz, PCH=C); δ ^{31}P NMR ($CDCl_3$) +58.7; IR (Nujol) 1550 cm^{-1} (C=C); ^{13}C NMR (Table I).

Anal. Calcd for $C_9H_{16}NOPS$: C, 49.77; H, 7.37; N, 6.45; P, 14.28; S, 14.74. Found: C, 49.81; H, 7.33; N, 6.34; P, 14.44; S, 14.62.

1-Methyl-3-cyclohexylamino-2-phospholene 1-Sulfide (10). A mixture of 5.4 g (0.03 mol) of 1-methyl-3-chloro-2-phospholene 1-sulfide and 25 mL of freshly distilled cyclohexylamine was refluxed with stirring under nitrogen for 12 h. The product (5.3 g, 72%) was isolated by the procedure used for **8**: mp 114–115 °; ^{1}H NMR ($CDCl_3$) δ 1.24–2.0 (m, $-(CH_2)_5-$), 1.86 (d, $^2J_{PH}$ = 13 Hz, PCH_3), 2.12–2.88 and 3.08 (m, overlapping PCH_2CH_2 and cyclohexyl H), 3.5 (broad singlet, NH, disappeared in D_2O), 4.28 ppm (d, $^2J_{PH}$ = 24 Hz, PCH=C); ^{31}P NMR ($CDCl_3$) +60.1; IR (Nujol) 1581 (C=C), 3150 cm^{-1} (NH); ^{13}C NMR (Table I).

Anal. Calcd for $C_{11}H_{20}NPS$: C, 57.64; H, 8.73; N, 6.11; P, 13.54; S, 13.97. Found: C, 57.86; H, 8.59; N, 6.17; P, 13.71; S, 14.15.

1-Methyl-1-methylthio-3-pyrrolidino-2-phospholenium Iodide (12). A solution of 1 g (0.005 mol) of phosphine sulfide **7** was stirred at room temperature under nitrogen for 24 h in 6 mL of benzene containing 0.7 g (0.005 mol) of methyl iodide. A white precipitate appeared within a few minutes of stirring. The product (1.7 g, 100%) was recrystallized from hot chloroform by adding benzene: mp 125–126 °C; ^{1}H NMR ($CDCl_3$) δ 2.04 (m, 4 H), 2.31 (d, $^2J_{PH}$ = 14 Hz, PCH_3 or SCH_3), 2.41 (d, $^2J_{PH}$ = 15 Hz, PCH_3 or $PSCH_3$), 2.6–3.92 ppm (m, 9 H, CH_2 and =CH); ^{31}P NMR ($CDCl_3$) +69.8; IR (Nujol) 1565 cm^{-1} (C=C); ^{13}C NMR (Table II).

Anal. Calcd for $C_{10}H_{19}INPS$: C, 35.01; H, 5.54; N, 4.08; P, 9.03; S, 9.33. Found: C, 34.83; H, 5.79; N, 3.89; P, 9.21; S, 9.25.

1-Methyl-1-methylthio-3-piperidino-2-phospholenium Iodide (13). A solution of 1.80 g (0.0084 mol) of phospholene sulfide **8** in 120 mL of dry benzene and 1.20 g (0.0085 mol) of methyl iodide was stirred under nitrogen at room temperature for 10 h. The precipitate was filtered off and washed with warm benzene: yield 1.8 g (60%); mp 119–120.5 °C after recrystallization from a hot chloroform solution on addition of benzene; ^{1}H NMR ($CDCl_3$) δ 1.73 (m, 6 H, $NCH_2CH_2CH_2$), 2.40 and 2.45 (both d, J_{PH} = 13 Hz, PCH_3 and SCH_3, unassigned), 3.00 (m, PCH_2CH_2), 3.30 (m, PCH_2), 3.50 (m, 4 H, NCH_2), 4.10 (d, $^2J_{PH}$ = 24 Hz, PCH=C). IR (Nujol) 1562 cm^{-1} (C=C); ^{31}P NMR δ +71.0 ($CDCl_3$); ^{13}C NMR (Table II).

Anal. Calcd for $C_{11}H_{21}INPS$: C, 37.00; H, 5.88; N, 3.92; P, 8.67. Found: C, 37.10; H, 5.82; N, 3.74; P, 8.87.

1-Methyl-1-methylthio-3-morpholino-2-phospholenium Iodide (14). A solution of 1 g (0.005 mol) of phosphine sulfide **9** in 60 mL of hot benzene was refluxed gently with 0.7 g (0.005 mol) of methyl iodide for 2 h under nitrogen. Within a few minutes a precipitate began to form. The product (1.1 g, 62%) was recrystallized from a mixture of chloroform and benzene: mp 160–161 °C; ^{1}H NMR ($CDCl_3$) δ 2.44 (d, $^2J_{PH}$ = 15 Hz, PCH_3 or SCH_3), 2.47 (d, $^2J_{PH}$ = 14 Hz, PCH_3 or SCH_3), 2.64–3.7 (m, overlapping PCH_2CH_2 and CH_2NCH_2), 3.76–4.0 (m, CH_2OCH_2), 4.31 ppm (d, $^2J_{PH}$ = 22 Hz, PCH=C); ^{31}P NMR ($CDCl_3$) +72.2; IR (Nujol) 1556 cm^{-1} (C=C); ^{13}C NMR (Table II).

Anal. Calcd for $C_{10}H_{19}INOPS$: C, 33.42; H, 5.29; N, 3.89; P, 8.63; S, 8.91. Found: C, 33.60; H, 5.47, N, 3.82; P, 8.77; S, 8.84.

1-Methyl-1-methylthio-3-cyclohexylamino-2-phospholenium Iodide (15). A solution of 0.4 g (0.0017 mol) of phosphine sulfide **10** in 25 mL of benzene was treated with 0.53 g (0.0017 mol) of methyl iodide. The mixture was stirred at room temperature for 15 h, following which the precipitated salt was recovered by filtration (0.4 g, 63%). Recrystallization by adding benzene to a hot chloroform solution gave **15**, mp 140.5–142 °C; ^{1}H NMR ($CDCl_3$) δ 1.26–1.98 (CH_2 groups of cyclohexyl), 2.32 (d, J_{PH} = 14 Hz, PCH_3 or SCH_3), 2.35 (d, J_{PH} = 15 Hz, PCH_3 or SCH_3), 2.6–3.6 (CH_2 groups of phospholene sulfide), 3.28 (CH of cyclohexyl), 3.85 (d, $^2J_{PH}$ = 27 Hz, PCH=C); ^{31}P NMR ($CDCl_3$) +69.6; ^{13}C NMR (Table II).

Anal. Calcd for $C_{12}H_{23}INPS$: C, 38.84; H, 6.20; P, 8.35; N, 3.71. Found: C, 38.80; H, 6.28; P, 8.27; N, 3.53.

Methyl Methyl(3-oxobutyl)phosphinothiolate (17). A solution of 2 g (0.0058 mol) of phospholenium salt **12** in 5 mL of dichloromethane was stirred at room temperature under nitrogen for 2 h with 1 mL of 3 N HCl. The aqueous layer was separated, neutralized, and extracted with chloroform (3 × 5 mL). The combined extracts were washed with saturated sodium bicarbonate and sodium chloride solutions, dried over sodium sulfate, and freed of solvent on the rotary evaporator. The reside (0.45 g, 43%) was purified by Kugelrohr distillation: ^{1}H NMR ($CDCl_3$) δ 1.81 (d, $^2J_{PH}$ = 14 Hz, PCH_3), 2.24 (s, $COCH_3$), 2.35 (d, $^3J_{PH}$ = 11 Hz, $PSCH_3$), 2.14–2.45 and 2.73–3.04 ppm (both m, CH_2CH_2); ^{31}P NMR ($CDCl_3$) +58.7; IR (Nujol) 1700 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$) δ 9.95 (d, $^2J_{PC}$ = 5 Hz, SCH_3), 19.24 (d, $^1J_{PC}$ = 70 Hz, PCH_3), 27.43 (d, $^1J_{PC}$ = 65 Hz, PCH_2), 29.65 (s, CCH_3), 35.84 (d, $^2J_{PC}$ = 5 Hz, CH_2C=O), 203.31 (d, $^3J_{PC}$ = 15 Hz, C=O).

Anal. Calcd for $C_6H_{13}O_2PS$: C, 40.00; H, 7.22; P, 17.22; S, 17.77. Found: C, 39.94; H, 6.98; P, 16.91; S, 17.51.

1-Methyl-3-pyrrolidino-2-phospholene Oxide (21). A mixture of the phospholenium salt **12** (1.6 g, 0.0046 mol) in 5 mL of dichloromethane and 1 mL of 3 N sodium hydroxide was refluxed under nitrogen for 1 h. The aqueous layer was separated and extracted with dichloromethane (3 × 5 mL). The combined dichloromethane solutions were washed with saturated sodium chloride, dried over sodium sulfate, and then stripped of the solvent on a rotary evaporator. The yield of oily product was 0.6 g (70%): ^{1}H NMR ($CDCl_3$) δ 1.65 (d, $^2J_{PH}$ = 13 Hz, PCH_3), 1.8–2.16 (m, 4 H, NCH_2CH_2), 2.36–2.96 (m, 4 H, PCH_2CH_2), 3.04–3.42 (m, 4 H, CH_2N), 4.16 (d, $^2J_{PH}$ = 20 Hz, PCH=C); IR (neat) 1565 (C=C), 1100 cm^{-1} (P=O). A sample was purified by Kugelrohr distillation for analysis.

Anal. Calcd for $C_9H_{16}NOP$: C, 58.38; H, 8.65; N, 7.57; P, 16.75. Found: C, 58.25 H, 8.56; N, 7.65; P, 16.57.

The same compound was formed by 16 h of refluxing of a mixture of 1 g (0.0067 mol) of 1-methyl-3-chloro-2- and 3-phospholene oxide[2] in 50 mL of benzene with 0.95 g (0.0134 mol) of pyrrolidine. The salt that precipitated was filtered off. The product obtained by evaporation of the solvent had ^{1}H NMR and IR spectra identical with those for the product from the basic hydrolysis of **12**.

Variable Temperature ^{13}C NMR Measurement. A sample of enamino salt **12** was dissolved in Me_2SO-d_6 and the chemical shifts were recorded relative to external Me_4Si in $CDCl_3$. The spectrum was recorded at probe temperature (about 30 °C) and the peak separation of the carbons α to nitrogen (30 Hz) was taken as the slow exchange limit. Coalescence occured at about 97 °C; due to the relatively small peak separation of the very sharp individual lines, it was difficult to make an accurate measurement of T_c by this method. The rate constant (k_c) for the process was determined from the expression $k_c = \pi\Delta\nu/\sqrt{2}$; with $\Delta\nu$ = 30 Hz, k_c is 66.6. The free energy of activation ($\Delta G_c^{\ddagger}$) was then determined from the expression $\Delta G_c^{\ddagger} = 2.3RT_c(10.32 + \log T_c/k_c)$; with T_c = 370 K, $\Delta G_c^{\ddagger}$ is 18.7 kcal/mol.

Registry No.—1, 22356-35-0; **2**, 58311-81-2; **12** charged, 64010-87-3; **12** uncharged, 64010-88-4; **13** charged, 64010-89-5; **13** uncharged, 64010-90-8; **14** charged, 64010-91-9; **14** uncharged, 64010-92-0; **15** charged, 64010-93-1; **15** uncharged, 64010094-2; **17**, 64010-95-3; **21**, 64010-96-4; pyrrolidine, 123-75-1; piperidine, 110-89-4; morpholine, 110-91-8; cyclohexylamine, 108-91-8; methyl iodide, 74-88-4.

References and Notes

(1) This work was supported by U.S. Public Health Service Research Grant CA-05507, National Cancer Institute.
(2) L. D. Quin and R. C. Stocks, *J. Org. Chem.*, **39**, 687 (1974).
(3) C. Symmes, Jr., and L. D. Quin, *J. Org. Chem.*, **41**, 1548 (1976).
(4) J. Emsley and D. Hall, "The Chemistry of Phosphorus", Harper and Row, Ltd., London, 1976, Chapter 2.
(5) T. A. Albright, W. J. Freeman, and E. E. Schweizer, *J. Org. Chem.*, **40**, 3437 (1975).
(6) R. D. Rieke, C. K. White, and C. M.Milliren, *J. Am. Chem. Soc.*, **98**, 6872 (1976).
(7) D. Tourwé, G. Van Binst, S. A. G. DeGraaf, and U. K. Pandit, *Org. Magn. Reson.*, **7**, 433 (1975).
(8) A. C. Rojas and J. K. Crandall, *J. Org. Chem.*, **40**, 2225 (1975).
(9) T. A. Albright, S. V. DeVoe, W. J. Freeman, and E. E. Schweizer, *J. Org. Chem.*, **40**, 1650 (1975).
(10) L. D. Quin and C. E. Roser, unpublished results.
(11) For a recent example, see J. C. Meslin, Y. T. N. Guessan, and H. Quiniov, *Tetrahedron*, **31**, 2679 (1975).
(12) L. Maier, *Top. Phosphorus Chem.*, **2**, 116 (1965).
(13) J. B. Lambert, H. F. Shurvell, L. Verbit, R. G. Cooks, and G. H. Stout, "Organic Structural Analysis", Macmillan, New York, N.Y., 1976, p 116.
(14) M. L. Filleux-Blanchard, A. Chevalier, G. J. Martin, *Tetrahedron Lett.*, 5057 (1967).

(15) L. M. Jackman and F. A. Cotton, Ed., "Dynamic Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, N.Y., 1975, Chapter 7.
(16) M. L. Filleux-Blanchard, F. Mabon, and G. J. Martin, *Tetrahedron Lett.*, 3907 (1974).
(17) M. L. Filleux-Blanchard, F. Clesse, J. Bignebat, and G. J. Martin, *Tetrahedron Lett.*, 981 (1969).
(18) C. E. Roser and L. D. Quin, *J. Org. Chem.*, **39**, 3423 (1974).

Synthesis of Some *B*-Nor-6,8-secoestranes and *B*,19-Dinor-6,8-secopregnanes

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Dehydrogenation of dehydroepiandrosterone (**1a**) and pregnenolone (**1b**) with DDQ, followed by dienone–phenol rearrangement and then hydrolysis and methylation, gave 3-methoxy-1-methylestra-1,3,5(10),6-tetraen-17-one (**3e**) and 3-methoxy-1-methyl-19-norpregna-1,3,5(10),6-tetraen-20-one (**3f**). The 6,7-olefinic moiety of **3e** and **3f** was cleaved with osmium tetroxide–sodium periodate to yield dialdehyde products **4a** and **4b**. Individual rotational isomers of the dialdehydes were seen in their ^{1}H NMR spectra. Decarbonylation of dialdehydes **4a** and **4b** to *B*-nor-6,8-secoestratriene **5a** and *B*,19-dinorpregnatriene **5b**, respectively, was accomplished with tris(triphenylphosphine)chlororhodium. The *B*-nor-6,8-secosteroids **5a** and **5b** were used as intermediates to prepare variously 17-substituted compounds **5c–e** and 4-en-3-one compounds **6a** and **6b**.

Since there are no reports in the literature of the preparation of either *B*-nor-6,8-secoestranes or *B*,19-dinor-6,8-secopregnanes, we undertook the synthesis of steroids with this feature. A brief degradative route (Scheme I) from naturally occurring steroids was chosen for investigation since this would provide final products with the natural stereochemical configuration.

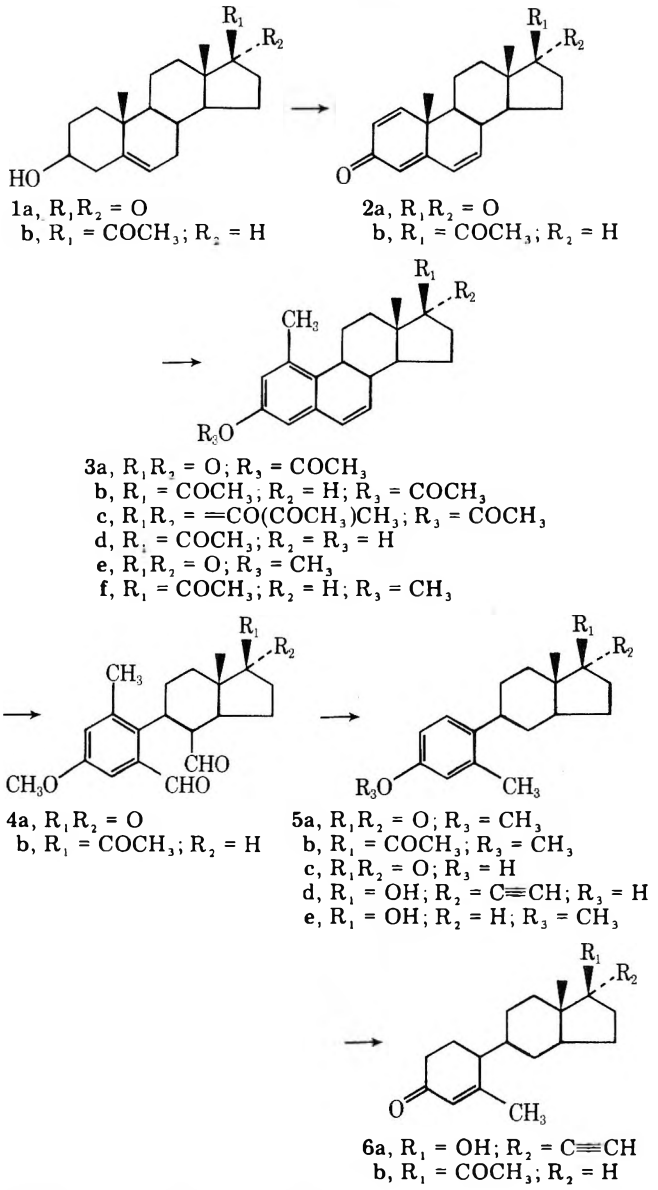
Dehydroepiandrosterone (**1a**) and pregnenolone (**1b**) were dehydrogenated with dichlorodicyanoquinone (DDQ) in refluxing dioxane to the corresponding trienes **2a** and **2b**.[1] On dienone–phenol rearrangement in acetic anhydride with toluenesulfonic acid catalyst, triene **2a** was converted to tetraene **3a**,[2] while triene **2b** was converted to a mixture of tetraene **3b** and diacetate **3c** with **3c** the major product.

The need for additional quantities of **3b** prompted a study of the hydrolysis of diacetate **3c** to determine if the 17-acetyl functionality with the normal β configuration and free of any 17α isomer contamination could be regenerated from the $\Delta^{17,20}$ enol acetate. Precedent existed for the conversion since Rubin and Blossey[3] have shown that pregnanes with the abnormal 17α configuration can be equilibrated to a mixture (85:15) of 17β and 17α isomers. The ^{1}H NMR spectrum of the crude phenol **3d**, obtained from basic hydrolysis of diacetate **3c**, had C-18 methyl absorptions at δ 0.52 and 0.87 ppm, clearly indicating the presence of both 17β- and 17α-acetyl moieties. Phenol **3d** was chromatographed and both early and late fractions gave identical ^{1}H NMR spectra; none of the 17α isomer could be found. Hydrolysis of monoacetate **3b** gave phenol **3d** whose melting point and ^{1}H NMR spectrum were identical with those of the phenol obtained from diacetate **3c**.

Hydrolysis of diacetate **3c** with methanolic sodium hydroxide followed by methylation with dimethyl sulfate also gave only the 17β isomer of *O*-methyl ether **3f**. This was confirmed by hydrolysis and methylation of monoacetate **3b**. In subsequent preparations, the mixture of acetates **3b** and **3c**, after filtration through a short column of alumina to remove polar impurities, was hydrolyzed, methylated, and purified. None of the 17α isomer could be detected in the *O*-methyl ether product **3f**.

Attempts to transform the 6,7-olefinic moieties of compounds **3e** and **3f** into dialdehyde functionalities employing sodium periodate and a catalytic amount of osmium tetroxide

Scheme I



1a, R_1R_2 = O
b, R_1 = $COCH_3$; R_2 = H

2a, R_1R_2 = O
b, R_1 = $COCH_3$; R_2 = H

3a, R_1R_2 = O; R_3 = $COCH_3$
b, R_1 = $COCH_3$; R_2 = H; R_3 = $COCH_3$
c, R_1R_2 = =$CO(COCH_3)CH_3$; R_3 = $COCH_3$
d, R_1 = $COCH_3$; R_2 = R_3 = H
e, R_1R_2 = O; R_3 = CH_3
f, R_1 = $COCH_3$; R_2 = H; R_3 = CH_3

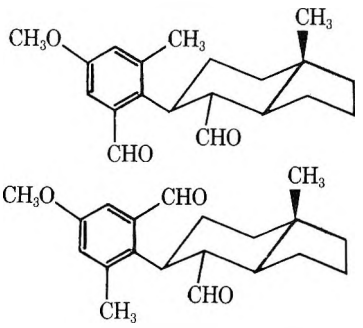
4a, R_1R_2 = O
b, R_1 = $COCH_3$; R_2 = H

5a, R_1R_2 = O; R_3 = CH_3
b, R_1 = $COCH_3$; R_3 = CH_3
c, R_1R_2 = O; R_3 = H
d, R_1 = OH; R_2 = C≡CH; R_3 = H
e, R_1 = OH; R_2 = H; R_3 = CH_3

6a, R_1 = OH; R_2 = C≡CH
b, R_1 = $COCH_3$; R_2 = H

0022-3263/78/1943-0113$01.00/0

Chart I



produced vastly different results depending upon the reaction medium. In tetrahydrofuran–water, no hydroxylation or cleavage products were detectable even after heating, and a quantitative yield of starting material was reclaimed. However, in acetic acid–water medium,[4,5] new products were apparent by both GLC and TLC analysis within a few hours. After 3 days at room temperature, all the starting material was consumed and there was no further change in the reaction composition. After chromatography, aldehydes **4a** and **4b** were isolated in 47 and 49% yield, respectively.

Strikingly, the ^{1}H NMR spectrum of aldehydes **4a** and **4b** each clearly showed the presence of two rotational isomers. Both the C-18 and C-6 methyl resonances consisted of double absorptions, while the 3-*O*-methyl signal was a singlet because of its symmetric position (Chart I). The aromatic hydrogens were also configurationally split, but the presence of two isomers was most clearly shown by the aldehyde absorptions, which were well separated in their chemical shifts and each distinctly split into two bands. The ratios of isomers for the individual aldehydes **4a** and **4b** were quite different. For estrone dialdehyde **4a** the ratio was 4:1, while the ratio was 2:1 for pregnane compound **4b.** Chart I emphasizes the point that all the functionalities described, except the 3-*O*-methyl group, should have different structural environments and therefore different chemical shifts. Attempts to separate the isomers by chromatography were unsuccessful.

The reaction medium was also found to affect the outcome of bisdecarbonylation of dialdehydes **4a** and **4b** to *B*-nor-6,8-secosteroids **5a** and **5b.** In refluxing benzene containing two molar equivalents of tris(triphenylphosphine)chlororhodium, the starting aldehyde rapidly disappeared, but the absence of gas evolution and the failure to detect new products indicated a stable complex was being formed. However, when the reaction was conducted in refluxing benzonitrile, gas evolution was readily apparent, and after workup, products **5a** and **5b** were isolated in 70 and 67% yield, respectively.

The transformation of *B*-nor-6,8-secosteroid **5b** to progesterone analogue **6b** was accomplished by initially reducing the 20-ketone moiety to a mixture of epimeric alcohols followed by Birch reduction of the A ring. Acid hydrolysis of the dihydro product to an α,β-unsaturated ketone followed by Jones oxidation of the 20-alcohol to a ketone completed the preparation of *B*,19-dinor-6,8-secoprogesterone (**6b**).

Estrone 3-methyl ether analogue **5a** was likewise used as an intermediate to prepare various 17-substituted products. Thiophenoxide demethylation[8] of **5a** gave a poor yield of difficultly purifiable phenol **5c.** An improved yield of **5c** was achieved by pyridine hydrochloride fusion[9] of **5a.** Treatment of **5c** with lithium acetylide–ethylenediamine complex gave the *B*-nor-6,8-seco analogue of mestranol (**5d**).

The *B*-nor-6,8-seco analogue of norethindrone (**6a**) was also prepared from **5a.** Sodium borohydride reduction of **5a** in ethanol gave alcohol **5e** which was then reduced with sodium in liquid ammonia to the dihydro intermediate.[10] Attempted steam distillation of the solvent to isolate the dihydro intermediate resulted in extensive oxidation and hydrolysis of the product. In subsequent preparations, the isolation step was omitted and the 17-hydroxyl of the crude product was directly oxidized to the corresponding ketone under Oppenhauer conditions with cyclohexanone.[11] This intermediate also proved to be labile and after vacuum removal of most of the cyclohexanone, the product was ethynylated with a large excess of lithium acetylide. After workup, pure **6a** was isolated in 46% overall yield for the three step sequence (**4a**–**6a**).

Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 337 spectrophotometer. Ultraviolet spectra were run on a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Model HA-100, using tetramethylsilane (Me_4Si) as an internal standard. Chemical shifts are expressed in δ units. Coupling constants (J) are expressed in hertz (Hz).

3-Acetoxy-1-methylestra-1,3,5(10),6-tetraen-17-one (3a). A modification of the procedure described by Djerassi et al.[2] was employed. Androstratriene **3a**[1] (5.8 g, 206 mmol) and *p*-toluenesulfonic acid (1.46 g) in acetic anhydride (225 mL) were heated on the steam bath for 5 h, then cooled and evaporated under reduced pressure to remove excess acetic anhydride. Residual acetic anhydride was removed by stirring with saturated sodium bicarbonate, then extracting with methylene chloride (2 × 100 mL). The residue remaining after vacuum removal of the solvent was chromatographed on alumina (activity III, 180 g, benzene) to give 3.8 g (57%) of pure **3a:** mp 152–153 °C; (lit.[1] mp 152–153 °C).

Dienone–Phenol Rearrangement of Pregna-1,4,6-tetraene-3,20-dione (2b). The reaction was performed as described above. From trienone **3b**[1] (2.0 g, 6.45 mmol), toluenesulfonic acid (458 mg), and acetic anhydride, there was isolated 2.7 g of crude product containing **3b** and **3c.** The mixture was separated by chromatography (silica gel, 100 g). Elution with 10% methylene chloride–benzene gave 1.35 g (38%) of compound **3c** as a foam: NMR ($CDCl_3$) δ 0.93 (s, 3, 18-CH_3), 1.81 (s, 3, 21-CH_3), 2.10 (s, 3, O_2CCH_3), 2.23 (s, 3, O_2CCH_3), 2.47 (s, 3, $ArCH_3$), 5.96 (dd, J = 8 Hz, 1, =CH), 6.37 (dd, J = 8, 3 Hz, 1, =CH), 6.6 ppm (s, 2, Ar-H), m/e = 394.

Anal. Calcd for $C_{25}H_{30}O_4$: C, 76.11; H, 7.70. Found: C, 75.97; H, 7.70.

Elution with 50% methylene chloride gave 1.15 g (51%) of **3b** as an oil: NMR (CCl_4) δ 0.86 (s, 3, 18-CH_3), 1.75 (s, 3, 21-CH_3), 2.04 (s, 3, 20-OAc), 2.16 (s, 3, 3-OAc), 2.49 (s, 3, $ArCH_3$), 5.9 (d, 1, J = 10 Hz, =CH), 6.32 (dd, 1, J = 10, 3 Hz, =CH), and 6.56 ppm (s, 2, ArH).

Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.25; H, 7.95.

In subsequent preparations the yield and ratio of products **3b** and **3c** were found to be variable. Prolonged heating gave increased amounts of **3c.**

3-Hydroxy-1-methyl-19-norpregna-1,3,5(10),6-tetraen-20-one (3d). Hydrolysis of **3c** and **3b** was performed with 10% methanolic sodium hydroxide. The ^{1}H NMR spectrum of the crude phenol product from hydrolysis of **3c** had absorptions at δ 0.52 and 0.87 ppm (17α- and 17β-acetyl configuration, respectively) for the C-18 methyl group. Both products gave, after chromatography (silica gel; 10% EtOAc–CH_2Cl_2), pure phenol **3d:** mp 227–230 °C (methanol); NMR (acetone-d_6) δ 0.64 (s, 3, 18-CH_3), 2.08 (s, 3, $COCH_3$), 2.44 (s, 3, $ArCH_3$), 5.87 (d, 1, J = 10 Hz, =CH), 6.27 (s, 0.5, =CH), 6.4 ppm (s, 2.5, ArH, =CH).

3-Methoxy-1-methylestra-1,3,5(10),6-tetraen-17-one (3e) and 3-Methoxy-1-methyl-19-norpregna-1,3,5(10),6-tetraen-20-one (3f). Either **3a** or **3b** (2 g) in methanol (60 mL) was refluxed with 10% methanolic sodium hydroxide until TLC analysis (silica gel; 5% ethyl acetate–chloroform) indicated that the acetate was converted to the phenol. Dimethyl sulfate (4 mL) was added, and the course of the reaction was followed by TLC analysis and monitoring the pH. When the solution became acidic, additional quantities of sodium hydroxide and dimethyl sulfate were added. The methanol was evaporated and water (100 mL) was added to precipitate the product which was collected and recrystallized from methanol–water. The yield of **3e** was 1.55 g (85%); mp 151–152 °C (lit.[2] mp 151.5–152 °C). The yield of **3f,** an oil, was 1.45 g (79%): NMR (CCl_4) δ 0.71 (s, 3, 18-CH_3), 2.01 (s, 3, $COCH_3$), 2.46 (s, 3, $ArCH_3$), 3.68 (s, 3, OCH_3), 5.83 (dd, J = 9 Hz, 1, =CH), 6.24 (d, J = 3 Hz, 0.5, =CH), 6.35 ppm (s, 1.5, ArH and =CH).

Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.42; H, 8.70. Found: C, 81.30; H, 8.59.

3-Methoxy-1-methyl-17-oxo-6,7-secoestra-1,3,5(10)-triene-6,7-dial (4a). A mixture of sodium metaperiodate (4.35 g, 20.3 mmol), steroid **3e** (2.00 g, 6.76 mmol), water (34 mL), and acetic acid (150 mL) was heated on a steam bath until the solids dissolved. When the solution cooled to room temperature, osmium tetroxide (20 mg in 2 mL of CCl_4) was added, and the reaction was stoppered and stirred. After 18–24 h, TLC (silica gel; 5% EtOAc/$CHCl_3$) and GLC analysis (1% OV-17) indicated that steroid **3e** was completely consumed. An additional 24-h period was required for GLC analysis to show no further change in the product ratios. The acetic acid was removed under vacuum, water (50 mL) was added, and the product was extracted with chloroform (3 × 10 mL). The chloroform extracts were washed with saturated sodium bicarbonate and then with water and dried ($MgSO_4$). After vacuum removal of the solvent, the residue was chromatographed (30 g; silica gel; CH_2Cl_2–4% EtOAc/CH_2Cl_2) to give 1.05 g (47% yield) of pure dialdehyde **4a** as a gum. The presence of two rotational isomers in an approximate ratio of 4:1 was apparent in the NMR spectrum. The minor rotamer product is marked with an s: NMR ($CDCl_3$) δ 1.00 (s), 1.20 (s, 3, 18-CH_3), 2.36, 2.53 (s) (s, 3, 1-CH_3), 3.80 (s, 3, OCH_3), 6.84 (s), 6.87, 7.00 (s), 7.14 (d, J = 3 Hz, Ar-H), 9.25 (s), 9.8 (d, J = 4 (s), J = 3 Hz, CHO), 10.02 (s), 10.07 ppm (s, 1, ArCHO).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.39; H, 7.45.

3-Methoxy-1-methyl-20-oxo-19-nor-6,7-secopregna-1,3,5-(10)-triene-6,7-dial (4b). The experimental conditions and workup for this preparation were identical with the procedure used to prepare dialdehyde **4a.** From tetraene **3f** (3.65 g, 11.25 mmol), sodium periodate (7.27 g, 34 mmol), and osmium tetroxide (60 mg) in acetic acid (240 mL)–water (60 mL), there was obtained 1.95 g (49% yield) of pure dialdehyde **4b** as a gum. The ^1H NMR spectrum of aldehyde **4b** showed the presence of two isomers in an approximate ratio of 2:1. The smaller absorption is marked with an s: NMR ($CDCl_3$) δ 0.82 (s), 0.94 (s, 3, 18-CH_3), 2.15 (s, 3, $COCH_3$), 2.41, 2.54 (s) (s, 3, $ArCH_3$), 6.88 (s), 6.95, 7.10 (s), 7.24 (d, J = 3 Hz, 2, Ar-H), 9.33 (s), 9.40 (d, J = 4 (s), J = 0.5 Hz, 1, RCHO), 10.17 (s), 10.37 ppm (s, 1, ArCHO).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.96; H, 8.10.

3-Methoxy-*B*-nor-6,8-secoestra-1,3,5(10)-trien-17-one (5a). A mixture of dialdehyde **4a** (0.285 g, 0.87 mmol) and tris(triphenylphosphine)chlororhodium[6] (1.44 g, 1.57 mmol) in benzonitrile (1 mL) was heated under nitrogen at 180–190 °C for 1.5 h. After the reaction cooled, ethanol (50 mL, 95%) was added and the yellow solid which precipitated was removed by filtration. The filtrate was evaporated under vacuum and the residue was chromatographed on alumina (III; 50 g; 10% CH_2Cl_2–C_6H_6). The solvent was evaporated and the residue was sublimed to give 166 mg (70% yield) of pure nor-seco steroid **5a:** mp 110–112 °C; NMR ($CDCl_3$) δ 1.01 (s, 3, 18-CH_3), 3.31 (s, 3, 6-CH_3), 3.77 (s, 3, OCH_3), 6.74 (s, d, 2, Ar-H), 7.17 ppm (d, J = 8 Hz, Ar-H); IR (CH_2Cl_2) 1745 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.24; H, 8.96.

3-Methoxy-*B*,19-dinor-6,8-secopregna-1,3,5(10)-trien-20-one (5b). The reaction conditions for this decarbonylation were described for the preparation of compound **5a.** Dialdehyde **4b** (2.29 g, 6.42 mmol) and tris(triphenylphosphine)chlororhodium (11.125 g) in benzonitrile (3 mL) were reacted. The catalyst was precipitated with methanol and filtered. After evaporation of the solvent, the residue was chromatographed on alumina (50 g, activity III, CH_2Cl_2) to give a yellow oil. A TLC analysis of this product showed the presence of remaining polar impurities, while analysis of the ^1H NMR spectrum showed that both triphenylphosphine and benzonitrile were present. Rechromatography of the product on alumina (activity II, 100 g, benzene) effected complete purification of this product. There was obtained 1.3 g (66% yield) of steroid **5b** as an oil: NMR ($CDCl_3$) δ 0.71 (s, 3, CH_3), 2.10 (s, 3, $COCH_3$), 2.25 (s, 3, $ArCH_3$), 3.70 (s, 3, OCH_3), 6.70 (m, 2, ArH), 7.14 ppm (m, 1, ArH).

Anal. Required for $C_{20}H_{28}O_2$: *m/e* 300.2089. Found: *m/e* 300.2085.

***B*,19-Dinor-6,8-secopregn-4-ene-3,20-dione (6b).** To a stirred solution of steroid **5b** (1.287 g, 3.9 mmol) in ethanol (50 mL, 95%) was added sodium borohydride (3.04 g) in small portions. TLC analysis of the reaction after 30 min of stirring indicated that no starting material remained. Acetone (10 mL) was added dropwise to destroy excess sodium borohydride and the solution was evaporated to dryness at reduced pressure. The residue was taken up in water (50 mL) and extracted with methylene chloride (3 × 50 mL). The solution was dried ($MgSO_4$) and the solvent evaporated to give 0.91 g (76.9% yield) of an epimeric alcohol mixture which was used without purification in the next step.

The alcohol mixture (634 mg, 2.08 mmol), dissolved in tetrahydrofuran (30 mL) and *tert*-butyl alcohol (30 mL), was added dropwise to freshly distilled refluxing liquid ammonia. Sodium (200 mg) was added and the solution was vigorously magnetically stirred until the blue color disappeared (1.5–2 h). Ammonium chloride (2 g) was cautiously added, followed by dropwise addition of methanol (10 mL). The ammonia was allowed to evaporate before the remaining solution and solids were transferred with methanol wash to a flask and evaporated to dryness at reduced pressure. Water (75 mL) was added to dissolve solids and the resulting solution was extracted with methylene chloride (3 × 75 mL) and then dried (Na_2SO_4). The solvent was removed at reduced pressure to give 631 mg of crude dihydro steroid. A ^1H NMR spectrum of the product showed that the reduction was complete: NMR (CCl_4) δ 0.77 (s, 3, CH_3), 1.66 (s, 3, $=CCH_3$) and 3.52 ppm (s, 3, OCH_3).

The dihydro product in methanol (25 mL) and hydrochloric acid (15 mL, 3 N) was heated at reflux for 10 min on the steam bath, then cooled and neutralized with sodium bicarbonate. Methanol was removed at reduced pressure and additional water (50 mL) was added. The solution was extracted with methylene chloride (3 × 75 mL), dried ($MgSO_4$) and evaporated to give 726 mg of crude product.

The hydrolysis product from above (726 mg) was dissolved in acetone (85 mL) and stirred while Jones reagent was added dropwise until the orange color persisted. Stirring was continued under nitrogen for 10 min further while the completeness of the reaction was established by TLC analysis. Isopropyl alcohol was added to destroy excess oxidizing agent; then the solvent was removed at reduced pressure.

The residue was diluted with water (50 mL), extracted with methylene chloride (3 × 75 mL), and dried ($MgSO_4$). The solvent was removed at reduced pressure and the residue was chromatographed to give 448 mg (65% yield) of pure steroid **6b** as a viscous oil: IR (CH_2Cl_2) 1713 and 1695 cm^{-1}; NMR ($CDCl_3$) δ 0.60 (s, 3, CH_3), 0.60 (s, 3, CH_3), 1.98 (s, 3, $=CCH_3$), 2.12 (s, 3, $COCH_3$), 5.91 ppm (br s, 1 H, =CH).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.97; H, 9.84.

***B*-Nor-6,8-secoestra-1,3,5(10)-trien-17α-yne-3,17β-diol (5d).** Steroid **5a** (241 mg, 0.886 mmol) was fused at 210–220 °C for 1 h with pyridine hydrochloride (9.5 g). The reaction mixture was cooled, diluted with water (50 mL), extracted with methylene chloride, and dried. The residue remaining after removal of the solvent was chromatographed (silica gel, 30 g, CH_2Cl_2–10% EtOAc/CH_2Cl_2) to yield 77 mg (34% yield) of phenol **5c** which was used without further purification: NMR ($CDCl_3$) δ 1.02 (s, 3, 18-CH_3), 2.28 (s, 3, Ar-CH_3), 4.95 (br, 1, OH), 6.58 (m, 2, Ar-H), 7.05 ppm (d, J = 10 Hz, 1 H, Ar-H).

Lithium acetylide–ethylenediamine complex (292.9 mg, 3.18 mmol) was added to a solution of phenol **5c** (77 mg, 0.298 mmol) in toluene (7 mL) and dimethyl sulfoxide (7 mL), then stirred at room temperature under nitrogen for 20 h. Ammonium chloride (2 g) and water were added, and the solution was extracted with methylene chloride. The solvent was dried (Na_2SO_4) and then evaporated at reduced pressure, and the residue was chromatographed (silica gel, 30 g, CH_2Cl_2–10% EtOAc/CH_2Cl_2) to give 41 mg (49% yield) of **5d:** mp 110–112 °C; IR (KBr) 3260 cm^{-1} (C≡CH); NMR ($CDCl_3$) δ 0.99 (s, 3, 18-CH_3), 2.27 (s, 3, Ar-CH_3), 2.98 (s, 1, ≡CH), 4.90 (br, 1, OH), 6.65 (m, 2, Ar-H), 7.10 ppm (d, J = 8 Hz, 1, Ar-H).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.06; H, 8.60.

17-Hydroxy-*B*,19-dinor-6,8-seco-17α-pregn-4-ene-20-yn-3-one (6a). A solution of sodium borohydride (2.05 g, 54 mmol) in ethanol (30 mL, 95%) was added to a stirred solution of keto-steroid **5a** (0.977 g, 3.6 mmol) in ethanol (20 mL) at room temperature. After the reaction was stirred overnight, it was diluted with water (50 mL) and extracted with methylene chloride (3 × 75 mL). The extracts were dried ($MgSO_4$) and the solvent was evaporated to give 0.880 g (90%) of **5e** which was used without further purification.

The above steroid (0.443 g, 1.62 mmol), dissolved in tetrahydrofuran (30 mL) and *tert*-butyl alcohol (30 mL), was added dropwide to liquid ammonia (60 mL) being stirred at reflux under nitrogen. Sodium (0.109 g) was added and the resulting dark blue solution faded to become colorless within 2 h. Ammonium chloride (3 g) and methanol (30 mL) were carefully added. The solution remaining after evaporation of the ammonia was evaporated at reduced pressure, diluted with water (60 mL), extracted with methylene chloride, and dried (Na_2SO_4). The solvent was evaporated at reduced pressure, and a ^1H NMR spectrum of the residue indicated that less than 10% starting material remained: NMR (CCl_4) δ 0.73 (s, 3, 18-CH_3), 1.62 (s, 3, $=CCH_3$), 3.47 (s, 4, $(=C)_2CH_2$), 4.50 (m, 1, CHOH), 5.26 ppm (s, 1, =CH).

To the above product dissolved in freshly distilled toluene (15 mL)

was added cyclohexanone (3.8 mL, 3.6 g, 36.7 mmol) and aluminum isopropanoxide (0.432 g, 2.12 mmol). The reaction was distilled slowly for 1 h (5 mL distillate was collected which was replaced with toluene) and then refluxed for 3 h. The cooled solution was diluted with potassium–sodium tartrate solution (25 mL) and water (25 mL) and then extracted with toluene (3 × 50 mL). After drying (Na_2SO_4), the solvent was evaporated under vacuum to give an oil which was chromatographed (alumina, III, 30 g, toluene). The collected product showed no 4.50 ppm (CHOH) absorption in the ^1H NMR spectrum but did contain cyclohexanone as an impurity.[12] This product was dissolved in toluene (3 mL) and dimethyl sulfoxide (2.7 mL) before lithium acetylide–ethylenediamine complex (2.3 g, 2.5 mmol) was added. After the solution was stirred at room temperature under nitrogen for 20 h, ammonium chloride (3 g) was cautiously added, followed by dropwise addition of water (10 mL). Additional water (50 mL) was added and the solution was extracted with methylene chloride. The residue remaining after drying (Na_2SO_4) and evaporating the solvent was chromatographed (alumina, III, 50 g, toluene–5% EtOAc/toluene): NMR (CCl_4) δ 0.82 (s, 3, CH_3), 1.65 (s, 3, $=CCH_3$), 2.44 (s, 1, $\equiv CH$), 3.56 (s, 3, OCH_3), 7.1 ppm (s, 1, $=CH$).

To the above product in methanol (25 mL) was added 3 N hydrochloric acid (15 mL) and the resulting solution was heated for 15 min on the steam bath. Solid sodium bicarbonate was added to neutralize the hydrochloric acid. The solution was evaporated, diluted with water (50 mL), extracted with methylene chloride, and dried ($MgSO_4$). The solvent was removed under vacuum and the residue was chromatographed (alumina, III, 50 g) to give 212 mg (46% yield) of pure steroid **6a**: mp 122–124 °C; IR (CH_2Cl_2) 3260 ($C\equiv CH$) and 1685 cm^{-1} ($=CC=C$); NMR (CCl_4) δ 0.79 (s, 3, CH_3), 1.95 (s, 3, $=CCH_3$), 2.42 (s, 1, $\equiv CH$), 5.80 ppm (s, 1, $=CH$).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.75; H, 9.12.

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Registry No.—**2b,** 4192-93-2; **3b,** 63976-96-5; **3c,** 63976-97-6; **3d,** 63976-98-7; **3f,** 63976-99-8; **4a,** 63977-00-4; **4b,** 63977-01-5; **5a,** 63977-02-6; **5b,** 63977-03-7; **5b** epimeric alcohol derivative, 63977-04-8; **5b** epimeric alcohol derivative 2, 63977-05-9; **5b** dihydro alcohol derivative, 63977-06-0; **5c,** 63977-07-1; **5d,** 63977-08-2; **5e,** 63977-09-3; **5e** dihydro derivative, 63977-10-6; **5e** dihydro ketone derivative, 63988-55-6; **5e** dihydro ethynylated derivative, 639777-11-7; **6a,** 63977-12-8; **6b,** 63977-13-9; **6b** 20 alcohol derivative, 63977-14-0.

References and Notes

(1) A. B. Turner, *J. Chem. Soc. C*, 2568 (1968).
(2) C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki, and S. Kaufmann, *J. Am. Chem. Soc.*, **72**, 4540 (1950).
(3) M. B. Rubin and E. C. Blossey, *J. Org. Chem.*, **29**, 1932 (1964).
(4) D. Dvornik and O. E. Edwards, *Can. J. Chem.*, **35**, 860 (1957).
(5) H. Vorbrueggen and C. Djerassi, *Tetrahedron Lett.*, 119 (1961); *J. Am. Chem. Soc.*, **84**, 2990 (1962).
(6) J. A. Osborn and G. Wilkinson, *Inorg. Synth.*, **10**, 67 (1967).
(7) K. Ohno and J. Tsuji, *Tetrahedron Lett.*, 3969 (1971); *J. Am. Chem. Soc.*, **90**, 99 (1968).
(8) G. I. Feutrill and R. N. Mirrington, *Tetrahedron Lett.*, 1327 (1970).
(9) J. C. Sheehan, W. F. Erman, and P. A. Cruickshank, *J. Am. Chem. Soc.*, **79**, 147 (1957).
(10) H. L. Dryden, G. M. Webber, R. B. Burtner, and J. A. Celia, *J. Org. Chem.*, **26**, 3327 (1961).
(11) P. Wieland and G. Anner, *Helv. Chim. Acta.*, **50**, 1453 (1967).
(12) Efforts to remove the cyclohexanone by heating under vacuum resulted in rearomatization of the dihydro intermediate. Attempted steam distillation of the cyclohexanone from the crude reaction resulted in hydrolysis of the 3-*O*-methyl ether.

Halogenated Alicyclic Monoterpenes from the Red Algae *Plocamium*

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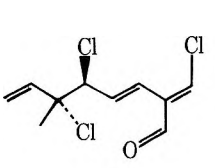
The red algae *Plocamium violaceum* (Farlow) and *P. cartilagineum* (Dixon), collected from the vicinity of Monterey Bay, Calif., yield a number of halogenated alicyclic terpenes. The structures of plocamene D (**4**), plocamene D′ (**5**), and plocamene E (**8**) have been elucidated by a combination of spectroscopic and chemical experiments. Additional structural details and chemical properties are discussed for other *Plocamium* alicycles including plocamene B (**2**), violacene (**3**), and plocamene C (**9**). Their composite structures suggest several biosynthetic generalizations about these and other halogenated monoterpenes known from *Plocamium*.

The red alga *Plocamium* has been under study in our lab because it is a source of unique monterpenes.[1,2] Recent work by ourselves and others has shown that both acyclic and cyclic halogenated monoterpenes are elaborated by *Plocamium* (order Gigartinales),[3-5] and as well by other red algae including *Microcladia* (order Ceramiales)[6] and *Chondrococcus* (order Cryptonemiales).[7,8]

Our investigation of the natural products chemistry of *Plocamium* was first prompted by an observation that extracts of *Plocamium cartilagineum* (Dixon) and *Plocamium violaceum* (Farlow) collected from Four-Mile Beach (Santa Cruz County, Calif.) showed toxicity in two bioassays. A nonpolar chromatographic fraction from either of these *Plocamium* species was highly toxic to goldfish,[9] and these extracts exhibited LC_{50} growth inhibition against mosquito larvae at 0.03 and 0.09 ppm dilutions, respectively.[10] Subsequent isolation work yielded cartilagineal (**1**) as a major component from *P. cartilagineum*[1] and plocamene B (**2**) as a major component from *P. violaceum*.[2] In both *Plocamium* species we observed another major haloterpene component,[2] violacene (**3**),[11] whose structure has been recently revised after



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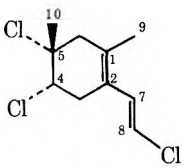
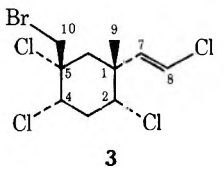


2



3

x-ray study.[12] Interestingly, both plocamene B (**2**) and violacene (**3**) are highly toxic to goldfish, and they display significant growth inhibition against mosquito larvae. In order to further explore the toxic metabolites from *Plocamium*, we extended out study of *P. violaceum* to several other collection sites in the Monterey Bay area. This yielded new halogenated

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Table I. ^{13}C NMR Data at 25.15 MHz[a]

	3[c]			4[c]	5[c]	6[c]		7[c]			8[c]	9[c]		
C	δ (ppm)		J (Hz)	δ (ppm)	δ (ppm)	δ (ppm)		δ (ppm)		J (Hz)	δ (ppm)	δ (ppm)		J (Hz)
1	42.0	(s)			43.4	39.3	(s)	43.4	(s)		142.6	67.4	(s)	
2	64.1	(d)	140[a]	65.1	65.5	67.3	(d)	67.9	(d)	155[a]	49.8	52.4	(d)	125
3	38.3	(t)	134	43.5	44.1	38.2	(t)	29.7	(t)	126	39.0	35.0	(t)	132
4	59.0	(d)	140[a]	58.2	49.4	59.9	(d)	32.7	(t)	133	65.5	65.1	(d)	142
5	71.3	(s)		140.9	140.7	72.1	(s)	143.1	(s)		72.2	71.2	(s)	
6	48.8	(t)	125[a]	45.5	45.2	41.5	(t)	44.5	(t)	133	44.2	57.1	(t)	134
7	135.4	(br d)	156	133.3	133.5	23.4	(t)	136.2	(d)	160	133.0	131.3	(d)	161
6	119.5	(dd)	10/193	120.8	120.6	8.0	(q)	119.1	(dd)	9/194	119.2	120.7	(dt)	7/7/194
9	27.4	(q)	129	26.3	26.1	27.0	(q)	26.0	(q)	126	112.7	28.0	(q)	128
10	38.8	(t)	163	113.6	116.1	39.5	(t)	111.4	(t)	155	30.9	31.9	(q)	129

[a] Potential error in J value ±5 due to overlapping multiplets. [b] For carbon numbering, see Schemes I and IV. [c] Registry no.: 3, 54279-01-5; 4, 62560-51-4; 5, 63883-43-2; 6, 63886-49-9; 7, 63866-50-2; 8, 63866-51-3; 9, 62532-55-2.

monoterpenes, and we now report these structures.

An Overview from GC/MS Data. Haloterpenes **1–3** possess distinctly different carbon skeletons and each exhibits a diagnostic mass spectral fragmentation pattern. The principal fragments from **1–3** can be designated as type I, II, or III, respectively. An acyclic octa-1,5,7-triene, such as cartilagineal (**1**), displays a type I fragmentation, giving a base peak cluster at 89/91 due to a $[C_4H_6Cl]^+$. Alternatively, the trialkyl-substituted ring system as in plocamene B (**2**) exhibits intense type II fragmentation by a way of a $[C_{10}H_{11}Cl]^+ = 167/169$ to an aromatic nucleus $[C_{10}H_{11}]^+ = 131$. Finally, the *gem*-alkyl-substituted system as in violacene (**3**) cannot easily aromatize, but instead displays an $M^+ - CH_3$ fragment and successive $M^+ -$ halogens, type III fragmentation.

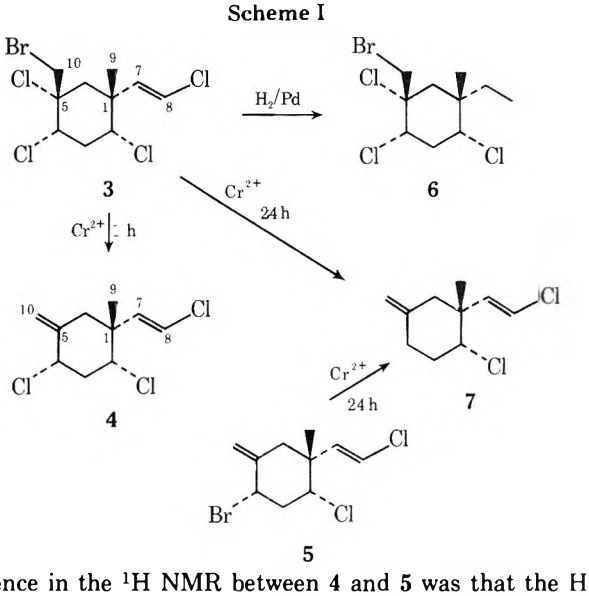
GC–MS of various *P. cartilagineum* and *P. violaceum* extracts revealed unknown components with types II and III fragmentation. Peaks displaying type III fragments were especially noticeable from *P. violaceum* and *P. cartilagineum* from Santa Cruz, Monterey and San Mateo counties. Four isomeric $C_{10}H_{13}X_3$ components could be identified in various collections whose appearance was highly dependent upon species and location.[13] As one example, the relative amounts of two $C_{10}H_{13}Cl_3$ isomers, plocamene D and plocamane E, varied from 91:9, 78:28 to 25:75 from *P. violaceum* at Four Mile Beach, Davenport Landing, and Pigeon Point, respectively.

Results and Discussion

Two new components, plocamene D and plocamane D′, exhibiting type III mass spectral fragments were isolated. Plocamene D (**4**) of molecular formula $C_{10}H_{13}Cl_3$ (M^+ = 238/240/242) was most easily purified from the *P. violaceum* extract from Four-Mile Beach. A monocyclic ring was established by the four vinyl carbons in the ^{13}C NMR (Table I). In the ^1H NMR (360 MHz, $CDCl_3$), the 13 protons of plocamene D appeared as separate resonances: δ 1.22 (3 H, s, CH_3), 2.11 (1 H, d, J = 14.2 Hz, H_{6a}), 2.10 (1 H, q, J = 12.5 Hz, H_{3a}), 2.58 (1 H, dt, J = 12.5, 4.0 Hz, H_{3e}), 2.61 (1 H, d, J = 14.2 Hz, H_{6e}), 3.83 (1 H, dd, J = 12.4, 3.8 Hz, H_{2a}), 4.34 (1 H, br d, J = 12.4, 3.8 Hz, H_{4a}), 5.00 and 5.41 (1 H each, s, H_{10} and H_{10}'), 6.02 (1 H, d, J = 13.7 Hz, H_8), 6.10 (1 H, d, J = 13.7 Hz, H_7). The several subfeatures recognizable from this data, a quaternary CH_3, a $>CCH_2C<$ unit, a $-(Cl)CHCH_2CH(Cl)-$ group, a $>C{=}CH_2$, and a $-CH{=}CH-$ residue, could best be combined in the gross structure **4**. Diequatorial Cl's at C_2 and C_4 were indicated by the large J_{a-a} couplings.

Plocamene D′ (**5**), M^+ = 282/284/286 ($C_{10}H_{13}Cl_2Br$), was isolated from *P. violaceum* from Asilomar Beach. The ^{13}C NMR shifts for **5** were similar to those of **4** (Table I), except that one of the halogen-bearing carbons in **5** was shielded by 9 ppm relative to its counterpart in **4**. Likewise, the only difference in the ^1H NMR between **4** and **5** was that the H_4 broadened doubled doublet in **5** was deshielded relative to that in **4**. These two observations indicated that the gross structure of **5** differed from **4** by only a Br substituent at C_4.

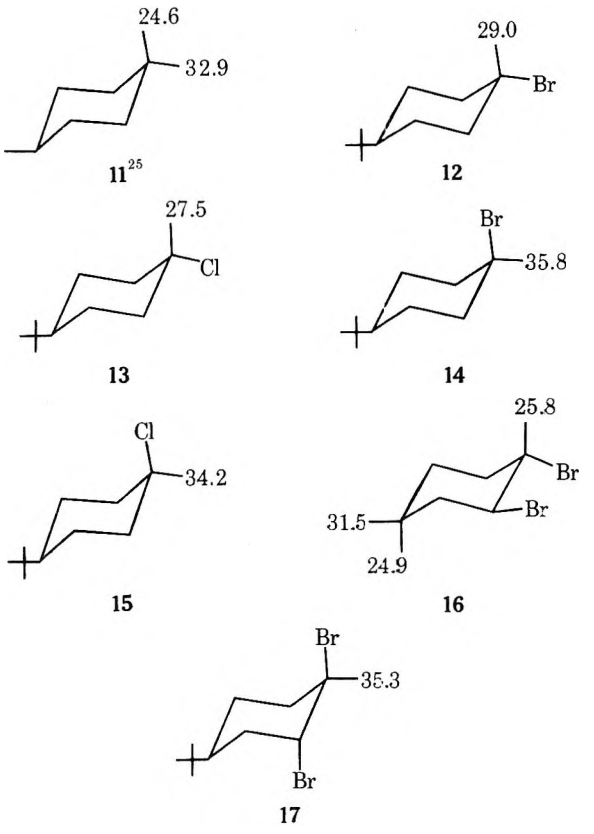
Scheme I



The assignment of the *gem*-methyl, *trans*-chlorovinyl stereochemistry at C_1 in **4** and **5** was approached by a correlation based upon ^{13}C NMR chemical shifts. This seemed reasonable because methyl shifts are sensitive to configurational changes, and a particularly relevant example is afforded by the methyl shift differences of 5–6 ppm observed by Wenkert for pairs of pimaradienes epimeric at a $-C(C_2H_3)CH_3$ position.[14] To provide some background for interpreting carbon shifts in polyfunctional six-membered rings, two violacene derivatives **6** and **7**, prepared by hydrogenation and reductive dehalogenation (Scheme I), were examined in order to determine the sensitivity of their ^{13}C methyl shifts to substituent changes. Comparison of the methyl shifts between **3** vs. **6** and **7** (Table I) revealed that an anticipated homoallyl shielding effect[15] was negligible and that the δ effect though larger than expected was still small.[16] The closeness of the methyl carbon shifts of **7** (26.0) to that of **4** (26.3) and **5** (26.1) indicated that the C_1 configuration of these latter two must be identical to that of **3**. The chemical interconversions shown in Scheme I provided further confirmation on this point, and yielded the absolute stereochemical assignments shown.

GC/MS data of a *P. violaceum* extract from Pigeon Point revealed that it was especially rich in a component, plocamene E (**8**), with type II fragmentation. Interestingly, a second collection of this alga (1.3 kg, wet wt) from a single rock at that location gave a crude oil whose ^1H PFT NMR showed plocamene E as the only haloterpene component. After purifi-

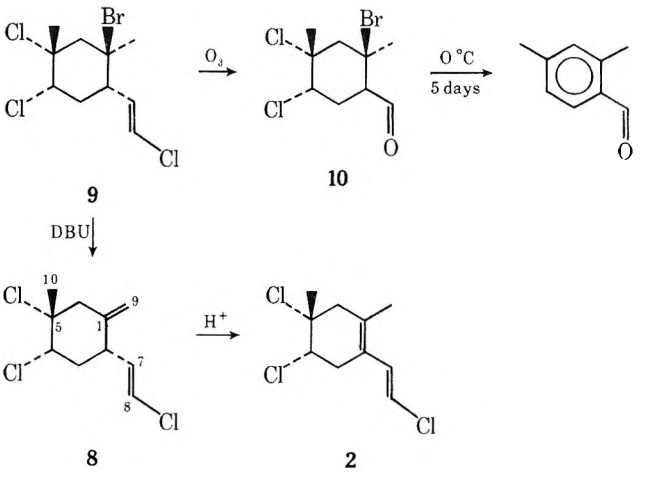
Scheme II



cation by HPLC, this compound displayed a mass spectrum parent *m/e* 238/240/242 ($C_{10}H_{13}Cl_3$). A single ring was indicated by the four vinyl and two quaternary carbons in the ^{13}C NMR (Table I). The ^1H NMR (360 MHz, $CDCl_3$) exhibited additional structural features including a single quaternary methyl (δ 1.73, s), an isolated methylene (δ 2.41, br d, J = 14.8 Hz; δ 2.77 d, J = 14.7 Hz) and *exo*-methylene (δ 4.84 and 4.90), and a –(Cl)CHCH$_2$CH(CH=CHCl)–: δ 2.05 (q, J = 12.8 Hz, H_{3a}), 2.11 (dt, J = 12.6, 4.5, 4.5 Hz, H_{3e}), 2.79 (m in Bz-d_6 spin decoup at H_9 converted this peak into an eight-line multiplet with J = 14, 9.5 Hz, H_{2a}), 3.95 (dd, J = 11.2, 4.5 Hz, H_{4a}), 5.94 (dd, J = 13.4, 7.9 Hz, H_7), and 6.04 (d, J = 13.4 Hz, H_8). These J values were characteristic of a six-membered ring of gross structure 8 with diequatorial substituents at C_2 and C_4. The choice of the attachment of the *exo*-methylene to position C_1 or C_5 was confirmed as the former by an observed long-range coupling from the *exo*-methylene H's to H_{2a} and H_{6a} which was collapsed by spin decoupling at the *exo*-methylene.

The problem of the C_5 CH_3 stereochemistry in 8 was resolved with the aid of ^{13}C chemical shifts, and it was assigned as equatorial. Axial and equatorial cyclohexyl quaternary methyls exhibit different and characteristic carbon shifts.[17] For example, an axial–equatorial methyl-shift difference of 8 ppm is observed for a noninverting 1,1-dimethylcyclohexane **11**, with Me(e) = δ 33 and Me(a) = δ 25. A similar large difference, Me(a) − Me(e) = 7 ppm, is observed for a cyclohexyl methyl gem to a halogen (Cl or Br) as shown by **12**–**15** in Scheme II. In order to apply this shift correlation to compounds such as **2** and **8**, the effects due to additional γ substituents must first be estimated. The comparative data among compound sets **12** and **16** and **14** and **17**, along with data from several other model compounds that will be discussed elsewhere, show that the shielding imparted by an added γ halogen gauche to an axial methyl or an equatorial methyl is δ 4 or 1, respectively. Thus, a characteristic methyl shift can be estimated for a 1-methyl-1,2-dihalocyclohexane as δ 33–35 Me(e) and δ 23–25 Me(a). In view of this analysis, the methyl shift of 8 (δ 30.9) falls into a range that is consistent

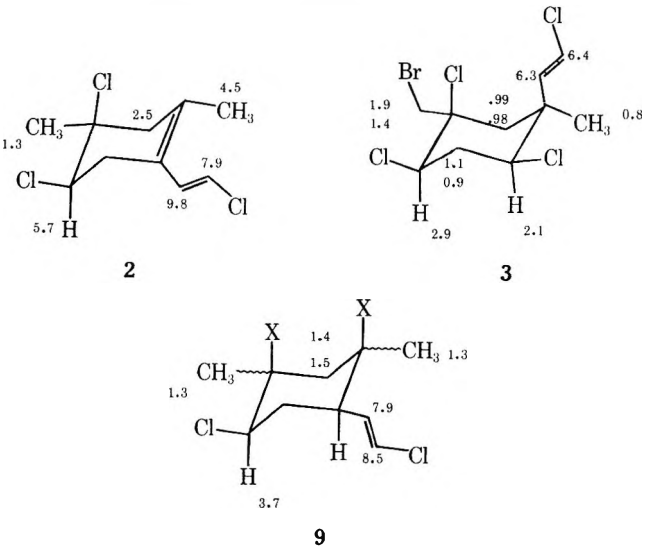
Scheme III



with an equatorial assignment. In addition, our earlier suggestion of an equatorial type methyl in **2** (δ 30.3)[2] is further substantiated by this analysis.

The final compound isolated, plocamene C (**9**), was a major component of the Pigeon Point oil, but it was present in only low concentration in the Four-Mile Beach oil. The ^{13}C and ^1H NMR of **9** showed many similarities to **8** with differences in the mass spectrum (M^+ 318, $C_{10}H_{14}Cl_3Br$), the ^{13}C NMR spectrum (two vinyl carbons), and the ^1H NMR spectrum (s Me's δ 1.67 and 1.95) which indicated that the structure of **9** differed from **8** by only an HBr. The closeness of the CH_3 ^1H δ values in **9** to those in 1,1-chloromethylcyclohexane (δ 1.58) and 1,1-bromomethylcyclohexane (δ 1.80)[18] indicated also that chlorines were at both C_5 and C_8 in **9**. The use of a relaxation reagent Gd(fod)$_3$[19] provided evidence for the placement of the single Br at C_1. Ozonalysis of **9** yielded aldehyde **10** (Scheme III) with methyls at δ 1.64 and 2.0 ($CDCl_3$) representing a methyl gem to a chlorine and bromine, respectively. Addition of Gd(fod)$_3$ caused the low-field signal to broaden considerably owing to an efficient relaxation between it and the lanthanide reagent, whereas the high-field methyl remained sharp. While our work on this structure was in progress, a publication appeared on the x-ray of (1*R*,2*S*,4*S*,5*R*)-1-bromo-*trans*-2-chlorovinyl-4,5-dichloro-1,5-dimethylcyclohexane (**9′**)[4a] which had the same molecular formula and similar ^1H NMR properties as **9**. Differences in their melting points (**9** = 78.5–79 °C, and **9′** = 43.5–44.5 °C) and chemical behavior at first suggested that **9** and **9′** might be isomers, but further careful comparison between **9** and an authentic sample

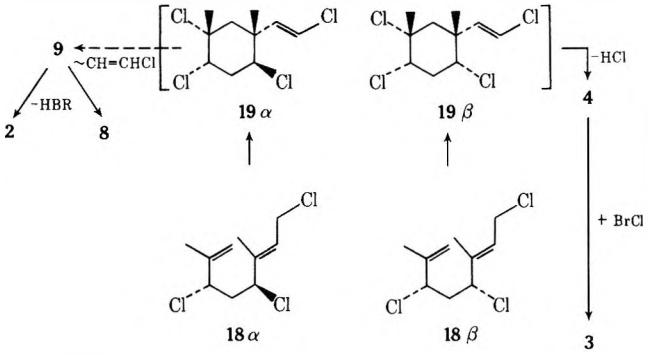
Scheme IV. Proton T_1 Data



of **9'** revealed that they were identical.[20] Before the above comparison was completed, we explored the use of T_1 data to set the **9** C_1 and C_5 halogen substitution and stereochemistry. Relaxation rates for both ^1H and ^{13}C are sensitive to a number of factors including steric environment.[21] Proton T_1's were available for **2** and **3**[22] and were measured for **9** and tabulated in Scheme IV. Dipole relaxation is a dominant mechanism in the data of **2** and **3** as shown by the expected T_1 increase for protons in **2** along the series CH_3 (1.3), $-CH_2-$ (H_{6e} = 2.5) and C=C(H)- (9.8). Although the structurally different methyls in **2** display different T_1 values, a similar expected difference did not carry over into the methyl T_1 values of **9**.

The chemical relationships established in Scheme III led to the absolute stereochemical assignments for both plocamene B (**2**) and plocamene E (**8**). In our hands, **9** was inert to loss of HBr in the presence of acid.[4a] On the other hand, basic treatment of **9** with 1,5-diazobicyclo[5.4.0]undec-5-ene (DBU) in refluxing dioxane yielded **8** which could then be rearranged to the more stable **2** by acid catalysis.

The chemical and stereostructural features of the alicyclic compounds established above provide some insight into their possible biogenesis. Comparison among the six-membered ring substituent stereochemistries of plocamene C (**9**) and plocamene D (**4**) along with the relative stereochemistries known for acyclic epimers 18α and 18β, also isolated from *P. violaceum*,[3b] suggests a hypothetical set of structures **19**α and **19**β as a relay to both rearranged and nonrearranged sets of alicycles **9** and **4**.[26] Plocamene C (**9**) is quite stable to loss of



HBr at both elevated temperatures and in neutral solution for long periods of time. The structural similarities then between **9** vs. plocamene B (**2**) and plocamene E (**8**) suggest that the latter two are derived from the former by some type of biological dehydrohalogenation. The contrasting process of biological halogenation seems also to be occurring in that enzymatic chlorobromination undoubtedly converts **4** into **3**.

Experimental Section

The NMR spectra were recorded on a JEOL PS 100 PFT spectrometer operating on 100 MHz for ^1H and 25.1 MHz for ^{13}C. The 360-MHz ^1H NMR spectra were recorded at the Stanford Magnetic Resonance Laboratory. Optical rotations were measured on a Perkin-Elmer 141 polarimeter with a 1-dm cell (5 mL). GC/MS data were recorded on a Finnigan 4000 system equipped with a $\frac{1}{8}$ in. × 3 ft glass column packed with 3% OV-17 on Chromasorb G and temperature programmed 120–190 °C at 2 °C/min. Routine low-resolution mass spectra data were recorded on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. High-performance liquid chromatography (HPLC) was done on a Waters ALC 201 using Porasil columns $\frac{3}{8}$ in. × 8 ft. All solvents were reagent grade and distilled for HPLC use. Spectral-grade solvents were used for NMR (Me_4Si standard) and optical rotation determinations. Low-boiling petroleum ether was used in all instances.

Collections and Extractions. *Plocamium violaceum* was collected interdially from several locations (wet weight and yield of extract) including: Davenport Landing, Santa Cruz County, Oct. 16, 1974 and Nov. 12, 1974 (1 kg, 2.33 g, 0.23% yield); Four-Mile Beach, Santa Cruz County, Nov. 11, 1974 (0.7 kg, 2.06 g, 0.29% yield); Pigeon Point, San Mateo County, Oct. 15, 1974 and Nov. 14, 1974 (1 kg, 2.68 g, 0.23% yield); Pigeon Point, Nov. 2, 1975 (1.3 kg, 1.10 g, 0.08% yield); and Asilomar Beach, Monterey County, July 27, 1975 (320 g, 0.9 g, 0.28% yield).

The freshly collected algae were either directly extracted or held frozen until extraction. All samples were cold extracted twice with $CHCl_3$ and once with EtOH (95%) over a period of 3–7 days. The combined extract was then chromatographed through silica gel (Grace grade 62, 60–200 mesh, activated) using petroleum ether followed by petroleum ether/benzene (1:1). The resulting semipurified oil was then subjected to HPLC using petroleum ether/benzene (95:5).

Isolations. Following the procedure above, Plocamene C, D, D', and E were isolated.

Plocamene D (4) was obtained as clear mobile oil, HPLC fraction no. 18 (20-mL fractions, 39 mg), from Four-Mile Beach: $[\alpha]^{20}_D$ −4.1° (*c* 0.73, $CHCl_3$); MS *m/e* 238, 240, 242, (M^+), 223, 225 ($M^+ - CH_3$), 203, 205, 207 (M^+ − Cl), 167, 169 (M^+ − Cl, HCl), 131 (M^+ − Cl, HCl, HCl); 91 base $(C_7H_7)^+$ and NMR discussed in the text.

Plomacene D' (5) was obtained as a clear mobile oil, HPLC fraction no. 10 (40 mg), from Asilomar Beach: MS *m/e* 282, 284, 286 (M^+), 267 269 ($M^+ - CH_3$), 247, 249, 251 (M^+ − Cl), 203, 205, 207 (M^+ − Br), 167, 169 (M^+ − Br, Cl, H), 91 base $(C_7H_7)^+$; ^1H NMR ($CDCl_3$ 100 MHz) δ 1.26 (s, CH_3), 2.1–2.8 (m, 2 H), 2.18 (d, 1 H, J = 15 Hz), 2.71 (d, 1 H, J = 15 Hz), 3.87 (dd, 1 H, J = 4, 12 Hz), 4.53 (br d, 1 H, J = 4, 12 Hz), 5.10 (br s, 1 H), 5.46 (br s, 1 H), 6.03 (d, 1 H, J = 12 Hz), 6.15 (d, 1 H, J = 12 Hz).

Plocamene E (8) was obtained as a clear mobile oil, HPLC fraction no. 21–24 (359 mg), from Pigeon Point: $[\alpha]^{20}_D$ −105° (c 4.57, $CHCl_3$); MS *m/e* 238, 240, 242 (M^+), 203, 205, 207 (M^+ − Cl), 167, 169 (M^+ − Cl, HCl), 131 base (M^+ − Cl, HCl, HCl) and NMR discussed in the text.

Plocamene C (9) was isolated from collections at Pigeon Point (283 mg) and both Davenport Landing collections, HPLC fraction no. 17–19 (83 mg), and it was recrystallized (ETOH) to a mp 78.5–79 °C (uncorrected). The absolute methyl carbon shifts were derived by relating ^{13}C peaks to ^1H peaks by the graphical off-resonance decoupling method.[23] In addition to NMR discussed in the text: ^1H NMR (360 MHz, $CDCl_3$) δ 1.67 (s, CH_3), 1.95 (s, CH_3), 2.03 (dt, 1 H, J = 3.8, 13.5 Hz), 2.15 (dt, 1 H, J = 12.1, 13.5 Hz), 2.69 (d, 1 H, J = 15.1 Hz), 2.89 (m, 1 H, J = 3.8, 7.7, 12.1 Hz), 2.95 (d, 1 H, J = 15.1 Hz), 3.89 (dd, 1 H, J = 3.8, 12.1 Hz), 6.05 (dd, 1 H, J = 7.7, 13.3), 6.16 (d, 1 H, J = 13.3 Hz); $[\alpha]^{20}_D$ −84° (*c* 0.32, $CHCl_3$); MS *m/e* 318, 320, 322, 324 (M^+), 282, 284, 286 (M^+ − HCl), 238, 240, 242 (M^+ − HBr), 203, 205, 207 (M^+ − H, Br, Cl), 167, 169 (M^+ − Br, 2Cl, 2 H), 131 base (M^+ − Br, 3 Cl, 3 H). Plocamene C ((**9**) was compared by GC/MS to an authentic sample of compound (**9'**) provided by Professor D. J. Faulkner. Their retention times and mass spectra were identical. Plocamene C (**9**) was found to be thermally quite stable in that a GLC before and after melting were identical.

Hydrogenation of Violacene (3) to 6. Violacene (**3**), 100 mg, and 5 mg of Pd on carbon (10%) in 20 mL of EtOH were hydrogenated until 1 equiv of H_2 was absorbed (ca. 12 h) to yield quantitatively the dihydro compound **6**: ^1H NMR ($CDCl_3$) δ 0.92 (t, CH_3, J = 7.3 Hz), 1.01 (s, CH_3), 1–2 (m, 2 H), 1.89 (d, 1 H, J = 16.1 Hz), 2.28 (d, 1 H, J = 16.1 Hz), 2.42 (dt, 1 H, J = 4.3, 11.7), 2.64 (q, 1 H, J = 11.7 Hz), 3.51 (d, 1 H, J = 10.7 Hz), 3.81 (dd, 1 H, J = 4.4, 11.7 Hz), 3.93 (d, 1 H, J = 10.7 Hz), 4.32 (dd, 1 H, J = 4.4, 11.7 Hz); MS *m/e* 320, 322, 324, 326 (M^+).

Violacene (3) to Plocamene D (4) and 7. Violacene (**3**), 10 mg (in 2 mL of DMF), and an equivalent amount of Cr^{2+} ion (in DMF/H_2O solution)[24] were stirred for a period of 1 h at room temperature under a stream of N_2. The reaction mixture was worked up to yield a 1:1 mixture of starting material and plocamene D (**4**) whose PFT NMR spectral properties were identical to those described in the text. When this reaction was carried out for a longer period of time (24 h), upon workup **7** was the exclusive product: ^1H NMR (360 MHz, $CDCl_3$) δ 1.18 (3 H, s, CH_3), 1.88 (2 H, complex m, H_4), 2.06 (1 H, d, J = 14 Hz, H_6), 2.13 (1 H, m, H_3), 2.43 (1 H, complex m, H_3), 2.49 (1 H, d, J = 14 Hz, H_6), 3.90 (1 H, dd, J = 10, 4 Hz, H_{2a}), 4.70 and 4.81 (1 H each, s, H_{10} and $H_{10'}$), 6.04 (1 H, d, J = 14 Hz, H_7), 6.09 (1 H, d, J = 14 Hz, H_8); mass spectrum 204, 206, 208 (M^+), 169, 171 (M^+ − Cl), 91 base (C_7H_7).

Plocamene D' (5) to 7. Following the above procedure, plocamene D' (**5**) (20 mg) was converted to the compound **7**. Its spectral properties were identical to those mentioned above.

Plocamene C (6) to Plocamene E (5). Plocamene C (**6**) (10 mg) in a nitrogen atmosphere and dry dioxane (10 mL) was reacted with a slight excess of 1.5 diazobicyclo[5.4.0]undec-5-ene (DBU) at reflux for 24 h. After workup, the resulting product displayed PFT NMR spectral properties that were identical to those described above from plocamene E (**5**).

Plocamene E (5) to Plocamene B (2). Plocamene E (**5**) (10 mg)

and a catalytic amount of *p*-toluenesulfonic acid (HOTS) were dissolved in benzene (10 mL) under nitrogen. After a 2-h reflux, the resulting product displayed PFT NMR spectral properties that were identical to those of plocamene B (**2**).

Ozonolysis of Plocamene C (6) to Aldehyde (10). Plocamene C (**6**) (20 mg) in ethyl acetate (10 mL) was ozonized at −78 °C. The reaction mixture was worked up with dimethyl sulfide, and the resulting aldehyde displayed the following: NMR, 100 MHz ($CDCl_3$), δ 1.66 (s, CH_3), 2.00 (s, CH_3), 2.18 (m, 2 H), 2.70 (d, 1 H, J = 15.5 Hz), 2.89, (d, 1 H, J = 15.5 Hz), 3.51 (br m, 1 H), 3.84 (dd, 1 H, J = 4, 7.9 Hz), 8.92 (s, 1 H). Upon standing at room temperature overnight or at 0 °C for 5 days, the aldehyde **10** aromatized to 2,5 benzaldehyde.[2]

Treatment of Aldehyde (8) with Gd(fod)$_3$. To aldehyde 8 (15 mg) in $CDCl_3$ was added $Gd(fod)_3$ (6 mM solution in $CDCl_3$) in 100-μL portions until line broadening became apparent (450 μL). Final molar ratio of 8 to $Gd(fod)_3$ = 1.0:0.049.

Relaxation Time Measurements. The Fourier transform T_1 measurements were done using the standard 180°-τ-90° pulse sequence. The delay time (τ) was greater than $4T_1$ for the most rapidly relaxing protons. Dilute samples were prepared in benzene-d_6 with added Me_4Si. All samples were degassed (five freeze–pump–thaw cycles) and then sealed.

Carbon NMR of Model Compounds. The ^{13}C NMR data for **11** was taken from the literature.[25] Compounds **12–17** were prepared by addition of HX or X_2 (X = Cl, Br) to the corresponding olefins. ^{13}C NMR data were obtained on 80% solutions in $CDCl_3$. Unseparated epimeric mixtures of **12** and **14**, and **13** and **15** were used.

Acknowledgment. We thank Professor I. A. Abbott (Hopkins Marine Station) for guidance in alga identification. We also thank the NOAA office of Sea Grant and UCSC Committee on Research for support of this research, and the NSF Chemical Instrumentation Program for their financial assistance in the purchase of a GC/MS apparatus.

Registry No.—**10**, 63866-52-4.

References and Notes

(1) P. Crews and E. Kho, *J. Org. Chem.*, **39**, 3303 (1974).
(2) P. Crews and E. Kho, *J. Org. Chem.*, **40**, 2568 (1975).
(3) (a) P. Crews, *J. Org. Chem.*, **42**, 2634 (1977); (b) P. Crews and E. Kho-Wiseman, *J. Org. Chem.*, **42**, 2812 (1977).
(4) (a) J. S. Mynderse, D. J. Faulkner, J. Finer, and J. Clardy, *Tetrahedron Lett.*, 2175 (1975); (b) J. S. Mynderse and D. J. Faulkner, *Tetrahedron*, **31**, 1963 (1975).
(5) (a) P. Kazlauskas, P. T. Murphy, R. J. Quinn and R. J. Wells, *Tetrahedron Lett.*, 4451 (1976); (b) D. B. Stierle, R. M. Wing, and J. J. Sims, *ibid.*, 4455 (1976).
(6) P. Crews, P. Ng, E. Kho-Wiseman, and C. Pace, *Phytochemistry*, **15**, 1707 (1976).
(7) N. Ichikawa, Y. Naya, and S. Enomoto, *Chem. Lett.*, 1333 (1974).
(8) (a) B. J. Burreson, F. X. Woolard, and R. E. Moore, *Tetrahedron Lett.*, 2155 (1975); (b) B. J. Burreson, F. X. Woolard and R. E. Moore, *Chem. Lett.*, 1111 (1975).
(9) This bioassay is based upon procedures described by: G. J. Bakus and G. Green, *Science*, **185**, 951 (1974).
(10) The bioassay result was kindly provided by Dr. G. Staal, Biology Research Department, Zoecon Corp. See also note 2a, ref 2.
(11) We initially named this compound plocamene A: ref 2, footnote 4, but while our work was in progress it was reported as violacene by J. S. Mynderse and D. J. Faulkner, *J. Am. Chem. Soc.*, **96**, 6771 (1974).
(12) D. VanEngen, J. Clardy, E. Kho-Wiseman, P. Crews, and D. J. Faulkner, unpublished results.
(13) For a more extensive study of this phenomenon, see: P. Crews, L. Campbell, and E. Heron, *J. Phycol.*, **13**, 297 (1977).
(14) (a) E. Wenkert and B. Buckwalter, *J. Am. Chem. Soc.*, **94**, 4367 (1972); (b) F. Orsini, P. Pellizoni, A. T. McPhail, K. D. Onan, and E. Wenkert, *Tetrahedron Lett.*, 1085 (1977).
(15) E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Kotner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *J. Am. Chem. Soc.*, **95**, 4990 (1973).
(16) See Table I: N. K. Wilson and J. B. Stothers, *Top. Stereochem.*, **8**, 1 (1973).
(17) (a) Reference 2, note 10; (b) Y. Senda, J. Ishiyama, and S. Imaizumi, *Tetrahedron*, **31**, 1601 (1975); (c) A. G. Gonzalez, C. G. Francisco, R. Freire, R. Hernandez, J. A. Salazar, and E. Suarez, *Tetrahedron Lett.*, 1897 (1976); (d) L. F. Johnson and W. C. Jankowski, "Carbon-13 N.M.R. Spectra", Wiley-Interscience, New York, N.Y., 1972, no. 360.
(18) H. J. Hageman and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 1141 (1966): also reported are CH_3 shift data for *trans*-1,2-dichloro-1-methyl-4-*tert*-butylcyclohexane (δ 1.70) and *trans*-1,2-dibromo-1-methyl-4-*tert*-butylcyclohexane (δ 1.95).
(19) Gd complexes cause induced line broadening rather than induced shifts for protons: G. N. LaMar and J. W. Faller, *J. Am. Chem. Soc.*, **95**, 3817 (1973); K. Ajisaka and M. Kainosho, *J. Am. Chem. Soc.*, **97**, 330 (1975).
(20) It is noteworthy that the stereochemically different methyls in **9** exhibit predictable shift values. The equatorial C_5 CH_3 = δ 31.9 is within the range described in the text for such a methyl. The axial C_1 CH_3 = δ 28.0 is slightly shielded vs. the range discussed in the text for an axial methyl with the incremental shift arising because of the axial C_5 Cl substituent as expected according to: S. H. Grover and J. B. Stothers, *Can. J. Chem.*, **52**, 870 (1974).
(21) (a) G. C. Levy and G. R. Nelson, "Carbon-13 NMR for Organic Chemists", Wiley, New York, N.Y., 1973; (b) K. Nakanishi, R. Crouch, I. Miura, X. Dominiguez, A. Zamudio, and R. Villarreal, *J. Am. Chem. Soc.*, **96**, 609 (1974); (c) C. W. M. Grant, L. D. Hall, and C. M. Preston, *J. Am. Chem. Soc.*, **95**, 7742 (1973).
(22) P. Crews, unpublished results.
(23) G. Gray, *Anal. Chem.*, **47**, 546A (1975).
(24) W. C. Kray, Jr., and C. E. Castro, *J. Am. Chem. Soc.*, **86**, 4603 (1964).
(25) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **94**, 5318 (1972).
(26) Added in Proof. Wells[27] just recently reported mertense (**20**) which is related to gross structure 19β. The stereochemistry suggested at both the *gem*-methyl/chlorovinyl and the *gem*-methyl/chloride for **20** may be in error. Based upon ^{13}C methyl chemical shifts, the former methyl in **20** at δ 26.1 is similar to the shift and stereochemistry in **3–5** and the shift of the latter, δ 20.1, is consistent with an axial placement as discussed in the text.
(27) Added in Proof. R. S. Norton, R. G. Warren, and R. J. Wells, *Tetrahedron Lett.*, 3905 (1977).

A Diels–Alder Approach to the Pyridine C Ring of Streptonigrin

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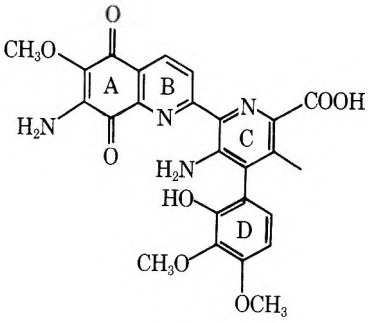
A model synthetic approach to synthesis of the pyridine C ring of the antitumor agent and antibiotic streptonigrin (**1**) is described. A hetero-Diels–Alder reaction is used as the method of ring construction. Studies of the reaction of dienophile **6** with dienes **13–16** and **18** are described in detail, particularly in regard to regioselectivity. A mechanistic model is proposed to rationalize the results. Adduct **27** has been converted to an acetylpyridine **42**, which possesses four of the five substituents present in the desired streptonigrin synthon **3**.

Streptonigrin (**1**) is a tetracyclic antitumor antibiotic produced by *Streptomyces flocculus*.[2] Considerable work has appeared describing approaches to the synthesis of streptonigrin and of streptonigrin analogues.[3-7] Progress has also been made in elucidating the mechanism of action of **1** as an antitumor agent.[8]



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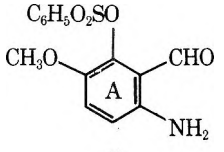
We have recently been engaged in studies directed toward the total synthesis of this challenging molecule. Our projected approach involves coupling aminoaldehyde **2** with pentasubstituted acetylpyridine **3** in a Friedlander condensation to give tetracyclic quinoline **4**. Elaboration of the A-ring



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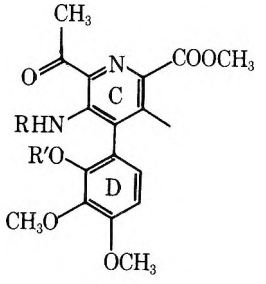

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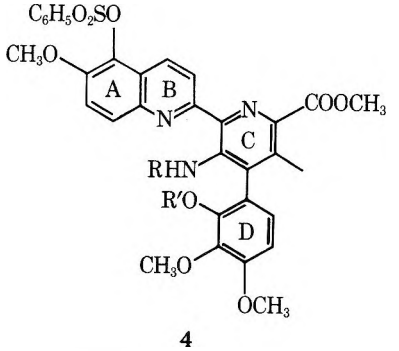
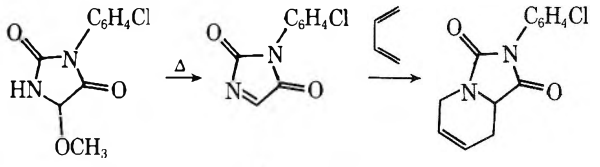


4

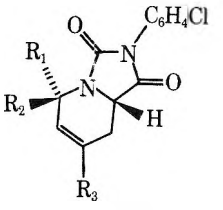
functionality and removal of the protecting groups would lead to streptonigrin (**1**). We have tested the final steps of this synthetic strategy and reported[7] synthesis of a model streptonigrin quinolinequinone AB-ring system. In this and the following paper[9] is described the synthesis of model CD-ring pyridines related to **3** using a hetero-Diels–Alder reaction to construct the C ring.

It has been reported [10a] that 1-(*p*-chlorophenyl)-2,5-imidazolidinedione (**6**), which can be formed in situ by elimination of methanol from readily available 3-(*p*-chlorophenyl)-5-methoxyhydantoin (**5**),[11] undergoes Diels–Alder reactions with a variety of simple dienes either thermally or under Lewis acid catalysis to produce adducts such as **7**. Al-

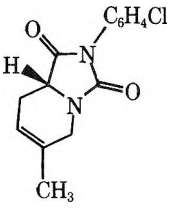


5 **6** **7**

though the stereochemistry of this reaction has been studied,[10] relatively little was known at the outset of our work about the orientational preferences of this cycloaddition when using unsymmetrically substituted dienes. It was known that thermal condensation of **6** with isoprene gives about a 1:1 mixture of the orientational isomers **8** and **11**. However,



8, $R_1 = R_2 = H$; $R_3 = CH_3$
9, $R_2 = R_3 = H$; $R_1 = CH_3$
10, $R_1 = R_2 = R_3 = CH_3$



11

thermal condensation of **6** with *trans*-piperylene or acid-catalyzed condensation of **6** with 1,1,3-trimethylbutadiene gives exclusively isomers **9** and **10**, respectively.[10a] We have prepared several substituted dienes of potential use in synthesis of pyridine **3** and studied the regiochemistry of their reactions with dienophile **6**.

Aldehyde **12**, which is readily prepared by aldol condensation of phenylacetaldehyde with acetaldehyde,[12] was converted to dienes **13** and **14** by treatment with propylene and ethylene Wittig reagents, respectively. Both dienes were isolated as mixtures of isomers about the disubstituted double bond. The ratio of trans to cis isomers varied depending upon the solvent used. In ether solvent the trans isomer predominated by about 2:1 whereas in THF about a 3:4 mixture of trans to cis was obtained. The overall yield of dienes was best, however, if the reaction was run in THF. No serious attempt was made to find optimum reaction conditions for synthesis of the trans isomer in this model series. Since the cis isomers do not react in the Diels–Alder step (vide infra), a procedure will have to be found in the real D-ring series to prepare

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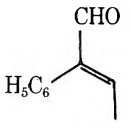

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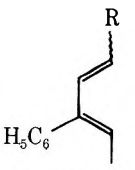
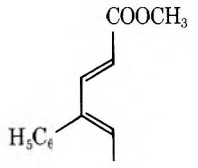
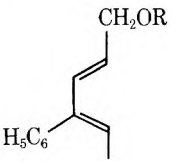


13, R = CH_2CH_3
14, R = CH_3
15, R = H



16



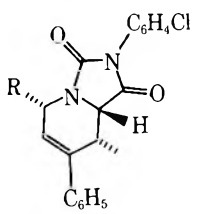
17, R = H
18, R = $COCH_3$

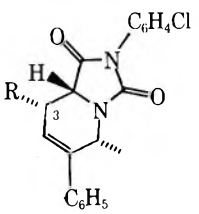
stereochemically pure trans dienes. This work is now in progress.

Treatment of aldehyde **12** with the methylene ylide produced diene **15** in 53% yield.[18] Condensation of aldehyde **12** with the anion derived from trimethylphosphonoacetate gave diene **16** as the stereochemically pure trans product in 77% yield. Reduction of **16** with lithium aluminum hydride produced alcohol **17** (87%) which could be acetylated with acetic anhydride in pyridine to provide **18** stereochemically pure in 84% yield. Dienes **13–16** and **18** were refluxed with methoxyhydantoin **5** in xylene for 3 days. The ratios of Diels–Alder orientation products were determined by NMR integration of the crude reaction mixture or by careful isolation by preparative TLC of an aliquot. The products were then isolated by column chromatography and fully characterized by complete 100-MHz NMR decoupling. Stereochemistry was also determined by NMR decoupling.

The reaction by diene **16** with dienophile **6** was quite sluggish and after 3 days a considerable amount of starting material remained. The sole product of this reaction was adduct **20** which on attempted purification by preparative TLC gave a 1:1 mixture of C-3 epimers. None of isomer **19** was detected. Diene **15** reacted with dienophile **6** somewhat faster to give primarily adduct **22** along with a small amount of **21**. Here again, starting material remained after 3 days in refluxing xylene but no serious attempt was made to push the reaction to completion.[13] The major isomers formed in the above two cases are in the undesired series of adduct (i.e., phenyl and N in a "meta" relationship).

On the other hand, dienes **13, 14,** and **18** showed a different orientational preference in the Diels–Alder reaction from dienes **15** and **16.** In these cases the desired (i.e., phenyl and N are "para") adducts **23, 25,** and **27** were the major products and lesser amounts of the undesired isomers **24, 26,** and **28**

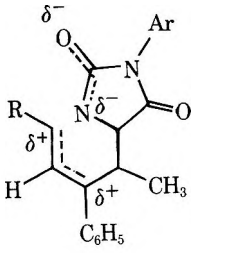




	Ratio, %	
19, R = $COOCH_3$	0:100	20, R = $COOCH_3$
21, R = H	8:92	22, R = H
23, R = CH_2OCOCH_3	55:45	24, R = CH_2OCOCH_3
25, R = CH_3	67:33	26, R = CH_3
27, R = CH_2CH_3	75:25	28, R = CH_2CH_3

were found. In these cases also, starting material remained after 3 days.[13] However, with dienes **13** and **14,** recovered starting material was highly enriched in the cis isomers which apparently do not react with **6.** No adducts could be detected which had stereochemistry expected from cycloaddition of a *cis*-diene.

These results might be rationalized if one postulates nonsynchronous[14] bond formation in the [4 + 2] cycloaddition and that the transition state for the reaction has dipolar character.[10b] With these assumptions one might envision transition states such as **29** and **30** leading to the "desired" and "undesired" series of products, respectively. The difference between these two transition states is that in **29** a positive charge is adjacent to both R and phenyl and in **30** the charge is adjacent to both H and CH_3. As the group R becomes more capable of stabilizing a positive charge (i.e., $COOCH_3 \rightarrow AcOCH_2 \rightarrow H \rightarrow CH_3 \rightarrow CH_2CH_3$) transition state **29** gradually becomes favored over transition state **30.** It appears that the substituents at the 1 and 4 positions of the dienes (i.e., R and CH_3) have the strongest effect upon orientation. This is in accord with the greater rate-enhancing ability of 1,4 substituents vs. 2, 3 substituents on butadiene in the Diels–Alder reaction.[15,16] Thus, when using diene **19** (R = $COOCH_3$) transition state **29** is destabilized since there is a positive charge adjacent to the R group at C-1. With diene **15** (R = H) the C-4 methyl substituent has a greater effect on stabilization of **30** than the 3-phenyl substituent has on stabilizing **29.** In the cases where R = CH_2OAc, CH_3, and CH_2CH_3, the C-1 and C-4 substituents nearly cancel each other, and orientation is governed mainly by the relative stabilizing abilities of phenyl vs. H. Although these interrelationships are complex, using this model one might qualitatively predict the major orientational isomer in these hetero-Diels–Alder reactions.



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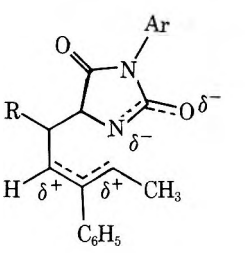
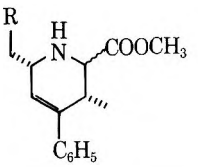
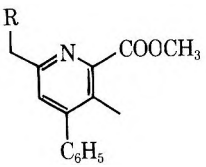


30

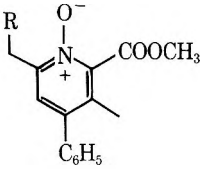
Adduct **27,** on hydrolysis with barium hydroxide followed by esterification with methanolic HCl, gave amino ester **31** as a mixture of epimers. This mixture could be aromatized to the ethylpyridine **33** by treatment with either chloranil (59%) or



31, R = CH_3
32, R = H

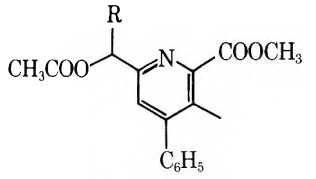


33, R = CH_3
34, R = H

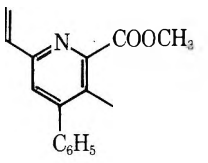


35, R = CH_3
36, R = H

5% Pd/C in refluxing toluene (50%). Although the yield was slightly better using chloranil, the ease of purification of product using Pd/C made this the reagent of choice. Likewise, adduct **25** could be converted to the methylpyridine **34** via **32** by an identical sequence of reactions. Oxidation of pyridines **33** and **34** with *m*-chloroperbenzoic acid in methylene chloride (100% in both cases) gave pyridine *N*-oxides **35** and **36,** respectively. On heating with acetic anhydride, **35** smoothly rearranged to give the acetoxy compound **37** (86% yield) along with a small amount (9%) of vinylpyridine **39.**[17] Similarly, *N*-oxide **36** could be transformed to acetate **38** in 83% yield. Hydrolysis of esters **37** and **38** with potassium carbonate in anhydrous methanol gave alcohols **40** and **41,** respectively.



37, R = CH_3
38, R = H



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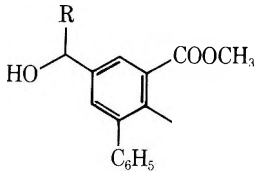
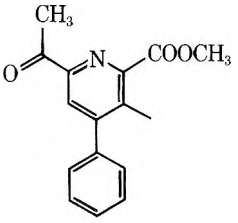


40, R = CH_3
41, R = H

Oxidation of alcohol **40** with activated manganese dioxide gave the acetylpyridine **42** in 81% yield.



42

Thus, we can readily construct a pyridine similar to **3** but still lacking a 3-amino substituent. In the following paper we describe studies dealing with introduction of this final C-ring substituent.[9]

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were measured on either a Perkin-Elmer 137 or 197 spectrometer. NMR spectra were taken at 60 MHz on Varian A-60A or Perkin-Elmer R-12 spectrometers. The 100-MHz spectra were recorded on a Varian XL-100 instrument. All spectra were taken in deuteriochloroform. The 270-MHz NMR spectra were obtained on a Bruker 270 HX instrument at Yale University on a facility supported by NIH Grant 1-PO7-PROO798. High-resolution mass spectra were obtained on a CEC 21-110B spectrometer at MIT under NIH Grant PR 00317. Elemental analyses were done by Microtech Laboratories, Skokie, Ill. E. M. Merck silica gel 60 (0.05–0.20 mm) was used for column chromatography and silica gel PF_{254} was used for both analytical and preparative TLC.

3-Phenyl-2,4-heptadiene (13). To a suspension of 25.4 g (66 mmol) of *n*-propyltriphenylphosphonium bromide in 500 mL of anhydrous ether was slowly added 33 mL (60 mmol) of 1.82 M *n*-butyllithium in hexane in 20 mL of anhydrous ether at room temperature under nitrogen. To this mixture, cooled in an ice bath, was added 8.7 g (60 mmol) of aldehyde **12**, and the mixture was stirred overnight at room temperature. The reaction mixture was filtered and the filter cake was washed well with ether. The filtrate was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was distilled in vacuo to give 4.2 g (40%) of a mixture of dienes **13:** NMR δ 1.0 (3 H, t, J = 7 Hz), 1.5–2.3 (5 H, m), 5.0–6.4 (3 H, m), 7.3 (5 H, m).

3-Phenyl-2,4-hexadiene (14). To a suspension of 50 g (135 mmol) of ethyltriphenylphosphonium bromide in 800 mL of anhydrous THF was added dropwise 60 mL (130 mmol) of 2.17 M *n*-butyllithium in hexane at room temperature under nitrogen with stirring during 1.5 h and the mixture was stirred for an additional 1 h until a negative Gilman test was observed. To this deep orange-red solution, cooled in an ice bath, was added a solution of 18 g (123 mmol) of aldehyde **12** in 20 mL of anhydrous THF and the resulting mixture was stirred for 18 h at room temperature. The mixture was filtered and the filter cake was washed well with ether. The organic filtrate was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was vacuum distilled to give 15.3 g (78%) of a mixture of dienes **14:** NMR δ 1.5 (6 H, m), 4.8–6.4 (3 H, m), 7.3 (5 H, m).

3-Phenyl-1,3-pentadiene (15). To a suspension of 12.86 g (36 mmol) of methyltriphenylphosphonium bromide in 300 mL of anhydrous ether was added 16.7 mL of 1.8 M *n*-butyllithium (30 mmol) in 10 mL of anhydrous ether at room temperature. To this solution was added dropwise 4.39 g (30 mmol) of 2-phenylcrotonaldehyde (**12**) in 20 mL of anhydrous ether, and the mixture was stirred for 2 h at room temperature. The mixture was filtered, and the organic filtrate was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was vacuum distilled to give 2.2 g (53%) of diene **15:** bp 40 °C (3 Torr); [lit.[18] bp 72–73 °C (12 Torr)]; NMR δ 1.6 (3 H, d, J = 7 Hz), 4.9 (2 H, m), 5.8 (1 H, q, J = 7 Hz), 6.7 (1 H, m), 7.3 (5 H, m).

Methyl 4-Phenyl-2,4-hexadienoate (16). A flame-dried 3-L three-necked round-bottom flask equipped with a mechanical stirrer, dropping funnel, and gas inlet tube was charged with 11 g (229 mmol) of a 50% dispersion of sodium hydride in mineral oil and 1 L of dry benzene under a nitrogen atmosphere. To this stirred mixture was added dropwise 45 g (247 mmol) of trimethyl phosphonoacetate. During the addition period the temperature was maintained at 30–35 °C. After the addition was complete, the mixture was stirred for 1 h at room temperature. To this mixture was added dropwise 30 g (205 mmol) of aldehyde **12** while maintaining the temperature at 20–25 °C. The resulting mixture was stirred overnight and diluted with benzene. The organic phase was washed with water and saturated brine, dried over anhydrous $MgSO_4$, and clarified. Evaporation of the solvent and vacuum distillation gave 32 g (77%) of ester **16:** bp 100–104 °C (0.35 Torr); IR (neat) 1720 cm^{-1}; NMR δ 1.2 (3 H, d, J = 7 Hz), 3.7 (3 H, s), 5.45 (1 H, d, J = 17 Hz), 6.3 (1 H, q, J = 7 Hz), 7.3 (5 H, m), 7.6 (1 H, d, J = 17 Hz).

1-Hydroxy-4-phenyl-2,4-hexadiene (17). To a suspension of 6 g (158 mmol) of lithium aluminum hydride in 500 mL of anhydrous ether was added 32 g (158 mmol) of ester **16** at ice-bath temperature under nitrogen. The mixture was warmed to room temperature, stirred for 4 h, and hydrolyzed by successive addition of 6 mL of water, 6 mL of 15% NaOH, and 18 mL of water. The mixture was filtered, and the collected solid was washed well with ether. The combined solution was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. Distillation under reduced pressure gave 24 g (87%) of alcohol **17:** bp 104–107 °C (0.9 Torr); NMR δ 1.6 (3 H, d, J = 7 Hz), 4.1 (2 H, d, J = 6 Hz), 5.3 (1 H, t of d, J = 17, 6 Hz), 5.7 (1 H, q, J = 7 Hz), 6.0 (1 H, d, J = 17 Hz), 7.3 (5 H, m).

1-Acetoxy-4-phenyl-2,4-hexadiene (18). To a solution of 4.05 g (23.2 mmol) of alcohol **17** in 15 mL of pyridine was added dropwise 3 mL of acetic anhydride at ice-bath temperature. The solution was warmed to room temperature, allowed to stand for 20 h, and evaporated to dryness in vacuo. Vacuum distillation gave 4.24 g (84%) of acetate **18:** IR (neat) 1725 cm^{-1}; NMR δ 1.6 (3 H, d, J = 7 Hz), 2.0 (3 H, s), 4.5 (2 H, d, J = 6 Hz), 5.1 (1 H, t of d, J = 6, 16 Hz), 5.8 (1 H, q, J = 7 Hz), 6.5 (1 H, d, J = 16 Hz), 7.3 (5 H, m).

***N*-(*p*-Chlorophenyl)-6α-ethyl-3β,6β-dihydro-3α-methyl-4-phenyl-1,2β(2*H*)-pyridinedicarboximide (27) and *N*-(*p*-Chlorophenyl)-3α-ethyl-3β,6β-dihydro-6α-methyl-5-phenyl-1,2β(2*H*)-pyridinedicarboximide (28).** A solution of 1.0 g (5.8 mmol) of dienes **13** and 1.4 g (5.8 mmol) of 3-(*p*-chlorophenyl)-5-methoxyhydantoin (**5**) in 3 mL of *p*-xylene was refluxed for 3 days. The mixture was evaporated to dryness and the residue was chromatographed on silica gel (100 g) in hexane–ethyl acetate (9:1), affording 828 mg (37%) of adduct **27** and 200 mg (9%) of adduct **28.** The initial ratio of **27** to **28** (75:25) was determined by integration of the vinyl protons in the NMR spectrum of the crude mixture. **27:** IR (film) 1740 and 1780 cm^{-1}; NMR δ 1.1 (6 H, m), 2.5 (2 H, br m), 3.4 (1 H, br m), 4.35 (1 H, d, J = 4 Hz), 4.5 (1 H, br m), 5.9 (1 H, d, J = 3 Hz), 7.5 (9 H, m). For **28** an analytical sample obtained by recrystallization from $CHCl_3$–hexane had mp 162–163 °C; IR (film) 1740 and 1780 cm^{-1}; NMR δ 1.0–1.8 (5 H, m), 1.55 (3 H, d, J = 7 Hz), 2.9 (1 H, br m), 4.23 (1 H, d, J = 3 Hz), 4.7 (1 H, q, J = 7 Hz), 6.18 (1 H, d, J = 7 Hz), 7.5 (9 H, m). Anal. Calcd for $C_{22}H_{21}N_2O_2Cl$: C, 69.38; H, 5.56; N, 7.24. Found: C, 69.32; H, 5.57; N, 7.24.

***N*-(*p*-Chlorophenyl)-3β,6β-dihydro-3α,6α-dimethyl-4-phenyl-1,2β(2*H*)-pyridinedicarboximide (25) and *N*-(*p*-Chlorophenyl)-3β,6β-dihydro-3α,6α-dimethyl-5-phenyl-1,2β(2*H*)-pyridinedicarboximide (26).** A solution of 15.3 g (97 mmol) of a mixture of dienes **14** and 25 g (104 mmol) of 3-(*p*-chlorophenyl)-5-methoxyhydantoin (**5**) in 35 mL of *p*-xylene was refluxed for 3 days. The mixture was chromatographed on a column of silica gel in hexane–ethyl acetate (9:1), affording 9.1 g (26%) of pure adduct **25** and 4 g (11%) of pure adduct **26.** The ratio of **25** to **26** (67:33) was determined by careful preparative TLC of a small reaction aliquot. For **25** a sample recrystallized from ether–hexane had mp 129–131 °C; IR (film) 1720 and 1780 cm^{-1}; NMR δ 1.1 (3 H, d, J = 7 Hz), 1.75 (3 H,

d, J = 7 Hz), 2.35 (1 H, m), 4.3 (1 H, d, J = 7 Hz), 4.9 (1 H, m), 5.9 (1 H, d, J = 3 Hz), 7.4 (9 H, m). Anal. Calcd for $C_{21}H_{19}N_2O_2Cl$: *m/e* 366.11351. Found: *m/e* 366.11589. For **26** a sample recrystallized from ethyl acetate–hexane had mp 156–158 °C; IR (film) 1720 and 1780 cm^{-1}; NMR δ 1.1 (3 H, d, J = 7 Hz), 1.6 (3 H, d, J = 7 Hz), 3.0 (1 H, m), 4.25 (1 H, d, J = 4 Hz), 4.8 (1 H, q, J = 7 Hz), 6.25 (1 H, d, J = 7 Hz), 7.4 (9 H, m). Anal. Calcd for $C_{21}H_{19}N_2O_2Cl$: C= 68.76: H, 5.26. Found: C, 68.97; H, 5.37.

***N*-(*p*-Chlorophenyl)-3,6β-dihydro-6α-methyl-5-phenyl-1,2β(2*H*)-pyridinedicarboximide (22) and *N*-(*p*-Chlorophenyl)-3βb,6-dihydro-3α-methyl-4-phenyl-1,2β(2*H*)-pyridinedicarboximde (21).** A solution of 428 mg (3.0 mmol) of diene **15** and 510 mg (2.0 mmol) of 3-(*p*-chlorophenyl)-5-methoxyhydantoin (**5**) in 3 mL of *p*-xylene was refluxed for 3 days. The mixture was chromatographed on neutral alumina in benzene to give a solid, which was recrystallized from CH_2Cl_2–hexane to afford 200 mg (22%) of adduct **22** and 20 mg (2%) of adduct **21**. For **22** an analytical sample was obtained by recrystallization from methylene chloride–hexane: mp 199–201 °C; IR (film) 1720 and 1780 cm^{-1}; NMR δ 1.2 (3 H, d, J = 7 Hz), 2.7 (2 H, m), 4.2 (1 H, m), 5.2 (1 H, m), 6.0 (1 H, m), 7.5 (9 H, m). Anal. Calcd for $C_{20}H_{17}N_2O_2Cl$: *m/e* 352.0977. Found: *m/e* 352.0972. For **21** a sample recrystallized from ethyl acetate–hexane had mp 150–153 °C; IR (film) 1720 and 1775 cm^{-1}; NMR δ 1.0 (3 H, d, J = 7 Hz), 3.4 (1 H, m), 3.8–5.0 (3 H, m), 6.0 (1 H, t, J = 3 Hz), 7.4 (9 H, m).

6α-Acetoxymethyl-*N*-(*p*-chlorophenyl)-3β,6β-dihydro-3α-methyl-4-phenyl-1,2β(2*H*)-pyridinedicarboximide (23) and 3α-Acetoxymethyl-*N*-(*p*-chlorophenyl)-3β,6β-dihydro-6α-methyl-5-phenyl-1,2β(2*H*)-pyridinedicarboximide (24). A solution of 3.04 g (14.0 mmol) of diene **18** and 4.0 g (16.6 mmol) of 3-(*p*-chlorophenyl)-5-methoxyhydantoin (**5**) in 10 mL of *p*-xylene was refluxed for 3 days. The mixture was chromatographed on a column of silica gel in hexane–ethyl acetate (8:2) to give 2 g (34%) of pure adduct **23** and 1.3 g (22%) of pure adduct **24**. The initial ratio of **23** to **24** (55:45) was determined by the integration of the vinyl protons in the NMR spectrum of the crude reaction mixture. For **23**, an analytical sample obtained by recrystallization from ether–hexane had mp 134–135 °C; IR 1720, 1740, and 1775 cm^{-1}; NMR δ 1.1 (3 H, d, J = 7 Hz), 2.0 (3 H, s), 3.45 (1 H, m), 4.35 (1 H, d, J = 4 Hz), 4.6 (1 H, m), 5.0 (2 H, m), 5.85 (1 H, d, J = 3 Hz), 7.4 (9 H, m). Anal. Calcd for $C_{23}H_{21}N_2O_4Cl{\cdot}CH_3COOH$: *m/e* 364.09786. Found: *m/e* 364.09844. **24** gave NMR δ 1.6 (3 H, d, J = 7 Hz), 2.0 (3 H, s), 3.4 (1 H, m), 4.2 (3 H, m), 4.8 (1 H, q, J = 7 Hz), 6.1 (1 H, d, J = 7 Hz), 7.4 (9 H, m).

3α-Carbomethoxy-*N*-(*p*-chlorophenyl)-3β,6β-dihydro-6α-methyl-5-phenyl-1,2β(2*H*)-pyridinedicarboximide (20). A mixture of 168 mg (0.83 mmol) of diene **16** and 260 mg (1.0 mmol) of 3-(*p*-chlorophenyl)-5-methoxyhydantoin (**5**) in 3 mL of *p*-xylene was refluxed for 3 days. The mixture was evaporated to dryness, and the residue was purified by preparative TLC using hexane–ethyl acetate (8:2) to give 50 mg (13%) of a 1:1 mixture of adducts epimeric at C-3. Adduct **20** was initially formed exclusively but was partially epimerized on preparative TLC purification. The NMR of the mixture showed the C-3 proton in **20** at δ 4.3 (1 H, d, J = 4 Hz) and in the C-3 epimer at δ 4.9 (1 H, d, J = 11 Hz).

Methyl 6-Ethyl-1,2,3,6-tetrahydro-3-methyl-4-phenylpyridinecarboxylate (31). A mixture of 2.0 g (5.25 mmol) of Diels–Alder adduct **27** and 5.0 g of $Ba(OH)_2{\cdot}8H_2O$ in 50 mL of a 1:1 mixture of *p*-dioxane and water was refluxed under nitrogen for 17 h. A stream of CO_2 was passed through the mixture until no further precipitate was formed. The mixture was filtered and the filter cake was washed well with water. The aqueous filtrate was extracted with ether to remove neutral material and evaporated to dryness. A mixture of the residue and methanolic HCl (prepared from 200 mL of methanol and 20 mL of acetyl chloride) was refluxed for 22 h. The mixture was evaporated to dryness, taken up in water basified with 5% NaOH, and extracted with CH_2Cl_2. The organic fraction was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to give 916 mg (67%) of crude amine **31** as an oil which was used for the next step without further purification: IR (film) 1735 and 3330 cm^{-1}; NMR δ 3.8 (3H, s), 5.9 (1 H, d, J = 3 Hz).

Methyl 6-Ethyl-3-methyl-4-phenyl-2-pyridinecarboxylate (33). A. A mixture of 526 mg (3.18 mmol) of amine **31** and 150 mg of 5% Pd/C in 30 mL of toluene was gently refluxed for 22 h. The reaction mixture was filtered and evaporated to dryness. The residue was chromatographed on silica gel (30 g) in CH_2Cl_2–hexane–ethyl acetate (2:8:1), affording 255 mg (50%) of ethyl pyridine **33** as an oil: IR (film) 1600 and 1730 cm^{-1}; NMR δ 1.3 (3 H, t, J = 7 Hz), 2.3 (3 H, s), 2.87 (2 H, q, J = 7 Hz), 4.0 (3 H, s), 7.25 (1 H, s), 7.4 (5 H, m). Anal. Calcd for $C_{16}H_{17}NO_2$: *m/e* 255.12592. Found: *m/e* 255.12408.

B. A solution of 55 mg (0.21 mmol) of amine **31** and 210 mg (0.85 mmol) of chloranil in 10 mL of dry benzene was stirred at room temperature for 20 h, and the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 1% sodium dithionite–1% NaOH solution, saturated $NaHCO_3$, and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC in CH_2Cl_2–ethyl acetate (85:15) to give 32 mg (59%) of ethylpyridine **33** identical with that prepared in part A.

Methyl 6-Ethyl-3-methyl-4-phenyl-2-pyridinecarboxylate 1-Oxide (35). A solution of 400 mg (1.57 mmol) of pyridine **33** and 400 mg (1.85 mmol) of 85% *m*-chloroperbenzoic acid in 30 mL of CH_2Cl_2 was stirred at room temperature for 24 h. The solution was evaporated to dryness and the residue was taken up in ethyl acetate. The solution was washed with 5% $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to give 440 mg (100%) of **35** which was homogeneous by TLC and NMR. An analytical sample was obtained by preparative TLC (hexane–ethyl acetate–methanol, 8:1:1): IR (film) 1740 cm^{-1}; NMR δ 1.3 (3 H, t, J = 7 Hz), 2.15 (3 H, s), 2.96 (2 H, q, J = 7 Hz), 4.03 (3 H, s), 7.15 (1 H, s), 7.4 (5 H, m). Anal. Calcd for $C_{16}H_{17}NO_3$: *m/e* 271.1208. Found: *m/e* 271.1204.

Methyl 6-(1-Acetoxyethyl)-3-methyl-4-phenyl-2-pyridinecarboxylate (37) and Methyl 3-Methyl-4-phenyl-6-vinyl-2-pyridinecarboxylate (39). A solution of 440 mg (1.62 mmol) of pyridine *N*-oxide **35** was heated in 5 mL of freshly distilled acetic anhydride at 120 °C. The solution was evaporated to dryness in vacuo and the residue was purified by preparative TLC, affording 35 mg (9%) of vinlypyridine **39** and 420 mg (86%) of acetate **37** as oils. **37:** IR (film) 1740 cm^{-1}; NMR δ 1.63 (3 H, d, J = 7 Hz), 2.14 (3 H, s), 2.38 (3 H, s), 4.03 (3 H, s), 6.05 (1 H, q, J = 7 Hz), 7.4 (6 H, m). **39:** IR (film) 1735 cm^{-1}; NMR δ 2.4 (3 H, s), 5.5, 6.2, 7.0 (1 H each, AMX), 7.5 (6 H, m).

Methyl 6-(1-Hydroxyethyl)-3-methyl-4-phenyl-2-pyridinecarboxylate (40). To a solution of 380 mg (1.21 mmol) of acetate **37** in 30 mL of anhydrous methanol cooled in an ice bath was added 35 mg of anhydrous K_2CO_3. The resulting mixture was warmed to room temperature and stirred for 2 h. The solution was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to give 340 mg (100%) of alcohol **40** (mp 62–63 °C) as an oil which was found to be almost homogeneous by TLC. An analytical sample crystallized from ether–hexane had mp 62–63 °C: IR (film) 1730 cm^{-1}; NMR δ 1.5 (3 H, d, J = 7 Hz), 2.37 (3 H, s), 4.02 (3 H, s), 5.0 (1 H, q, J = 7 Hz), 7.4 (6 H, m). Anal. Calcd for $C_{16}H_{17}NO_2$: *m/e* 271.1208. Found: *m/e* 271.1192.

Methyl 1,2,3,6-Tetrahydro-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate (32). A mixture of 1.76 g (4.8 mmol) of adduct **25** and 5 g of $Ba(OH)_2{\cdot}8H_2O$ in 50 mL of a 1:1 mixture of *p*-dioxane and water was refluxed under nitrogen for 17 h. A stream of CO_2 was passed through the mixture until no further precipitate was formed. The mixture was filtered and the filter cake was washed well with water. The filtrate was extracted with ether to remove neutral material and evaporated to dryness. A mixture of the residue and methanolic HCl (prepared from 200 mL of methanol and 20 mL of acetyl chloride) was refluxed for 45 h. The mixture was evaporated to dryness, taken up in water, basified with 5% NaOH, and extracted with CH_2Cl_2. The organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to give 900 mg (77%) of crude amine **32** as an oil which was used in the next step without purification: NMR δ 3.8 (3 H, s), 5.8 (1 H, d, J = 3 Hz).

Methyl 3,6-Dimethyl-4-phenyl-2-pyridinecarboxylate (34). A mixture of 4.29 g (17.5 mmol) of **32** and 400 mg of 5% Pd/C in 150 mL of toluene was refluxed for 24 h. The reaction mixture was filtered and evaporated to dryness. The residue was chromatographed on silica gel in hexane–ethyl acetate (9:1) to give 2.1 g (50%) of pyridine **34** as an oil: NMR δ 2.35 (3 H, s), 2.6 (3 H, s), 4.0 (3 H, s), 7.2 (1 H, s), 7.4 (5 H, m).

Methyl 3,6-Dimethyl-4-phenyl-2-pyridinecarboxylate 1-Oxide (36). A solution of 340 mg (1.4 mmol) of pyridine **34** and 400 mg (1.97 mmol) of 85% *m*-chloroperbenzoic acid in 30 mL of CH_2Cl_2 was stirred at room temperature for 16 h. The solution was evaporated to dryness and the residue was taken up in ethyl acetate. The organic layer was washed with 10% $NaHSO_3$, 2% NaOH, and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to give 362 mg (100%) of *N*-oxide **36**, which was homogeneous by TLC and NMR: mp 107–108 °C; NMR δ 2.2 (3 H, s), 2.55 (3 H, s), 4.1 (3 H, s), 7.2 (1 H, s), 7.45 (5 H, m). Anal. Calcd for $C_{15}H_{15}NO_2$: *m/e* 257.1050. Found: *m/e* 257.1052.

Methyl 6-Acetoxymethyl-3-methyl-4-phenyl-2-pyridinecarboxylate (38). A solution of 1.55 g (5.83 mmol) of *N*-oxide **36** in 30 mL of acetic anhydride was heated at 120 °C for 2 h. The solution was evaporated to dryness in vacuo, and the residue was chromatographed on silica gel (30 g) in hexane–ethyl acetate (8:2) to afford 1.5

g (83%) of acetate **38** as a white solid: mp 85–87 °C; IR (film) 1740 cm^{-1}; NMR δ 2.1 (3 H, s), 2.35 (3 H, s), 4.0 (3 H, s), 5.3 (2 H, s), 7.4 (6 H, m).

Methyl 6-Hydroxymethyl-3-methyl-4-phenyl-2-pyridinecarboxylate (41). To a solution of 1.5 g (5 mmol) of acetate **38** in 50 mL of absolute methanol cooled in an ice bath was added 100 mg of anhydrous K_2CO_3. The resulting mixture was warmed to room temperature and stirred for 2 h. The mixture was evaporated to dryness and taken up in ethyl acetate. The organic phase was washed with saturated brine, dried over anhydous $MgSO_4$, and evaporated to give 1.3 g (100%) of alcohol **41** which was homogeneous by TLC: IR (film) 1730 and 3400 cm^{-1}; NMR δ 2.35 (3 H, s), 4.0 (3 H, s), 4.8 (2 H, s), 7.4 (6 H, m).

Methyl 6-Acetyl-3-methyl-4-phenyl-2-pyridinecarboxylate (42). A mixture of 30 mg (0.11 mmol) of alcohol **40** and 60 mg of activated MnO_2 in 25 mL of $CHCl_3$ was stirred at room temperature for 3 days. The mixture was filtered with the aid of Celite and evaporated to dryness. The residue was chromatographed on a small column of silica gel (5 g) in $CHCl_3$, affording 16 mg (81% based on reacted starting material) of **42** and 10 mg of recovered **40**. An analytical sample obtained by recrystallization from ether–hexane had mp 111 °C: IR (film) 1695 and 1735 cm^{-1}; NMR δ 2.43 (3 H, s), 2.76 (3 H, s), 4.04 (3 H, s), 7.4 (5 H, m), 8.03 (1 H, s). Anal. Calcd for $C_{16}H_{15}NO_2$: *m/e* 269.105. Found: *m/e* 269.105.

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References and Notes

(1) Fellow of the A. P. Sloan Foundation, 1975–1979; recipient of a Career Development Award from the National Institutes of Health (HL-00176).
(2) K. V. Rao, K. Biemann, and R. B. Woodward, *J. Am. Chem. Soc.*, **85,** 2532 (1963); Y.-Y. Chiu and W. N. Lipscomb, *ibid.*, **97,** 2525 (1975); J. W. Lown and A. Begleiter, *Can. J. Chem.*, **52,** 2331 (1974).
(3) T. Kametani, S. Tanaka, and A. Kozuka, *Yakugaku Zasshi*, **91,** 1068 (1971), and references cited therein.
(4) K. V. Rao, *J. Heterocycl. Chem.*, **12,** 725 (1975); K. V. Rao and P. Venkateswarlu, *ibid.* **12,** 731 (1975).
(5) T. K. Liao, W. H. Nyberg, and C. C. Cheng, *J. Heterocycl. Chem.*, **13,** 1063 (1976); T. K. Liao, P. J. Wittek, and C. C. Cheng, *ibid.*, **13,** 1283 (1976).
(6) J. W. Lown and S.-K. Sim, *Can. J. Chem.*, **54,** 2563 (1976).
(7) S. Hibino and S. M. Weinreb, *J. Org. Chem.*, **42,** 232 (1977).
(8) R. Cone, S. K. Hasan, J. W. Lown, and A. R. Morgan, *Can. J. Biochem.*, **54,** 219 (1976); J. W. Lown and S. Sim, *ibid.*, **54,** 446 (1976).
(9) D. Kim and S. M. Weinreb, *J. Org. Chem.*, following paper in this issue.
(10) (a) D. Ben-Ishai and E. Goldstein, *Tetrahedron*, **27,** 3119 (1971); (b) G. Krow, R. Rodebaugh, R. Carmosin, W. Figures, H. Pannella, C. DeVicaris, and M. Grippi, *J. Am. Chem. Soc.*, **95,** 5273 (1973).
(11) D. Ben-Ishai, G. Ben-Et, and A. Warshawsky, *J. Heterocycl. Chem.*, **7,** 1289 (1970).
(12) R. Kuhn and J. Michel, *Chem. Ber.*, **67,** 696 (1938).
(13) The dienes studied were unstable to attempted Lewis acid catalysis of the Diels–Alder reactions.
(14) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5,** 70 (1959).
(15) T. A. Titov, *Russ. Chem. Rev.*, **31,** 267 (1962).
(16) R. Sustmann, *Tetrahedron Lett.*, 2721 (1971).
(17) V. J. Traynelis in "Mechanisms of Molecular Migrations", Vol. 2, B. S. Thyagarajan, Ed., Interscience, New York, N.Y. 1969, p 1.
(18) K. Alder, J. Hayden, K. Heimbach, K. Neufang, G. Hansen, and W. Gerhard, *Justus Liebigs Ann. Chem.*, **586,** 110 (1954).

Elaboration of the Pyridine C-Ring Functionality in a Streptonigrin Precursor

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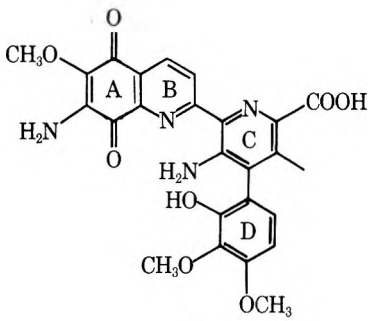
Model studies directed toward total synthesis of streptonigrin (**1**) are outlined. A number of attempts to introduce a 3-amino substituent into compounds **6** and **18**, prepared previously by Diels–Alder reactions, are described. A successful method for introduction of this substituent into a preformed pyridine via introduction of a functionalized carbon followed by Curtius rearrangement has been developed. Compound **52** has been prepared which contains all of the features present in the pyridine C ring of streptonigrin synthon **3**.

The antitumor agent and antibiotic streptonigrin (**1**)[2] has been the object of numerous synthetic studies in several laboratories.[3–8] Our projected synthetic strategy is based upon coupling of *o*-aminobenzaldehyde **2** with the highly substituted acetylpyridine **3** via a Friedlander condensation to give the tetracyclic quinoline **4**. Elaboration of the A-ring functionality will provide streptonigrin.[3]



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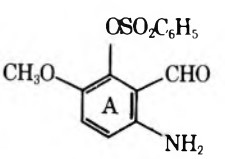

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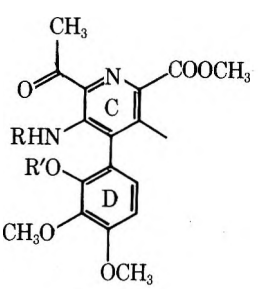

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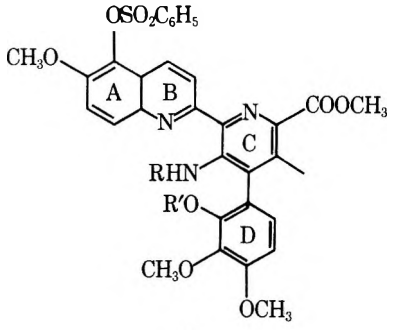

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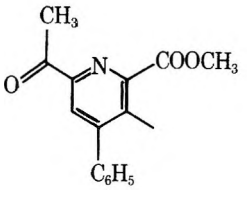
In the preceding paper were described studies directed toward synthesis of an analogue of acetylpyridine **3**. We reported preparation of pyridine **5** from compound **6**, a product



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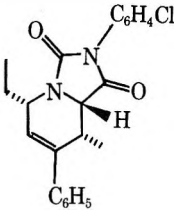
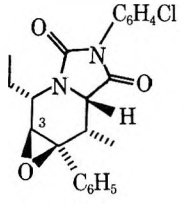


6

of a hetero-Diels–Alder reaction. Compound **5** contains four of the five substituents present in the desired pyridine **3** but lacks a 3-amino substituent. This paper describes the introduction of such functionality.

Our initial approach to the elaboration of this final C-ring functional group was directed toward introduction of a 3-nitrogen substituent at an early stage into a nonaromatic precursor such as **6**, followed by aromatization as described previously for preparation of pyridine **5**.[8] Thus, compound **6**[8] was treated with *m*-chloroperbenzoic acid in methylene chloride to give exclusively the β-epoxide **7** in 91% yield. An attempt was made to rearrange epoxide **7** to the C-3 ketone **8**, but on brief treatment with BF_3 etherate, epoxide **7** underwent ring contraction to afford only aldehyde **9**. Compound **9** is a single stereoisomer with an unknown configuration at



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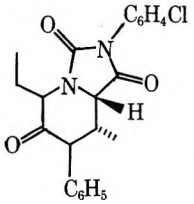

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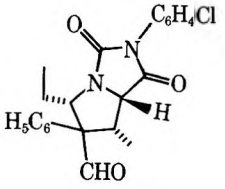
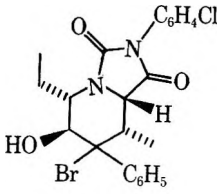


9

the quaternary carbon. Epoxide **7** could be opened cleanly to bromohydrin **10** on treatment with 48% hydrobromic acid in chloroform. However, attempts to oxidize **10** to the corresponding bromo ketone resulted only in recovery of starting material. The fact that this secondary alcohol is inert toward oxidation might be due to steric hindrance of removal of the carbinol proton from the crowded α face of the molecule.[9]

Treatment of epoxide **7** with acetic acid containing a small amount of *p*-toluenesulfonic acid, to our surprise, gave acetate **13** rather than the expected product **11**, as was evident from NMR spectroscopy. Likewise, treatment of **7** with trifluoroacetic acid gave trifluoroacetate **14** rather than **12**. The structure of **13** was also confirmed chemically: hydrolysis of trifluoroacetate **14** to diol **15**, followed by acetylation with acetic anhydride gave acetate **13**, identical with material formed by epoxide opening. Esters **11** and **12** are probably formed initially but rearrange to minimize steric crowding. In all of the above reactions single stereoisomers are formed, but the configuration of the quaternary center is unknown.[10]



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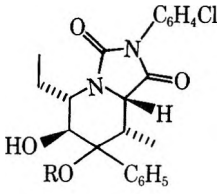
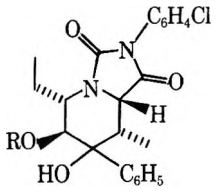


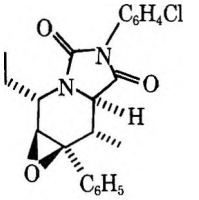
11, R = $COCH_3$
12, R = $COCF_3$



13, R = $COCH_3$
14, R = $COCF_3$
15, R = H
16, R = SO_2CH_3

Diol **15** was transformed to the monomesylate **16** with methanesulfonyl chloride in pyridine (75%) but all attempts to displace the mesyl group with nucleophiles such as azide, cyanide, and ammonia gave no characterizable products. Similarly, attempts were made to open epoxide **7** with the same nucleophiles, but in general only epimerization of the hydantoin occurred to give **17**.[11,12] We attribute our inability to displace a β-substituent at C-3 to steric interference of attack of a nucleophile from the α side of the molecule.

It appeared to us that the best way to overcome this steric problem would be to introduce a C-3 leaving group with an α configuration, thus requiring attack of a nitrogen nucleophile from the less hindered β face. Since all stereochemistry will ultimately be destroyed, the relative configuration of the various functional groups at this stage is presumably of no consequence. Therefore, adduct **18**, prepared as described in the previous paper,[8] was hydrolyzed with aqueous potassium carbonate to give alcohol **19**. Epimerization of the C-6 hydantoin proton also occurred under these conditions to give the thermodynamically favored stereoisomer shown in structure **19**.[11,12] Epoxidation of **19** with *m*-chloroperbenzoic acid gave the α-epoxide **20** as the major product (65%) along with a small amount of the β-epoxide **21** (13%). A syn-directing effect of a homoallylic alcohol on the stereochemistry of epoxidation has considerable precedence.[13] Epoxide configurations were established by the NMR coupling constant between the epoxide proton (H_3) and the adjacent proton (H_2) ($J_{2,3}$ = 4 Hz in **20** and $J_{2,3}$ = 0 Hz in **21** due to a 90° dihedral angle). In order to chemically confirm this stereochemical



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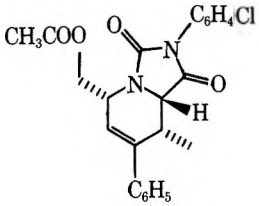

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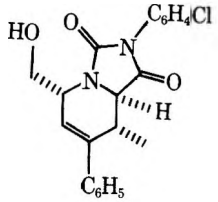

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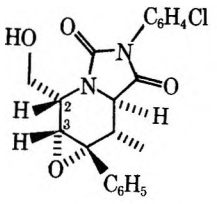

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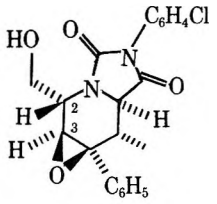

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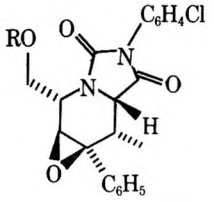
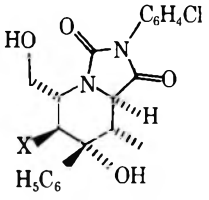
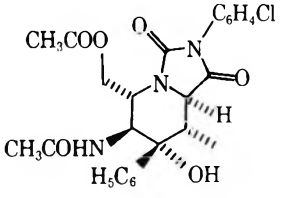


22, R = $COCH_3$
23, R = H

assignment, acetate **18** was epoxidized to give, as anticipated, exclusively the β-epoxide **22** (73%), which on hydrolysis afforded a mixture of alcohols **21** and **23**. Epoxy alcohol **21** prepared in this way was identical with material synthesized by direct epoxidation of alcohol **19**. α-Epoxide **20** could be readily opened with sodium azide using phase-transfer catalysis[14] to produce azido alcohol **24**. Reduction of **24** by catalytic hydrogenation gave amine **25** which on acetylation afforded amide **26**. Although compound **26** now has a nitrogen



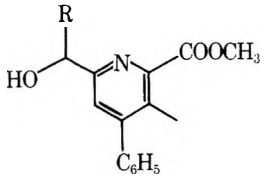
24, X = N_3
25, X = NH_2



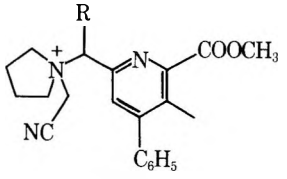
26

substituent in the desired C-3 position, we anticipated that serious problems might arise in the aromatization of this intermediate due to its high degree of functionalization. Rather than pursue this approach further at present, we have instead investigated introduction of a C-3 nitrogen substituent into a system which has already been aromatized to a pyridine. In this alternative approach our strategy was to introduce a functionalized carbon into the C-3 position of a preformed tetrasubstituted pyridine and by a suitable rearrangement (Hoffmann, Curtius, Schmidt, or Beckmann) subsequently put nitrogen into the pyridine nucleus.

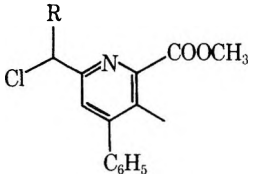
Therefore, alcohol **27**[8] was converted to the chloride **29** with thionyl chloride in pyridine (99% yield) which on warming at



27, R = H
28, R = CH_3

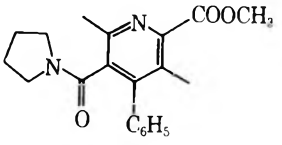


31, R = H
32, R = CH_3



29, R = H
30, R = CH_3

60 °C with *N*-cyanomethylpyrrolidine in Me_2SO gave the quaternary salt **31** (93%).[15] When this salt was treated with potassium *tert*-butoxide in THF–Me_2SO for several hours under nitrogen without rigorous exclusion of oxygen, the only isolable product was amide **33** (30%). We believe **33** is formed by a series of steps involving [2,3] sigmatropic rearrangement[16,17] of the ylide derived from **31** giving aminonitrile **34**, which is deprotonated to anion **36**.[18] Reaction of **36** with molecular oxygen would give peroxide **37**, which on reduction by



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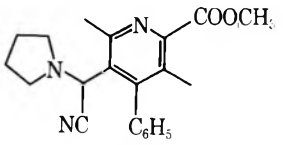

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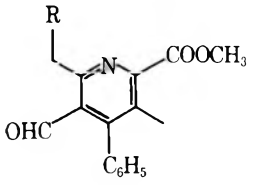
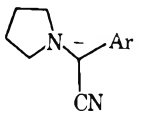


35a, R = H
35b, R = CH_3



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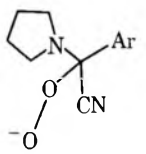

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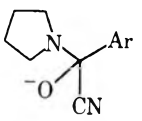
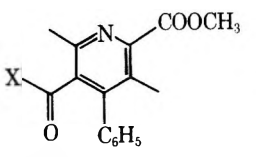


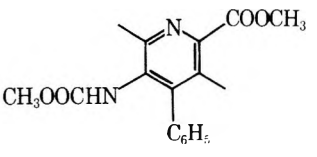
38

dimethyl sulfoxide[19] to **38** and loss of cyanide ion would give the observed amide **33**. After extensive experimentation, it was found that the initial [2,3] sigmatropic rearrangement product **34** could be isolated if salt **31** is treated with potassium *tert*-butoxide at −30 °C for 5 min in THF–HMPA–Me_2SO solvent under deoxygenated[20] argon. Hydrolysis of **34** with aqueous oxalic acid gave the aldehyde **35a** (43% yield from **31**). In a similar series of experiments, alcohol **28**[8] was converted to chloride **30** and a number of unsuccessful attempts were made to prepare the quaternary salt **32** by treatment of **30** with *N*-cyanomethylpyrrolidine. We had hoped that quaternary salt **32** could be transformed to the ethylpyridine aldehyde **35b** with a side chain having the correct number of carbons for eventual conversion to an acetylpyridine. We have thus been forced to concentrate our synthetic efforts on the 2-methyl series of compounds, with the hope of future conversion of methyl to acetyl.

Aldehyde **35a** was oxidized to the carboxylic acid **39** in 92% yield with potassium permanganate in aqueous acetone at room temperature, and this acid was then transformed to the amide **40** via the corresponding acid chloride. Amide **40** cleanly underwent a Hoffmann rearrangement[5b,21,22] on treatment with bromine and sodium methoxide in methanol, producing the urethane **41** in 100% yield. Alternatively, acid **39** could be directly converted to urethane **41** by a modified Curtius rearrangement[23] on treatment with diphenylphosphoryl azide and triethylamine in refluxing benzene, followed by addition of methanol (100% yield).

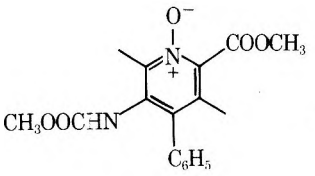


39, X = OH
40, X = NH_2



41

We next turned to the problem of functionalization of the 2-methyl group of **41**. Conversion of **41** into the *N*-oxide **42** was effected with *m*-chloroperbenzoic acid. Upon heating in acetic anhydride, **42** rearranged cleanly to the acetoxymethyl compound **43**.[24] Hydrolysis of **43** with potassium carbonate in methanol did not give the desired alcohol **44**, but instead afforded the cyclic urethane **45** in 100% yield.[25] Since a free 2-



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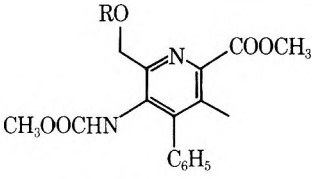
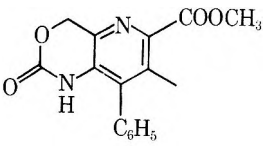


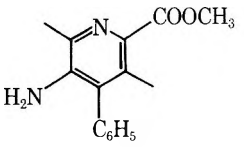
43, R = $COCH_3$
44, R = H



45

hydroxymethyl group was needed for further transformations, and since we envisioned potential future problems due to this sort of cyclization, we decided to protect the 3-amino functionality in a different manner.

Acid **39** was transformed directly to amine **46** by the modified Curtius rearrangement using water rather than methanol.[23] This amine proved to be quite nonbasic and did not react with acetic anhydride in pyridine at room temperature. On heating at 130 °C **46** was slowly converted to the imide **48** and not into the expected amide **47**. The low nucleophilicity of amine **46** may be partly due to steric factors and partly due to delocalization of electrons on nitrogen into the carbomethoxyl group. Thus, the reactivity of **46** might be expected



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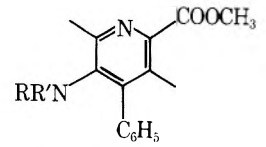
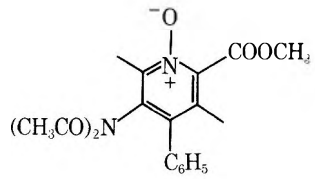


47, R = H; R′ = $COCH_3$
48, R = R′ = $COCH_3$



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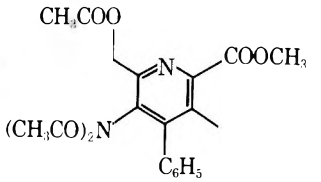

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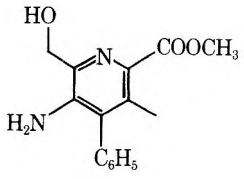

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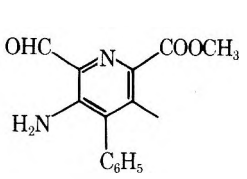

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to be similar to a vinylogous urethane. On treatment with *m*-chloroperbenzoic acid, imide **48** was converted to the corresponding *N*-oxide **49**, which on heating in acetic anhydride[24] was transformed to the acetoxymethylpyridine **50**. Upon being stirred at room temperature in methanol containing anhydrous potassium carbonate, **50** was transformed into the amino alcohol **51**. The ease of removal of both *N*-acetyl groups under such mild conditions is again indicative of the low basicity of the 3-amino nitrogen in these compounds. Amino alcohol **51** was stirred at room temperature with activated manganese dioxide in chloroform[26] to afford the stable, crystalline aminoaldehyde **52**.

We are now using the methodology described in this and the preceding paper[8] for the synthesis of the required synthon **3**. This work will be reported shortly.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were measured on either a Perkin-Elmer 137 or 197 spectrometer. NMR spectra were taken at 60 MHz on Varian A-60A or Perkin-Elmer R-12 spectrometers. 100-MHz spectra were recorded on a Varian XL-100 instrument. All spectra were taken in deuteriochloroform. The 270-MHz NMR spectra were obtained on a Bruker 270 HX instrument at Yale University on a facility supported by NIH Grant 1-P07-PR00798. High-resolution mass spectra were obtained on a CEC 21-110B spectrometer at MIT under NIH grant PR-00317. Elemental analyses were done by Microtech Laboratories, Skokie, Ill. E. M. Merck silica gel 60 (0.05–0.20 mm) was used for column chromatography and silica gel PF_{254} was used for both analytical and preparative TLC.

***N*-(*p*-Chlorophenyl)-2α-ethyl-5α-methyl-6α-phenyl-7-oxa-3-azabicyclo[4.1.0]heptane-3,4-dicarboximide (7).** A solution of 240 mg (0.63 mmol) of olefin **6** and 183 mg (0.90 mmol) of 85% *m*-chloroperbenzoic acid in 10 mL of CH_2Cl_2 was stirred at room temperature for 25 h, and the reaction mixture was diluted with $CHCl_3$. The organic layer was washed with 5% NaOH and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was crystallized from ether–hexane to give 228 mg (91%) of epoxide **7** as white crystals. An analytical sample prepared by recrystallization from ether–hexane had mp 169–170 °C: IR (film) 1720 and 1775 cm^{-1}; NMR δ 1.13 (6 H, m), 2.45 (2 H, m), 3.1 (1 H, m), 3.5 (1 H, s), 4.15 (1 H, t), 4.66 (1 H, d, J = 3 Hz), 7.5 (9 H, s). Anal. Calcd for $C_{22}H_{21}N_2O_3Cl$: C, 66.58; H, 5.33; N, 7.06. Found: C, 66.75; H, 5.42; N, 7.05.

***N*-(*p*-Chlorophenyl)-5α-ethyl-3-formyl-3α-methyl-4-phenyl-1,2-pyrrolidinedicarboximide (9).** To a solution of 150 mg (0.38 mmol) of epoxide **7** in 3 mL of dry benzene was added 1 mL of boron trifluoride etherate at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ after 10 min, and the mixture was diluted with ether. The organic layer was washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated to dryness to give 180 mg of crude solid material. Recrystallization from $CHCl_3$–hexane gave 90 mg (60%) of aldehyde **9** as white crystals. An analytical sample obtained by recrystallization from CH_2Cl_2–hexane had mp 205–207 °C: IR (film) 1720 and 1770 cm^{-1}; NMR δ 1.35 (6 H, m), 1.6–3.0 (3 H, br m), 4.1 (1 H, m), 4.4 (1 H, d, J = 11 Hz), 7.5 (9 H, m), 10.0 (1 H, br s). Anal. Calcd for $C_{22}H_{21}N_2O_3Cl$: C, 66.58; H, 5.33; N, 7.06. Found: C, 66.74; H, 5.35; N, 7.02.

4-Bromo-*N*-(*p*-chlorophenyl)-6α-ethyl-4β-hydroxyl-3α-methyl-4-phenyl-1,2α-piperidinedicarboximide (10). To a solution of 130 mg (0.33 mmol) of epoxide **7** in 2 mL of $CHCl_3$ was added 0.5 mL of 48% HBr at room temperature. The mixture was stirred overnight, washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC developing in $CHCl_3$ to afford 137 mg (88%) of bromohydrin **10** as a white foamy solid: IR (film) 1720, 1770 cm^{-1}; NMR δ 0.4 (3 H, d, J = 7 Hz), 1.3 (3 H, t, J = 7 Hz), 1.8 (1 H, d, J = 11 Hz, exchangeable), 2.4 (2 H, m), 3.0 (2 H, m), 3.7 (1 H, t, J = 11 Hz), 4.4 (1 H, d, J = 4 Hz), 7.0 (9 H, m).

5β-Acetoxy-*N*-(*p*-chlorophenyl)-6α-ethyl-4-hydroxy-3α-methyl-4-phenyl-1,2-piperidinecarboximide (13). A. A solution of 108 mg (0.27 mmol) of epoxide **7** in 5 mL of acetic acid was heated at 60 °C for 6 h in the presence of a catalytic amount of *p*-TosOH, and the reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated brine and evaporated to dryness. The residue was purified by preparative TLC in hexane–ethyl acetate (7:3) to give 60 mg (48%) of acetate **13** as white crystals. An analytical sample obtained by recrystallization from ether had mp 197–200 °C: IR (film) 1715, 1740, and 1780 cm^{-1}; NMR δ 0.7 (3 H, d, J = 7 Hz), 1.2 (3 H, t, J = 7 Hz), 1.3–2.7 (4 H, br m), 1.9 (3 H, s), 3.8 (1 H, m), 4.8 (1 H, d, J = 4 Hz), 5.75 (1 H, d, J = 10 Hz), 7.4 (9 H, s). Anal. Calcd for $C_{24}H_{25}N_2O_5Cl$: *m/e* 456.1450. Found: *m/e* 456.1440.

B. To a solution of 27 mg (0.07 mmol) of diol **15** in 1 mL of dry pyridine was added 0.1 mL of acetic anhydride. The resulting solution was stirred at room temperature for 22 h and evaporated to dryness in vacuo to afford 35 mg (100%) of acetate **14**, which was identical with material prepared in part A.

***N*-(*p*-Chlorophenyl)-6α-ethyl-5β-(trifluoroacetoxy)-4-hydroxy-3α-methyl-4-phenyl-1,2α-piperidinecarboximide (14).** To a solution of 100 mg (0.25 mmol) of epoxide **7** in 1 mL of chloroform was added 0.2 mL of trifluoroacetic acid. The solution was allowed to stand at room temperature for 22 h and diluted with ethyl acetate. The organic phase was washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC in hexane–ethyl acetate (8:2) to give 102 mg (80%) of trifluoroacetate **14:** IR (film) 1725 and 1795 cm^{-1}; NMR δ 0.8 (3 H, d, J = 7 Hz), 1.3 (3 H, t, J = 7 Hz), 1.8–2.9 (4 H, br m), 4.0 (1 H, br m), 4.85 (1 H, d, J = 4 Hz), 5.9 (1 H, d, J = 10 Hz), 7.4 (9 H, s).

***N*-(*p*-Chlorophenyl)-6α-ethyl-4,5β-dihydroxy-3α-methyl-4-phenyl-1,2α-piperidinecarboximide (15).** A solution of 65 mg (0.13 mmol) of trifluoroacetate **14** in 5 mL of methanol was stirred at room temperature for 2 h. The solution was evaporated to dryness to give 59 mg (100%) of diol **15** as white crystals: mp 175–178 °C; IR (film) 1710, 1770, and 3500 cm^{-1}; NMR δ 1.65 (3 H, d, J = 7 Hz), 1.2 (3 H, t, J = 7 Hz), 2.35 (4 H, br m), 3.55 (1 H, br m), 4.3 (1 H, br d, J = 10 Hz), 4.68 (1 H, d, J = 4 Hz), 7.4 (9 H, m). Anal. Calcd for $C_{22}H_{23}N_2O_4Cl$: *m/e* 414.1345. Found: *m/e* 414.1346.

5β-Methanesulfonyloxy-*N*-(*p*-chlorophenyl)-6α-ethyl-4-hydroxy-3α-methyl-4-phenyl-1,2α-piperidinecarboximide (16). A solution of 40 mg (9.096 mmol) of diol **15** and 0.05 mL of methanesulfonyl chloride in 1 mL of dry pyridine was stirred at room temperature for 24 h. The reaction mixture was evaporated to dryness, and the residue was purified by preparative TLC in hexane–ethyl acetate (6:4) to give 35 mg (75%) of mesylate **16:** NMR δ 0.9 (3 H, d, J = 7 Hz), 1.3 (3 H, t, J = 7 Hz), 2.2 (3 H, s), 2.4 (4 H, m), 3.8 (1 H, m), 4.7 (1 H, d, J = 6 Hz), 5.4 (1 H, d, J = 10 Hz), 7.4 (9 H, m).

***N*-(*p*-Chlorophenyl)-2α-ethyl-5α-methyl-6α-phenyl-7-oxa-3-azabicyclo[4.1.0]heptane-3,4β-dicarboximide (17).** A mixture of 200 mg of epoxide **7**, 3 mL of toluene, 200 mg of sodium azide dissolved in a minimum amount of water, and 0.1 mL of Aliquat 336[14] was refluxed at 105 °C. After 4 days the reaction mixture was diluted with $CHCl_3$. The organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC in hexane–ethyl acetate (8:2) to give 72 mg (36%) of epimer **17:** NMR δ 1.1 (5 H, m), 1.8 (2 H, m), 2.7 (1 H, m), 3.35 (1 H, s), 3.75 (1 H, d, J = 9 Hz), 4.6 (1 H, br t), 7.4 (9 H, m).

***N*-(*p*-Chlorophenyl)-3β,6β-dihydro-6α-(hydroxymethyl)-3α-methyl-4-phenyl-1,2α(2*H*)-pyridinedicarboximide (19).** To a solution of 218 mg (0.51 mmol) of acetate **18** in 15 mL of MeOH–THF–$CHCl_3$ (7:7:1) was added 1 mL of 2.5% aqueous K_2CO_3 solution at 0 °C. The resulting solution was warmed to room temperature and stirred for 6 h, and the reaction mixture was diluted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC in hexane–ethyl acetate (6:4) to give 130 mg (66%) of alcohol **19:** NMR δ 1.2 (3 H, d, J = 7 Hz), 2.9 (1 H, m), 3.8 (2 H, m), 4.03 (1 H, d, J = 10 Hz), 4.75 (1 H, m), 5.75 (1 H, d of d, J = 3.5 Hz), 7.3 (9 H, m).

***N*-(*p*-Chlorophenyl)-2α-(hydroxymethyl)-5α-methyl-6β-phenyl-7-oxa-3-azabicyclo[3.1.0]heptane-3,4β-dicarboximide (20) and *N*-(*p*-Chlorophenyl)-2α-(hydroxymethyl)-5α-methyl-6α-7-oxa-3-azabicyclo[4.1.0]heptane-3,4β-dicarboximide (21).** A solution of 181 mg (0.47 mmol) of alcohol **19** and 174 mg (0.69 mmol) of 85% *m*-chloroperbenzoic acid in 10 mL of CH_2Cl_2 was stirred at room temperature for 2 days. The solution was evaporated to dryness and the residue was taken up in ethyl acetate. The organic phase was washed with 5% $NaHSO_3$, saturated $NaHCO_3$, and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC in hexane–ethyl acetate (7:3) giving 120 mg (65%) of α-epoxide **20** and 25 mg (13%) of β-epoxide **21. 20:** mp 192–194 °C; IR (film) 1715, 1770, and 3450 cm^{-1}; NMR δ 1.2 (3 H, d, J = 7 Hz), 2.7 (2 H, m), 3.3 (1 H, d, J = 4 Hz), 3.9 (3 H, m), 4.55 (1 H, m), 7.3 (9 H, m). Anal. Calcd for $C_{21}H_{19}N_2O_4Cl$: *m/e* 398.10333. Found: *m/e* 398.10778. **21:** IR (film) 1715, 1770, and 3450 cm^{-1}; NMR δ 1.0 (3 H, d, J = 7 Hz), 2.3 (2 H, br m), 3.4 (1 H, s), 4.1 (3 H, m), 4.6 (1 H, m), 7.3 (9 H, m).

2α-(Acetoxymethyl)-*N*-(*p*-chlorophenyl)-5α-methyl-6α-phenyl-7-oxa-3-bicyclo[4.1.0]heptane-3,4α-dicarboximide (22). A solution of 40 mg (0.09 mmol) of olefin **18** and 25 mg (0.12 mmol) of *m*-chloroperbenzoic acid in 2 mL of $CHCl_3$ was stirred at room temperature for 20 h. The solution was evaporated to dryness, and the residue was taken up in ethyl acetate. The solution was washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to give 50 mg of crude product. Recrystallization from ether–pentane gave 30 mg (73%) of epoxide **22** as white crystals: mp 163 °C; IR (film) 1720, 1740, and 1775 cm^{-1}; NMR δ 1.0 (3 H, d, J = 7 Hz), 2.1 (3 H, s), 3.1 (1 H, m), 3.6 (1 H, s), 4.2–5.4 (4 H, m), 7.3 (9 H, s). Anal. Calcd for $C_{23}H_{21}N_2O_5Cl$: *m/e* 440.11390. Found: *m/e* 440.11542.

***N*-(*p*-Chlorophenyl)-2α-(hydroxymethyl)-5α-methyl-6α-phenyl-7-oxa-3-azabicyclo[4.1.0]heptane-3,4α-dicarboximide (23) and Epoxide 21.** To a solution of 30 mg (0.07 mmol) of epoxide **22** in 3.5 mL of THF–MeOH–$CHCl_3$ (3:1:1) was added 0.2 mL of 5% aqueous K_2CO_3 at room temperature. The mixture was evaporated to dryness and the residue was purified by preparative TLC (hexane–ethyl acetate, 7:3) to give 15 mg (55%) of alcohol **23** and 13 mg (45%) of alcohol **21,** which was identical with material prepared by epoxidation of **19. 23** gave the following spectral data: IR (film) 1715, 1770, and 3450 cm^{-1}; NMR δ 1.0 (3 H, d, J = 7 Hz), 3.1 (1 H, m), 3.6 (1 H, s), 4.0–5.0 (4 H, m), 7.5 (9 H, m).

5β-Azido-*N*-(*p*-chlorophenyl)-4α-hydroxy-6α-(hydroxymethyl)-3α-methyl-4β-phenyl-1,2β-piperidinedicarboximide (24). A mixture of 66 mg (0.17 mmol) of epoxide **20,** 50 mg of 99% sodium azide, 4 mL of toluene, 1 mL of H_2O, and 7 drops of Aliquat 336[14] was heated at 110 °C for 6 h, and the reaction mixture was diluted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified on a small column of silica gel (5 g) in hexane–ethyl acetate (1:1) to give 55 mg (75%) of azide **24** as white crystals which was used in the next step without further purification: IR (film) 1710, 1780, 2120, and 3400 cm^{-1}; NMR δ 1.2 (3 H, d, J = 6 Hz), 2.5–4.7 (8 H, m), 7.5 (9 H, m).

5β-*N*-(Acetylamino)-*N*-(*p*-chlorophenyl)-4α-hydroxy-6α-(acetoxymethyl)-3α-methyl-4β-phenyl-1,2β-piperidinedicarboximide (26). A mixture of 50 mg (0.11 mmol) of azide **24** and 15 mg of 5% Pd/C in 5 mL of ethyl acetate was hydrogenated at room temperature and atmospheric pressure for 7 h. The mixture was filtered and evaporated to give 20 mg of amine **25.** A solution of this crude product and 0.1 mL of acetic anhydride in 15 mL of pyridine was allowed to stand at room temperature overnight. The solution was evaporated to dryness in vacuo and the residue was purified by preparative TLC in hexane–ethyl acetate (1:1) to give 16 mg (30%) of amide **26** as white crystals: mp 254 °C; IR (Nujol) 1720, 1740, 1770, and 3350 cm^{-1}; NMR δ 1.65 (3 H, s), 1.75 (3 H, s), 2.05 (3 H, s), 2.7 (2 H, m), 4.0–5.2 (5 H, m), 6.0 (1 H, m), 7.4 (9 H, m). Anal. Calcd for $C_{25}H_{26}N_3O_6Cl$: *m/e* 499.1506. Found: *m/e* 499.1501.

Methyl 6-(Chloromethyl)-3-methyl-4-phenyl-2-pyridinecarboxylate (29). To a solution of 600 mg (2.33 mmol) of alcohol **27** in 20 mL of dry benzene was added 320 mg (2.69 mmol) of thionyl chloride at 0 °C. The resulting mixture was slowly warmed to room temperature and stirred for 1 h. The mixture was evaporated to dryness, and the residue was taken up in ether. The solution was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was chromatographed on silica gel (20 g) in hexane–ethyl acetate (9:1) to give 638 mg (99%) of chloride **29:** IR (film) 1735 cm^{-1}; NMR δ 2.35 (3 H, s), 4.0 (3 H, s), 4.7 (3 H, s), 7.4 (6 H, m).

Methyl 6-(1-Chloroethyl)-3-methyl-4-phenyl-2-pyridinecarboxylate (30). To a solution of 25 mg (0.092 mmol) of alcohol **28** in 1 mL of dry benzene was added a solution of 25 mg of thionyl chloride in 1 mL of dry benzene at 0 °C. The solution was warmed to room temperature and stirred for 2 h. The mixture was evaporated to dryness, and the residue was purified on a small column of silica gel (5 g) in $CHCl_3$ to give 20 mg (75%) of chloride **30:** IR (film) 1735 cm^{-1}; NMR δ 1.85 (3 H, d, J = 7 Hz), 2.3 (3 H, s), 4.0 (3 H, s), 5.4 (1 H, q, J = 7 Hz), 7.5 (5 H, s), 7.6 (1 H, s).

Preparation of Quaternary Salt 31. A solution of 250 mg (0.91 mmol) of chloride **29** and 200 mg (1.81 mmol) of *N*-cyanomethylpyrrolidine in 2 mL of dimethyl sulfoxide was heated at 50–60 °C for 1 day and at 40 °C for 2 days.[15] The solution was evaporated to dryness in vacuo, and the residue was crystallized from ethyl acetate–ether to give 327 mg (93%) of salt **31:** IR (Nujol) 1730 cm^{-1}; NMR δ 2.4 (4 H, br s), 2.43 (3 H, s), 4.0 (3 H, s), 4.3 (4 H, br m), 5.35 (2 H, s), 5.85 (2 H, s), 7.4 (5 H, m), 8.0 (1 H, s).

Preparation of Amide 33. A solution of 20 mg (0.07 mmol) of chloride **29** and 40 mg (0.36 mmol) of *N*-cyanomethylpyrrolidine[15] in Me_2SO-d_6 in an NMR tube was allowed to stand at room temperature for 48 h until quaternization was complete. The solution was transferred to a round-bottomed flask, diluted with small amount of dry THF, and cooled to −10 °C. To this solution was added 30 mg of potassium *tert*-butoxide, and the mixture was stirred for 2 h under nitrogen. The mixture was diluted with ether, and the organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC in hexane–ethyl acetate (3:7) to give 7 mg (30%) of amide **33:** IR (film)

1640 and 1735 cm^{-1}; NMR δ 1.65 (4 H, m), 2.2 (3 H, s), 2.55 (3 H, s), 2.9 (2 H, m), 3.2 (2 H, m), 4.0 (3 H, s), 7.3 (5 H, m). Anal. Calcd for $C_{20}H_{22}N_2O_3$: *m/e* 338.1628. Found *m/e* 338.1626.

Methyl 5-Formyl-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate (35a). To a solution of 120 mg (0.31 mmol) of quaternary salt **31** in 15 mL of HMPA–Me_2SO–THF (2:4:9) was added 70 mg of potassium *tert*-butoxide at −15 °C under oxygen-free argon.[20] The solution was stirred for 10 min and quenched with saturated NH_4Cl solution. The mixture was diluted with ethyl acetate, and the organic fraction was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. A mixture of the residue and 20 mg of oxalic acid in 7 mL of THF–H_2O (5/2) was refluxed for 1 h. The mixture was evaporated to dryness, and the residue was purified by chromatography on a column of silica gel (10 g) in ethyl acetate–hexane (2:8) to give 36 mg (43%) of aldehyde **35a** as a white solid: IR (film) 1700 and 1740 cm^{-1}; NMR δ 2.2 (3 H, s), 2.8 (3 H, s), 4.07 (3 H, s), 7.2–7.7 (3 H, m), 9.9 (1 H, s); mass spectrum *m/e* 269 (M^+).

Methyl 5-Carboxyl-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate (39). To a solution of 36 mg (0.134 mmol) of aldehyde **35a** in 6 mL of acetone–H_2O (2:1) was added 30 mg of potassium permanganate at room temperature. The mixture was stirred at room temperature for 1 h, and a small amount of sodium bisulfite was added. The mixture was filtered and the filtrate was washed well with acetone. The acetone was removed by evaporation and the remaining aqueous phase was extracted with $CHCl_3$. The organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness to give 35 mg (92%) of acid **39** as a white, crystalline solid, which was recrystallized from chloroform: mp 245 °C; IR (Nujol) 1720, 1740, and 2600 cm^{-1}; NMR δ 2.2 (3 H, s), 2.62 (3 H, s), 4.0 (3 H, s), 7.2–7.6 (5 H, m).

Methyl 5-Amido-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate (40). A solution of 22 mg (0.077 mmol) of acid **39** in minimum amount of pyridine was diluted with 4 mL of $CHCl_3$. To this solution was added 5 drops of thionyl chloride and the solution was stirred for 3 h at room temperature. A stream of anhydrous ammonia was passed through the solution cooled in an ice bath for 5 min, and the mixture was stirred for 20 min at room temperature. The mixture was partitioned between chloroform and water, and aqueous layer was extracted with $CHCl_3$. The combined $CHCl_3$ extract was washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was purified by preparative TLC in ethyl acetate to give 15 mg (70%) of amide **40:** IR ($CHCl_3$) 1680, 1735, 3400, and 3520 cm^{-1}; NMR δ 2.2 (3 H, s), 2.7 (3 H, s), 4.0 (3 H, s), 5.3–5.8 (2 H, br s), 7.2–7.6 (5 H, m).

Methyl 5-Carbamoyl-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate (41). A. To a solution of 18 mg (0.063 mmol) of amide **40** in 5 mL of absolute methanol was added 70 mg of sodium methoxide followed by 60 mg of bromine in a small amount of absolute methanol in an ice bath. The solution was stirred for 30 min at ice-bath temperature and then refluxed for 20 min. The solution was partitioned between $CHCl_3$ and H_2O, and the aqueous layer was extracted with $CHCl_3$ several times. The combined organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness to give 19 mg (100%) of urethane **41:** IR ($CHCl_3$) 1735 and 3420 cm^{-1}; NMR δ 2.2 (3 H, s), 2.6 (3 H, s), 3.7 (3 H, s), 4.0 (3 H, s), 5.8 (1 H, br s), 7.0–7.7 (5 H, m). Anal. Calcd for $C_{17}H_{18}N_2O_4$: *m/e* 314.1266. Found: *m/e* 314.1272.

B. A solution of 10 mg (0.035 mmol) of acid **39,** 2 drops of triethylamine, and 2 drops of diphenylphosphoryl azide in 3 mL of anhydrous benzene was refluxed for 1 h. To the solution was added 0.5 mL of dry methanol and the solution was refluxed for an additional 30 min. The solution was evaporated to dryness, and the residue was purified by preparative TLC in ethyl acetate–hexane (7:3) to give 10 mg (100%) of urethane **41** identical with material prepared in part A.

Methyl 5-Carbamoyl-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate 1-Oxide (42). A solution of 13 mg (0.04 mmol) of pyridine **41** and 24 mg (0.1 mmol) of 85% *m*-chloroperbenzoic acid in 3 mL of $CHCl_3$ was stirred at room temperature for 18 h. The solution was evaporated to dryness and the residue was taken up in ethyl acetate. The organic phase was washed with saturated $NaHSO_3$, $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and evaporated to give 15 mg (100%) of solid **42** which was homogeneous by TLC and NMR: NMR δ 2.0 (3 H, s), 2.5 (3 H, s), 3.7 (3 H, s), 4.05 (3 H, s), 6.1 (1 H, br s), 7.0–7.6 (5 H, m).

Methyl 6-Acetoxymethyl-5-carbamoyl-3-methyl-4-phenyl-2-pyridinecarboxylate (43). A solution of 15 mg (0.045 mmol) of pyridine *N*-oxide **42** in 2 mL of acetic anhydride was heated at 110 °C for 2 h. The solution was evaporated to dryness in vacuo to give 15 mg (88%) of acetate **43:** IR ($CHCl_3$) 1740 and 3400 cm^{-1}; NMR δ 2.1 (3 H, s), 2.2 (3 H, s), 3.6 (3 H, s), 4.0 (3 H, s), 5.3 (3 H, s), 6.4 (1 H, br s), 7.1–7.7 (5 H, m). Anal. Calcd for $C_{19}H_{20}N_2O_6$: *m/e* 372.133. Found: *m/e* 372.132.

Preparation of Urethane 45. A mixture of 15 mg (0.04 mmol) of acetate **43** and 35 mg of anhydrous K_2CO_3 in 3 mL of absolute methanol was stirred at room temperature for 1 h. The mixture was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated to dryness to give 12 mg (100%) of cyclic urethane **45:** IR ($CHCl_3$) 1735 and 3400 cm^{-1}; NMR δ 2.3 (3 H, s), 4.0 (3 H, s), 6.53 (2 H, s), 6.7 (1 H, br s), 7.3–7.7 (5 H, m). Anal. Calcd for $C_{16}H_{14}N_2O_4$: *m/e* 298.0952. Found: *m/e* 298.096.

Methyl 5-Amino-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate (46). A solution of 50 mg (0.175 mmol) of acid **39,** 0.1 mL of triethylamine, and 0.1 mL of diphenylphosphoryl azide in 5 mL of dry benzene was refluxed for 1 h.[23] To the solution was added 0.5 mL of water and the mixture was refluxed for an additional 30 min. The mixture was evaporated to dryness, and the residue was purified by chromatography on a column of silica gel (5 g) in hexane–ethyl acetate (8:2; 100 mL) followed by ethyl acetate (50 mL) to give 39 mg (87%) of aminopyridine **46:** IR ($CHCl_3$) 1720, 3400, and 3500 cm^{-1}; NMR δ 2.2 (3 H, s), 2.5 (3 H, s), 4.0 (3 H, s), 7.2–7.7 (5 H, m); mass spectrum *m/e* 256 (M^+).

Preparation of Imide 48. A solution of 39 mg (0.152 mmol) of aminopyridine **46** and 1 mL of acetic anhydride in 3 mL of pyridine was refluxed for 8 h (oil bath temperature 130 °C). The solution was evaporated to dryness in vacuo to give 49 mg (95%) of imide **48:** IR (film) 1720 and 1780 cm^{-1}; NMR δ 2.1 (6 H, s), 2.2 (3 H, s), 2.5 (3 H, s), 4.05 (3 H, s), 7.0–7.7 (5 H, m).

Methyl 5-Amino-6-hydroxymethyl-3-methyl-4-phenyl-2-pyridinecarboxylate (51). A solution of 49 mg (0.144 mmol) of imide **48** and 100 mg of 85% *m*-chloroperbenzoic acid in 10 mL of $CHCl_3$ was stirred at room temperature for 34 h. The solution was taken up in ethyl acetate. The organic phase was washed with saturated $NaHSO_3$, $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and evaporated to give *N*-oxide **49.** A solution of the *N*-oxide **49** in 2 mL of acetic anhydride was heated at 110 °C (oil bath temperature) for 2 h. The solution was evaporated to dryness in vacuo to give crude acetate **50.**

A mixture of the crude acetate **50** and 70 mg of anhydrous K_2CO_3 in 5 mL of dry methanol was stirred at room temperature for 7 h. The mixture was evaporated to dryness, and the residue was taken up in ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness to give 37 mg of crude amino alcohol **51.**

49: NMR δ 2.05 (3 H, s), 2.15 (6 H, s), 2.45 (3 H, s), 4.1 (3 H, s), 7.0–7.77 (5 H, m). **50:** NMR δ 2.1 (3 H, s), 2.5 (6 H, s), 2.25 (3 H, s), 4.05 (3 H, s), 5.17 (2 H, s), 7.0–7.7 (5 H, s). **51:** NMR δ 2.2 (3 H, s), 4.0 (3 H, s), 4.83 (2 H, s), 7.0–7.7 (5 H, m).

Methyl 5-Amino-6-formyl-3-methyl-4-phenyl-2-pyridinecarboxylate (52). A mixture of 37 mg of crude amino alcohol **51** and 100 mg of activated manganese dioxide[25] in 5 mL of chloroform was stirred at room temperature for 1 h. The mixture was filtered through a pad of Celite, and the filtrate was evaporated to dryness. The residue was purified by preparative TLC in ethyl acetate–hexane (4:1) to give 16 mg (34% in six steps from **48**) of aminoaldehyde **52:** IR (film) 1680, 1720, 3350, and 3475 cm^{-1}; NMR δ 2.3 (3 H, s), 4.0 (3 H, s), 5.8–6.5 (2 H, br s), 7.2–7.8 (5 H, m), 10.3 (1 H, s). Anal. Calcd for $C_{15}H_{14}N_2O_3$: *m/e* 270.1004. Found: *m/e* 270.1001.

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Registry No.—**6,** 64035-13-8; **7,** 64090-71-7; **9,** 64035-32-1; **10,** 64035-33-2; **13,** 64035-34-3; **14,** 64035-35-4; **15,** 64035-36-5; **16,** 64035-37-6; **17,** 64035-38-7; **18,** 64035-09-2; **19,** 64035-39-8; **20,** 64035-40-1; **21,** 64069-75-6; **22,** 64035-41-2; **23,** 64069-76-7; **24,** 64035-42-3; **25,** 64035-43-4; **26,** 64035-44-5; **27,** 64034-96-4; **28,** 64034-95-3; **29,** 64035-45-6; **30,** 64035-46-7; **31,** 64035-47-8; **33,** 64056-86-6; **35a,** 64035-48-9; **39,** 64035-20-7; **40,** 64035-21-8; **41,** 64035-22-9; **42,** 64035-23-0; **43,** 64035-24-1; **45,** 64035-25-2; **46,** 64035-26-3; **48,** 64035-27-4; **40,** 64035-28-5; **50,** 64035-29-6; **51,** 64035-30-9; **52,** 64035-31-0; trifluoroacetic acid, 76-05-1; methanesulfonyl chloride, 124-63-0; *N*-cyanomethylpyrrolidine, 29134-29-0.

References and Notes

(1) Fellow of the A. P. Sloan Foundation, 1975–1979; recipient of a Career Development Award from the National Institutes of Health (HL-00176).
(2) K. V. Rao, K. Biemann, and R. B. Woodward, *J. Am. Chem. Soc.*, **85,** 2532 (1963); Y.-Y. Chiu and W. N. Lipscomb, *ibid.*, **97,** 2525 (1975); J. W. Lown and A. Begleiter, *Can. J. Chem.*, **52,** 2331 (1974).

(3) S. Hibino and S. M. Weinreb, *J. Org. Chem.*, **42**, 233 (1977).
(4) T. Kametani, S. Tanaka, and A. Kozuka, *Yakugaku Zasshi*, **91**, 1068 (1971), and earlier work cited therein.
(5) (a) T. K. Liao, W. H. Nyberg, and C. C. Chang, *J. Heterocycl. Chem.*, **13**, 1063 (1976); (b) T. K. Liao, P. J. Wittek, and C. C. Cheng, *ibid.*, **13**, 1283 (1976).
(6) K. V. Rao, *J. Heterocycl. Chem.*, **12**, 725 (1975); K. V. Rao and P. Venkateswarlu, *ibid.*, **12**, 731 (1976).
(7) J. W. Lown and S.-K. Sim, *Can. J. Chem.*, **54**, 2563 (1976).
(8) D. Kim and S. M. Weinreb, *J. Org. Chem.*, preceding paper in this issue.
(9) Cf. E. J. Corey and L. S. Melvin, *Tetrahedron Lett.*, 929 (1975).
(10) It has been elegantly demonstrated by ^{18}O tracer studies that in the opening of a secondary–tertiary epoxide in the vitamin D series with acetic acid, acetate attack occurs at the tertiary center with retention of configuration at the secondary center, followed by transacetylation of the *tert*-acetyl group to the secondary alcohol: J. J. Partridge, S.-J. Shiuey, E. G. Baggiolini, B. Hennessy, and M. R. Uskokovic in "Proceedings of the Third Workshop on Vitamin D_3", W. deGruyter, Ed., New York, N.Y., 1977, p 47. Although firm evidence is lacking, it is probable that the facile acetyl migration of **11** to **13** is indicative of a cis relationship of the C-3 and C-4 oxygens.
(11) D. Ben-Ishai and E. Goldstein, *Tetrahedron*, **27**, 3119 (1971).
(12) Hydantoin configuration is easily established by NMR: $J_{H\text{-}5,6}$ (cis) = 4 Hz; $J_{H\text{-}5,6}$ (trans) = 11 Hz (see ref 11).
(13) G. Berti, *Top. Stereochem.*, **7**, 93 (1973).
(14) A. W. Herriot and D. Picker, *J. Am. Chem. Soc.*, **97**, 2345 (1975).
(15) A. Lespagnol, E. Cuingnet, and M. Debaert, *Bull. Soc. Chim. Fr.*, 383 (1960).
(16) L. N. Mander and J. V. Turner, *J. Org. Chem.*, **38**, 2915 (1973).
(17) E. B. Sanders, H. V. Secor, and J. I. Seeman, *J. Org. Chem.*, **41**, 2658 (1976).
(18) E. Leete, M. R. Shedekel, and G. B. Bodem, *J. Org. Chem.*, **37**, 4465 (1972).
(19) Cf. J. Gutzwiller and M. Uskokovic, *J. Am. Chem. Soc.*, **92**, 204 (1970), especially ref 10.
(20) L. F. Fieser, *J. Am. Chem. Soc.*, **46**, 2639 (1924).
(21) E. S. Wallis and J. F. Lane, *Org. React.*, **3**, 267 (1946).
(22) A. S. Tomcufcik and L. N. Starker in "Pyridine and Its Derivatives", Part Three, E. Klingsberg, Ed., Interscience, New York, N.Y., 1962, p 7.
(23) K. Ninomiya, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.*, **22**, 1398 (1974) T. Shiori, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, **94**, 6203 (1972); K. Ninomiya, T. Shioiri, and S. Yamada, *Tetrahedron*, **30**, 2151 (1974).
(24) For reviews of pyridine *N*-oxide rearrangements, see V. J. Traynelis in "Mechanisms of Molecular Migrations", Vol. 2, B. S. Thyagarajan, Ed., Interscience, New York, N.Y., p 1; S. Oae and K. Orino, *Heterocycles*, **6**, 583 (1977).
(25) Cf. W. Korytnyk and N. Angelino, *J. Med. Chem.*, 20, 745 (1977).
(26) A. J. Fatiadi, *Synthesis*, 65 (1976).

Mercury in Organic Chemistry. 12.[1] Synthesis of β-Chloro-$\Delta^{\alpha,\beta}$-butenolides via Mercuration–Carbonylation of Propargylic Alcohols[2]

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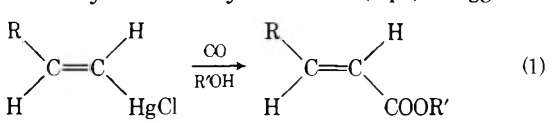
A number of propargylic alcohols react with mercuric chloride to give (*E*)-β-chloro-γ-hydroxyvinylmercuric chlorides. These can be readily carbonylated in a variety of solvents using stoichiometric amounts of palladium chloride and 1 atm of carbon monoxide to give essentially quantitative yields of the corresponding β-chloro-$\Delta^{\alpha,\beta}$-butenolides. Carbonylation can be effected using only catalytic amounts of palladium chloride if cupric chloride is used as a reoxidant and benzene as the solvent.

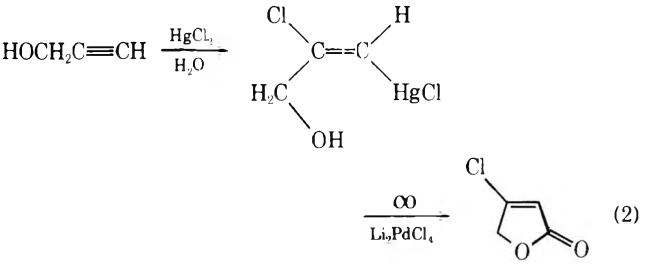
Unsaturated five-member ring lactones, butenolides, occur widely in nature[5] and possess an unusual range of biological activity.[6] They appear throughout the plant kingdom from the simple metabolites of lichens, mold, and fungi[7] to the more complex sesquiterpenes of the family Compositae[8] and steroidal glycosides of the families Ranunculaceae, Liliaceae, Scrophulariaceae, and Apocyanaceae.[9] More recently butenolides have been observed in such diverse animal species as sponges,[10–15] butterflies,[16] and insects.[17] In the latter species they appear to play a significant role as chemical defense weapons. Butenolides also hold promise as insecticides,[18] herbicides,[19] and seed and plant growth regulators.[20–22] Of considerable importance is their widespread allergenic,[23,24] antibacterial,[25,26] and antifungal[27–29] activity. Undoubtedly, vitamin C is the most physiologically important butenolide, but tremendous interest has also been generated by the cardiac glycosides which have the remarkable ability to reduce the frequency, but increase the amplitude of the heart beat.[9] Although in some cases carcinogenic,[30,31] an increasing number of butenolides exhibit cytotoxic and/or tumor inhibitory properties toward a variety of cancers.[32,33]

The unusual range of biological activity of butenolides has stimulated considerable research on the synthesis of these valuable compounds.[34] Of foremost interest are the $\Delta^{\alpha,\beta}$-butenolides. Recent work in our laboratory on the palladium promoted carbonylation of vinylmercurials (eq 1)[35] suggested



(1)

a novel new route to these butenolides. During that work we found that the β-chlorovinylmercurial[36] obtained by mercuric chloride addition to propargyl alcohol could be readily carbonylated to give β-chloro-$\Delta^{\alpha,\beta}$-butenolide [4-chloro-2(5*H*)-furanone] in 96% isolated yield (eq 2). The ease with which



(2)

both mercuration and carbonylation could be effected and the high yield of butenolide encouraged us to examine the full scope of both of these reactions. We wish now to report the complete experimental details of that investigation.

Results and Discussion

Mercuration of Propargylic Alcohols. The first step in our new approach to butenolides involves the mercuration of propargylic alcohols. Nesmeyanov and Kochetkov reported in 1949 that propargyl alcohol (55% yield), 2-methyl-3-butyn-2-ol (38%), 2-butyne-1,4-diol (87%), and 2,5-dimethyl-3-hexyne-2,5-diol (95%) readily react at room temperature with saturated aqueous solutions of sodium chloride

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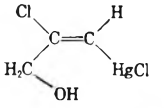
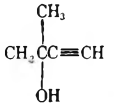
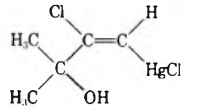
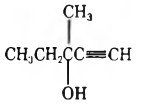
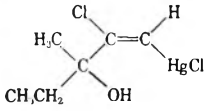
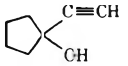
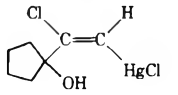
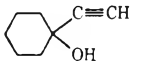
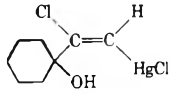
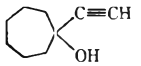
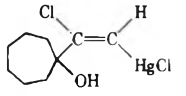
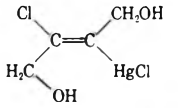
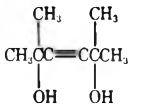
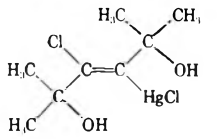
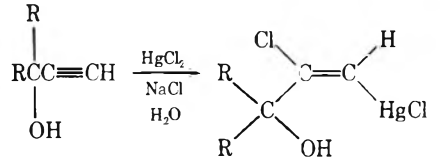
Table I. Mercuration of Propargylic Alcohols

Registry no.	Alcohol	Vinylmercurial	% isolated yield[a]	Mp, °C[a]
107-19-7	$HOCH_2C{\equiv}CH$		54 (55)	105 (105)
115-19-5			31 (38)	78 (70)
77-75-8			26	89-91
17356-19-3			37	104-105
78-27-3			31	137-138
2809-78-1			17	136-137
110-65-6	$HOCH_2C{\equiv}CCH_2OH$		45 (87)	120 (118)
142-30-3			85 (95)	93-220 (103)

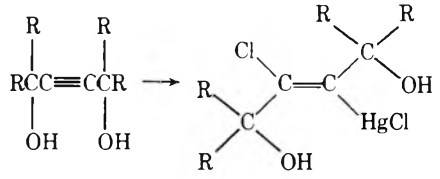
[a] Numbers in parentheses refer to ref 36.

and mercuric chloride to give the corresponding trans addition products in the yields indicated (eq 3, 4).[36] In repeating that



(3)

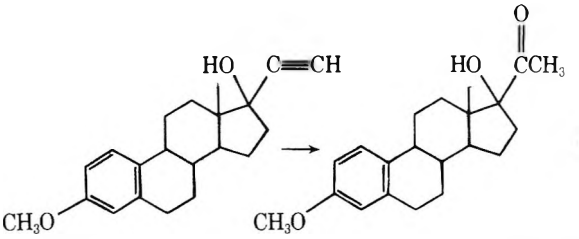
R = H, CH_3



(4)

R = H, CH_3

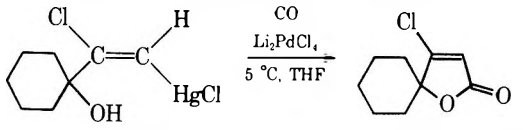
work we have generally gotten similar yields, except in the case of 2-butyne-1,4-diol, where we obtained a 45% yield. In the case of 2,5-dimethyl-3-hexyne-2,5-diol our product did not melt at 103 °C as indicated in the literature, but decomposed over a wide range (93–220 °C). Although the yields are not particularly good, the ease with which the compounds are prepared and isolated encouraged us to examine the mercuration of a whole range of propargylic alcohols. The results of that study are summarized in Table I. While we were able to obtain modest yields of vinylmercurials from several low molecular weight tertiary alcohols, increasing the molecular weight presented certain difficulties. The alcohols were no longer very soluble in the aqueous reaction mixture, and the addition of methanol as a cosolvent apparently not only increased the solubility of the propargylic alcohols, but the solubility of the vinylmercurials as well, and an insoluble white precipitate could no longer be obtained. Thus, the attempted mercuration of the tertiary alcohols 2-phenyl-3-butyn-2-ol, 3-methyl-1-heptyn-3-ol, 3-methyl-1-heptyn-6-en-3-ol, and 3-methyl-1-dodecyn-3-ol either gave no apparent reaction or the reaction mixtures turned dark. Similarly, many attempts to mercurate mestranol only gave starting material or the corresponding methyl ketone, although it appears that some of the desired vinylmercurial may have been formed (eq 5).



(5)

The attempted mercuration of several secondary alcohols (1-phenyl-2-propyn-1-ol, 3-butyn-2-ol, and 1-hexyn-3-ol) gave only dark reaction mixtures and no solid vinylmercurials. A closer look at these reactions by NMR (appearance of a vinyl proton in the correct region) suggested that some vinylmercurial was formed, but that for some reason it failed to precipitate. Thus, it appears that the desired trans addition products of mercuric chloride and propargylic alcohols are only formed and precipitate when relatively low molecular

Table II. Effect of Added Reagents



Reagent[a]	% yield[b]	Reagent[a]	% yield[b]
ZnF_2	47	Al_2O_3	79
	58	BaO	83
$MgSO_4$	61	Li_2CO_3	87
Na_2SO_4	66	K_2CO_3	94
$HC(OCH_3)_3$	68	CaO	95
HgO	76	MgO	95
NaOAc	76		

[a] 1 mmol of mercurial and 1 mmol of reagent. [b] All reactions were run until the maximum yield was obtained as determined by GLC analysis using an internal standard.

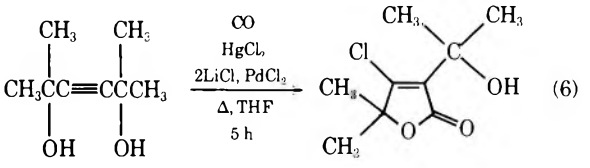
weight, symmetrically substituted propargylic alcohols are employed.

Several related reactions also failed. We were unable to obtain any vinylmercurial from propargyl alcohol when mercuric bromide and sodium bromide were employed, or when the corresponding iodides were used. Similarly the homopropargylic alcohol 3-butyn-1-ol also failed to give any β-chlorovinylmercurial under our usual reaction conditions.

Carbonylation of the β-Chloro-γ-hydroxyvinylmercurials. Although we were not able to prepare a large number of the desired vinylmercurials from mercuric chloride addition to propargylic alcohols, and the yields were often low, the mild reaction conditions and the facility with which this route leads to butenolides encouraged us to examine the carbonylation of these compounds as a simple route to butenolides. In our initial studies it became evident that these β-chloro-γ-hydroxyvinylmercurials are not as rapidly carbonylated as the simple vinylmercurials studied earlier,[35] and it therefore became unnecessary to start the reactions at −78 °C and to allow them to warm up slowly. Instead, we have found it convenient to run the reactions in a cold room at approximately 5 °C. We also observed, as indicated later, that the carbonylation reactions proceed well in most any solvent. We therefore switched from diethyl ether[35] to tetrahydrofuran (THF) for most reactions, because of the greater solubility of the mercurials in this solvent and the significantly increased rate of carbonylation.

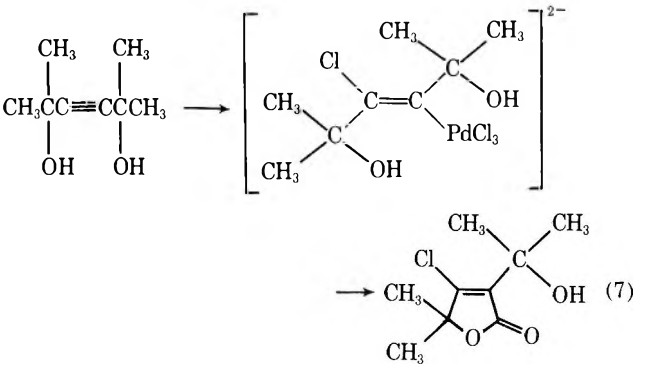
While the mercurials derived from propargyl alcohol (96% yield) and 2-methyl-3-butyn-2-ol (92%) were readily carbonylated using 1 equiv of palladium chloride, 2 equiv of anhydrous lithium chloride, 1 atm of carbon monoxide, THF as a solvent, a temperature of 5 °C, and a time of 24 h, the mercurial derived from 1-ethynylcyclohexanol gave only a 58% yield under these conditions. We reasoned that the lower yield might be due either to the 1 equiv of HCl generated during lactonization reacting with the tertiary allylic alcohol present in the starting mercurial or that the palladium chloride was so strongly coordinated to the alcohol group that it was no longer able to give rapid transmetalation with the mercurial moiety. This might in fact explain the slower rate of carbonylation of these alcohol-containing vinylmercurials. To examine these two possibilities we have run the carbonylation of the 1-ethynylcyclohexanol derived mercurial in the presence of a number of inorganic bases and drying agents, which might be expected either to react with HCl or more strongly to coordinate the hydroxy group, freeing the palladium for transmetalation (Table II). In line with this reasoning, all but one of the reagents used increased the yield, with the inorganic bases potassium carbonate, calcium oxide, and magnesium oxide providing the best results.

We have investigated the generality of this new carbonylation procedure using magnesium oxide by examining the carbonylation of the rest of the propargylic alcohol derived mercurials. In almost every case we have been able to obtain excellent yields of butenolides (Table III). However, the mercurial derived from 2,5-dimethyl-3-hexyne-2,5-diol gave none of the desired lactone under these conditions and only a 5% yield after 24 h at room temperature. On refluxing the reaction mixture, however, we were able to obtain a 94% yield of the desired butenolide. Since the starting mercurial in this case appears to decompose to mercuric chloride and the acetylene under these conditions, it appeared that we might be able to carbonylate the acetylenic diol directly by simply refluxing with all of the usual reagents. In fact, one can obtain a 92% yield in this fashion without isolating the intermediate mercurial (eq 6). Indeed, one can even omit mercuric chloride



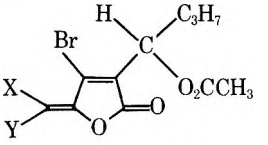
(6)

from the reaction and still obtain a 70% yield, although the reaction now requires approximately 20 h at reflux. No magnesium oxide is required in either of these reactions. Apparently dilithium tetrachloropalladate is itself able to add directly to the acetylene in a trans manner to give an intermediate vinylpalladium compound which is subsequently carbonylated and lactonized (eq 7). Previous workers have



(7)

studied the reaction of this same diol with aqueous solutions of the tetrachloropalladate dianion and reported a rather complex reaction product whose structure was assigned solely by infrared spectroscopy.[37] Later work also examined the analogous reaction of 2-methyl-3-butyn-2-ol.[38] Whatever intermediates are involved, this approach provides a very easy synthesis of the desired butenolide in one step from the commercially available diol. This particular butenolide is especially interesting due to its structural similarity to the acetoxyfimbrolides, a new class of halogenated lactones recently isolated from the red seaweed *Delisea fimbriata* and

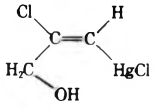
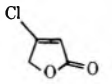
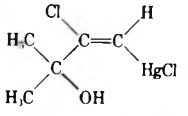
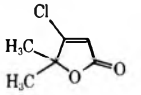
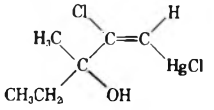
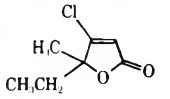
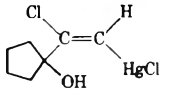
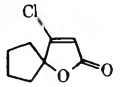
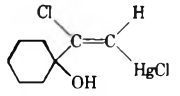
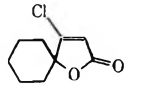
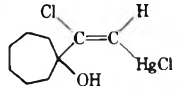
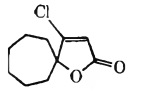
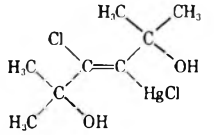
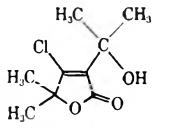


X, Y = H, Cl, Br, I

shown to have antimicrobial activity.[39,40] At present we are examining the scope of this new "direct" approach to butenolides.

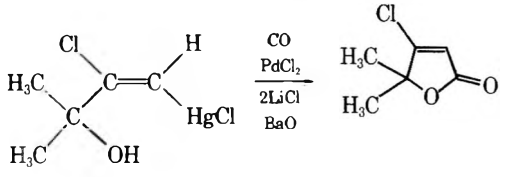
To date the only vinylmercurial which we have been unable to convert to the corresponding butenolide via carbonylation is the compound derived from 2-butyne-1,4-diol. Neither the

Table III. Synthesis of Butenolides via Carbonylation[a]

Registry no.	Mercurial	Butenolide	Registry no.	MgO[b]	% yield[c]	Mp, °C
56453-82-8			56453-85-1	—	(96)[d]	52-52.5[d]
63025-10-5			63025-15-0	—	92	66-66.5
				+	99 (88)	
63025-12-7			63025-16-1	+	98	64-64.5
63025-13-8			63025-17-2	+	99	36-36.5
63025-14-9			63025-18-3	—	58	55-55.5
				+	95 (92)	
63884-14-0			63884-15-1	+	81	~15-16
63025-11-6			63025-19-4	+	94[e]	102

[a] 1 mmol of $PdCl_2$, 2 mmol of LiCl, 10 mL of THF, 5 °C, 24 h. [b] 1 mmol or none. [c] Yields determined by GLC using an internal standard (isolated yields on a 5-mmol scale). [d] See ref 36. [e] Reaction run at reflux.

Table IV. Effect of Solvents on Carbonylation[a]



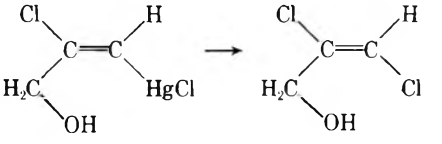
Solvent	% yield[b]	Reaction time, h[c]
Methanol	99	4
Acetone	95	<12
THF	99	24
Ether	99	36
Hexane	82	52[d]

[a] 1 mmol of mercurial, 1 mmol of $PdCl_2$, 2 mmol of LiCl, 1 mmol of BaO, 5 °C, 10 mL of solvent. [b] Yields determined by GLC using an internal standard. [c] Time required to reach maximum yield. [d] Reaction run at room temperature.

isolated mercurial nor our new direct approach gives the desired lactone. It certainly is not obvious to us at present why that should be so. The only product observed in these reactions is 4-chlorobutanol, a product of the direct reaction of THF and palladium chloride.

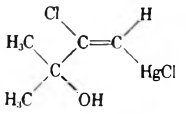
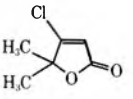
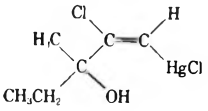
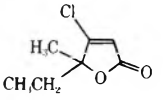
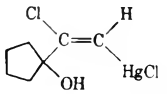
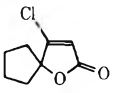
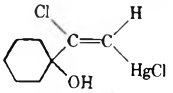
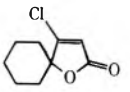
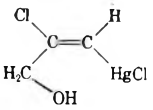
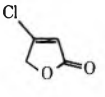
We have also examined the effect of several different solvents on the rates of lactone formation and the overall yield. As can be seen in Table IV, the polarity of the solvent makes little difference in the overall yield of the reaction, but dramatically affects the rate of butenolide formation. The more polar solvents give faster reactions, apparently due to increased solubility of the vinylmercurial and inorganic salts. These rates do not correlate well with the solubility of carbon monoxide in the indicated solvents, thus ruling out carbon monoxide as the rate-limiting reagent. It is indeed amazing that in hexane one can still obtain an 82% yield of butenolide even though none of the reagents are appreciably soluble in this solvent.

Palladium-Catalyzed Carbonylation. Although all of the above carbonylation reactions gave excellent yields using stoichiometric amounts of palladium chloride, it is obvious that the reaction would achieve even greater synthetic utility if a procedure could be developed requiring only catalytic amounts of palladium. In our early work with propargyl alcohol, we were able to obtain a 96% yield of β-chloro-$\Delta^{\alpha,\beta}$-butenolide using as little as 1% of either palladium chloride or 10% palladium on carbon, if we used anydrous cupric chloride as a reoxidant for palladium and diethyl ether as the solvent.[35] In scaling this reaction up from 10 to 50 mmol we found it necessary to carry out the reaction at 5 °C for several days (78% recrystallized yield). In THF, acetone, and methanol the major product was (*E*)-2,3-dichloro-2-propen-1-ol (eq 8). Even in ether the 2-methyl-3-butyn-2-ol derived


(8)

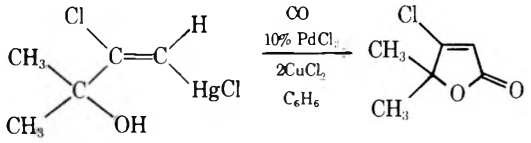
mercurial gave predominantly the *trans*-dichloro olefin. In fact, cupric chloride reacts readily with all of these vinylmercurials in polar solvents to give good yields of the corresponding dichloro olefins. Fortunately, we have been able to circumvent this undesirable side reaction by simply going to less polar solvents. Benzene proved ideal. Using 10% palladium chloride at room temperature in benzene without added

Table V. Palladium-Catalyzed Carbonylation[a]

Mercurial	% $PdCl_2$ catalyst	Reaction time, h	Butenolide	% yield[b]
	10	4		96[c]
	1	23		57[c]
	1	46		99
	10	24		100
	1	120		57
	10	19		93
	1	72		90
	10	19		(81)
	1	72		54
	1	432		77
	10	18		(78)[d]
	1	72		45[c]
	1	40		3

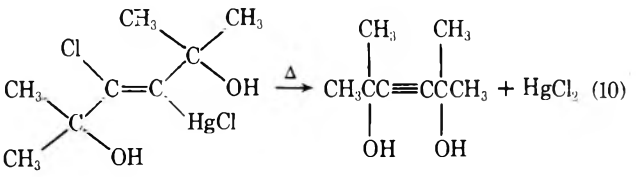
[a] 1 mmol of mercurial, 2 mmol of anhydrous $CuCl_2$, 1 mmol of MgO, 10 mL of benzene at room temperature. [b] GLC analysis using an internal standard (isolated, recrystallized yield). [c] No MgO present. [d] Isolated yield on a 50-mmol scale reaction using no MgO.

lithium chloride, we were able to obtain a 96% yield of the above butenolide in only 4 h (eq 9). While 1% palladium


(9)

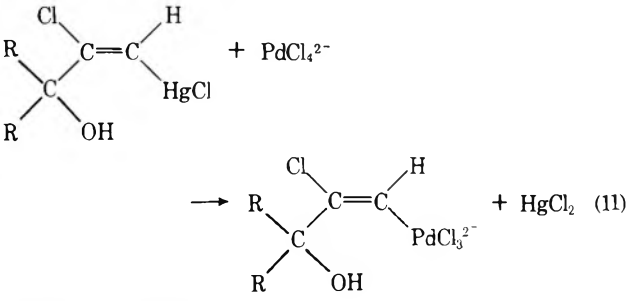
chloride catalyst gave only a 57% yield, the yield was increased to 99% by simply adding 1 equiv of magnesium oxide. Palladium on carbon proved less effective, giving only about 50% yields under similar conditions. Using this new catalytic procedure with either 1 or 10% palladium chloride and 1 equiv of magnesium oxide, in benzene, at room temperature, we have been able to obtain excellent yields of all of the previously prepared butenolides (Table V). In general 10% of the catalyst gives the best results. Surprisingly, this new catalytic procedure proved totally ineffective for the synthesis of β-chloro-$\Delta^{\alpha,\beta}$-butenolide. However, by omitting magnesium oxide we have been able to again achieve high yields of this particular butenolide. Obviously, there is a substantial difference in the effect of reaction conditions on the carbonylation of the tertiary alcohols vs. this primary alcohol.

Mechanism. The mechanism of the mercuric chloride addition to propargylic alcohols remains obscure. Since simple aliphatic terminal alkynes do not react with mercuric chloride under the reaction conditions employed in the mercuration of propargylic alcohols, it is obvious that the alcohol function plays an extremely important role in this reaction. Presumably the mercury salts are brought into the vicinity of the triple bond by coordination with the oxygen of the alcohol. It appears that the reaction is highly dependent on the steric environment of the alcohol and triple bond, and in a rather unusual way. The more sterically crowded tertiary alcohols react, while secondary alcohols give no precipitate at all. Since these reactions are most likely reversible, as indicated by the facile thermal decomposition of the mercurial derived from 2,5-dimethyl-3-hexyne-2,5-diol (eq 10), the insolubility of the

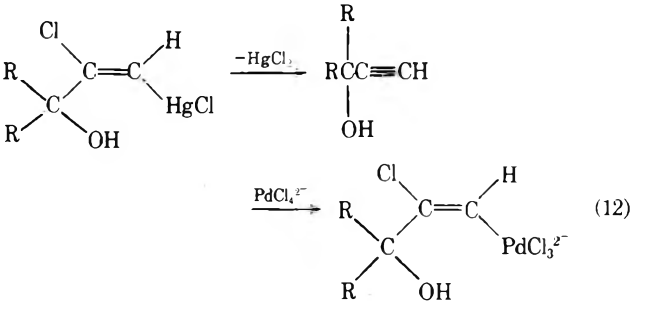

(10)

mercurial products may well determine the success or failure of the mercuration step. It is therefore not surprising that the more symmetrical propargylic alcohols give products, while the secondary alcohols possessing a chiral center fail to precipitate any mercurials at all.

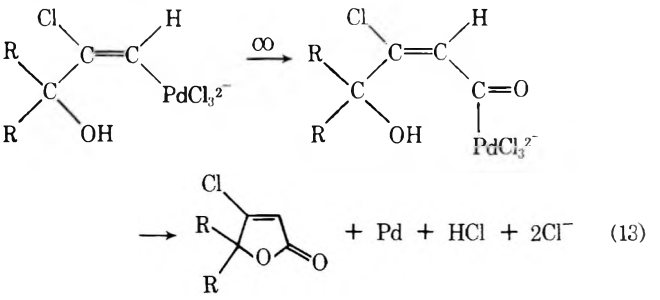
The carbonylation reaction presumably proceeds by an initial transmetalation reaction between the vinylmercurial and the palladium salt (eq 11), although it is possible that the


(11)

mercurial reversibly decomposes to the starting propargylic alcohol, which then adds the palladium salt in a trans manner (eq 12). Our results with the direct palladium chloride pro-


(12)

moted carbonylation of 2,5-dimethyl-3-hexyne-2,5-diol without mercuric chloride clearly indicate that the latter pathway is possible, but that it appears from our rate data to be a slower reaction and probably not a major pathway for generating the vinylpalladium intermediates. Once the vinylpalladium chloride or vinylpalladium trichloride dianion intermediates are formed, they probably immediately undergo carbon monoxide insertion and lactonization (eq 13). The


(13)

cupric chloride simply serves to reoxidize the palladium(0) back to palladium(II) chloride.

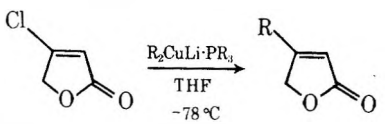
$$Pd + 2CuCl_2 \rightarrow PdCl_2 + Cu_2Cl_2 \quad (14)$$

The inorganic oxide or carbonate bases then entrap the HCl generated before it is able to destroy the tertiary allylic alcohol present in the vinylmercurial or -palladium intermediates.

Conclusion

Mercuric chloride readily adds to relatively low molecular weight propargylic alcohols containing either a primary or tertiary alcohol. Secondary alcohols do not precipitate vinylmercurial products. The resulting mercurials can be carbonylated in near quantitative yield by stirring with either an equivalent amount of palladium chloride and 2 equiv of lithium chloride under 1 atm of carbon monoxide at 5 °C in any of a variety of solvents, or better, with approximately 10% palladium chloride and 2 equiv of anhydrous cupric chloride in benzene at room temperature. The addition of magnesium oxide to these reactions generally substantially improves the yield of butenolide. In at least one case the carbonylation reaction can be carried out directly on the propargylic alcohol by simply refluxing all reagents together. We are presently examining the generality of this direct approach to the synthesis of β-chloro-$\Delta^{\alpha,\beta}$-butenolides.

The recent report of naturally occurring β-halo-$\Delta^{\alpha,\beta}$-butenolides possessing antimicrobial properties heightens interest in these compounds.[39,40] They also appear promising as intermediates for the synthesis of a wide varity of β-substituted butenolides, many of which might be expected to possess biological activity. For example, certain Gilman reagents appear to react instantaneously with the β-chloro-$\Delta^{\alpha,\beta}$-butenolides to give β-alkylbutenolides (eq 15). We are



(15)

presently studying a large number of these substitution reactions and hope to report on them before long.

Experimental Section

Reagents. All chemicals were used directly as obtained unless otherwise indicated. Propargyl alcohol, 1-ethynylcyclopentanol, and 3-methyl-1-pentyn-3-ol were purchased from Aldrich, and 2-methyl-3-butyn-2-ol, 2,5-dimethyl-3-hexyne-2,5-diol, and 1-ethynylcycloheptanol from Farchan. 1-Ethynylcyclohexanol was purchased from Matheson Coleman and Bell. Ether and THF were distilled from lithium aluminum hydride before use, while benzene was used directly as obtained from Fisher. The palladium chloride was generously supplied by Matthey Bishop, Inc., and Engelhard Industries. Mercuric chloride and anhydrous lithium chloride were purchased from Fisher and J. T. Baker, respectively. Cupric chloride (hydrated) was obtained from J. T. Baker and dried in a drying oven overnight at 130 °C before use.

The infrared and NMR spectra were recorded on a Beckman IR-4250 infrared spectrophotometer and Varian Associates A-60 NMR spectrometer, respectively. The mass spectra were obtained on an AEI MS-902 high-resolution mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc.

Mercuration of Propargylic Alcohols. All previously known propargylic alcohol derived mercurials were prepared according to the literature procedure.[36] All new mercurials were prepared as follows. A room-temperature saturated aqueous solution of mercuric chloride and sodium chloride (50 mL) (make certain the solution is saturated in both reagents) was placed in a water bath and 5 g of propargylic alcohol dissolved in 15 mL of methanol was added. After a few minutes of stirring, the solution became cloudy and a thick white precipitate formed. The mixture was stirred at room temperature for 1 h. The precipitate was collected by vacuum filtration and washed with a small amount of cold water. The solid was dried overnight at 0 °C in a vacuum desiccator, then ground up and dried one more day. The resulting powder was extracted with warm benzene and filtered by gravity. The filtrate was concentrated and then cooled to provide crystals.

The following β-chloro-γ-hydroxyvinylmercurials were prepared and characterized. (*E*)-2-Chloro-3-chloromercuri-2-propen-1-ol:[36] mp 105 °C (lit.[36] mp 105 °C); ^{1}H NMR (acetone-d_6) δ 3.2 (br s, 1, OH), 4.3 (d, 2, J = 1.8 Hz, CH_2), 6.27 (t, 1, J = 1.8 Hz, vinyl). (*E*)-3-Chloro-4-chloromercuri-2-methyl-3-buten-2-ol:[36] mp 78 °C (lit.[36] mp 70 °C); ^{1}H NMR (acetone-d_6) δ 1.5 (s, 6, CH_3), 5.05 (s, 1, OH), 6.01 (s, 1, vinyl). (*E*)-2-Chloro-1-chloromercuri-3-methyl-1-penten-3-ol: crude yield 36%, isolated yield 26%; mp 85–86 °C; ^{1}H NMR (acetone-d_6) δ 0.86 (t, 3, J = 7 Hz, $-CH_2CH_3$), 1.48 (s, 3, CH_3), 1.72 (q, 2, J = 7 Hz, CH_2), 4.84 (s, 1, OH), 6.06 (s, 1, vinyl). Anal. Calcd for $C_6H_{10}Cl_2HgO$: C, 19.57; H, 2.46. Found: C, 19.63; H, 2.62. (*E*)-1-(1-Chloro-2-chloromercuriethenyl)cyclopentanol: crude yield 81%, isolated yield 37%; mp 99–100 °C; ^{1}H NMR (acetone-d_6) δ 1.4–2.4 (m, 8, CH_2), 4.86 (s, 1, OH), 6.13 (s, 1, vinyl). Anal. Calcd for $C_7H_{10}Cl_2HgO$: C, 22.03; H, 2.64. Found: C, 21.86; H, 2.49. (*E*)-1-(1-Chloro-2-chloromercuriethenyl)cyclohexanol: crude yield 61%, isolated yield 31%; mp 137–138 °C; ^{1}H NMR (acetone-d_6) δ 1.3–2.0 (m, 10, CH_2), 4.5 (s, 1, OH), 6.03 (s, 1, vinyl). Anal. Calcd for $C_8H_{12}Cl_2HgO$: C, 24.28; H, 3.05. Found: C, 22.91; H, 2.82. (*E*)-1-(1-chloromercuriethenyl)cycloheptanol: crude yield 28%, isolated yield 17%; mp 136–137 °C; ^{1}H NMR (acetone-d_6) δ 1.4–2.4 (m, 12, CH_2), 5.07 (s, 1, OH), 6.10 (s, 1, vinyl). Anal. Calcd for $C_9H_{14}Cl_2HgO$: C, 26.38; H, 3.44. Found: C, 26.48; H, 3.49. (*E*)-2-Chloro-3-chloromercuri-2-butene-1,4-diol:[36] mp 120 °C (lit.[36] mp 118 °C); ^{1}H NMR (acetone-d_6) δ 3.18 (s, 1, OH), 4.3 (br s, 4, CH_2). (*E*)-3-Chloro-4-chloromercuri-2,5-dimethyl-3-hexene-2,5-diol:[36] mp 93–220°C (ethanol) (lit.[36] mp 103 °C); ^{1}H NMR (acetone-d_6) δ 1.41 (s, 12, CH_3), 3.55 (s, 1, OH).

Carbonylation of the β-Chloro-γ-hydroxyvinylmercurials. The butenolides were prepared according to the following representative procedure. Anhydrous lithium chloride (2 mmol, 0.085 g), 1 mmol of palladium chloride (0.178g), 1 mmol of magnesium oxide, and 10 mL of anhydrous THF were placed in a round-bottom flask with a septum inlet. While flushing with carbon monoxide at −78 °C, 1 mmol of the appropriate mercurial was added. A balloon filled with carbon monoxide was connected to the top of the flask, and the reaction mixture was allowed to warm up to ~5 °C and then stirred 24 h at that temperature. Saturated ammonium chloride solution (1 mL) and 10 mL of ether were added and stirring was continued for an additional hour at room temperature. The mixture was vacuum filtered, and the filtrate was washed with saturated potassium carbonate solution and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the crude product was recrystallized from pentane.

All yields determined by GLC analysis were run as above and an appropriate internal standard was added just prior to analysis. Internal standard correction factors were determined using authentic isolated butenolide samples. Isolated yields were obtained using both the above 1-mmol scale procedure and a 5-mmol scale procedure, in which case the yields were usually substantially higher.

The effect of various added reagents on the yield of butenolide obtained from carbonylation of (*E*)-1-(1-chloro-2-chloromercuriethenyl)cyclohexanol was studied by employing the 1-mmol procedure described above and substituting the appropriate reagents for magnesium oxide. The reactions were analyzed by GLC analysis using an internal standard and the results are summarized in Table II.

The effect of various solvents on the rate of formation and yield of butenolide in the carbonylation of (*E*)-3-chloro-4-chloromercuri-2-methyl-3-buten-2-ol was studied using a similar procedure, but employing 1 mmol of BaO as the added reagent and varying the solvent. The reactions were analyzed by GLC analysis using an internal standard and the results are summarized in Table IV.

The following new butenolides were prepared. 4-Chloro-5,5-dimethyl-2(5*H*)-furanone: isolated yield on a 1-mmol scale 59%, on a 5-mmol scale 88% (103% crude yield, mp 61–63 °C); mp 66–66.5 °C; ^{1}H NMR (CCl_4) δ 1.47 (s, 6, CH_3), 5.91 (s, 1, vinyl); IR (max) (KBr) 1776 (C=O), 1615 (C=C) cm^{-1}; *m/e* 146.0135 (calcd for $C_6H_7ClO_2$, 146.0138). 4-Chloro-5-ethyl-5-methyl-2(5*H*)-furanone: isolated yield on a 1-mmol scale 66%; mp 64–64.5 °C; ^{1}H NMR (CCl_4) δ 0.85 (t, 3, J = 7 Hz, $-CH_2CH_3$), 1.46 (s, 3, CH_3), 1.82 (q, 2, J = 7 Hz, CH_2), 5.9 (s, 1, vinyl); IR (max) (KBr) 1776 (C=O), 1615 (C=C) cm^{-1}; *m/e* 160.0288 (calcd for $C_7H_9ClO_2$, 160.0291). 4-Chloro-5,5-tetramethylene-2(5*H*)-furanone: isolated yield on a 1-mmol scale 63%; mp 36–36.5 °C; ^{1}H NMR (CCl_4) δ 1.6–2.0 (m, 8, CH_2), 5.9 (s, 1, vinyl); IR (max) (KBr) 1776 (C=O), 1617 (C=C) cm^{-1}; *m/e* (M − Cl, no parent observed) 137.0607 (calcd for $C_8H_9O_2$, 137.0603). 4-Chloro-5,5-pentamethylene-2(5*H*)-furanone: isolated yield on a 1-mmol scale 49%, on a 5-mmol scale 92% (105% crude yield, mp 52–56 °C); mp 55–55.5 °C; ^{1}H NMR (CCl_4) δ 1.4–2.0 (m, 10, CH_2), 5.91 (s, 1, vinyl); IR (max) (KBr) 1776 (C=O), 1615 (C=C) cm^{-1}; *m/e* 186.0453 (calcd for $C_9H_{11}ClO_2$, 186.0447). 4-Chloro-5,5-hexamethylene-2(5*H*)-furanone: isolated yield on a 1-mmol scale 45%; mp ~15–16 °C; ^{1}H NMR (CCl_4) δ 1.5–2.0 (m, 12, CH_2), 5.80 (s, 1, vinyl); IR (max) (KBr) 1776 (C=O), 1615 (C=C) cm^{-1}; *m/e* 200.0599 (calcd for $C_{10}H_{13}ClO_2$, 200.0604). 4-Chloro-5,5-dimethyl-3-(1-hydroxy-1-methylethyl)-2(5*H*)-furanone: prepared by refluxing the reaction mixture under carbon monoxide for 4 h; isolated yield on a 1-mmol scale 72%; mp 102 °C; ^{1}H NMR (CCl_4) δ 1.50 (s, 6, CH_3), 1.55 (s, 6, CH_3), 3.92 (s, 1, OH); IR

(max) (KBr) 1755 (C=O), 1645 (C=C) cm^{-1}; *m/e* (M − CH_3, no parent observed) 189.0298 (calcd for $C_8H_{10}ClO_3$, 189.0318). Anal. Calcd for $C_9H_{13}ClO_3$: C, 52.82; H, 6.40. Found: C, 53.02; H, 6.57.

In the direct carbonylation of 2,5-dimethyl-3-hexyne-2,5-diol, 1 mmol of acetylenic diol, 1 mmol of palladium chloride, 2 mmol of anhydrous lithium chloride, 1 mmol of mercuric chloride, and 10 mL of THF were mixed at room temperature and refluxed for 4 h under carbon monoxide. GLC analysis using an internal standard indicated a 92% yield of butenolide. Omission of mercuric chloride required that the reaction be refluxed for 20 h, but a 70% yield of butenolide could still be obtained under these conditions.

Palladium-Catalyzed Carbonylation. 4-Chloro-2(5*H*)-furanone (β-chloro-$\Delta^{\alpha,\beta}$-butenolide) was prepared on a 50-mmol scale using 10% palladium chloride as follows. To 5 mmol of palladium chloride (0.84 g), 100 mmol of lithium chloride (4.25 g), and 100 mmol of cupric chloride (13.45 g) in 250 mL of ether at −78 °C was added 50 mmol of (*E*)-2-chloro-3-chloromercuri-2-propen-1-ol (16.4 g). The flask was flushed with carbon monoxide and a large balloon filled with carbon monoxide was connected to the top of the flask. The cold bath was removed and the reaction mixture was stirred in a cold room (~5 °C) for 50 h. Saturated ammonium chloride solution (10 mL) was added and the mixture stirred an additional hour. The resulting suspension was vacuum filtered, washed with saturated ammonium chloride, and dried over anhydrous sodium sulfate. Evaporation of the ether afforded 6.18 g (105%) crude yield of product. Recrystallization from carbon tetrachloride provided a 78% isolated yield.

The 1-mmol scale catalytic carbonylation reactions summarized in Table V were carried out as follows. Anhydrous cupric chloride (2 mmol), the appropriate amounts of palladium chloride (0.01 or 0.10 mmol) and magnesium oxide (usually 1 mmol), and 5 mL of benzene were added to a round-bottom flask with septum inlet. After flushing with carbon monoxide and attaching a balloon full of carbon monoxide, an additional 5 mL of benzene containing 1 mmol of mercurial was added and the flask was stirred at room temperature for the appropriate length of time. An internal standard was then added and the reaction analyzed by GLC analysis. To determine the isolated yield of 4-chloro-5,5-pentamethylene-2(5*H*)-furanone on a 1-mmol scale, the catalytic carbonylation reaction was set up as described above and stirred for 19 h at room temperature. Then 1 mL of saturated ammonium chloride, 15 mL of ether, and charcoal were added. The mixture was stirred under carbon monoxide for 90 min longer, and the resulting suspension was filtered, washed with two 25-mL portions of saturated potassium carbonate, and dried over anhydrous sodium sulfate. Evaporation of the ether gave 0.3 g (112%) of crude product, which was then recrystallized from Skelly B in 81% isolated yield.

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Registry No.—Mercuric chloride, 7487-94-7; sodium chloride, 7647-14-5; (*E*)-2-chloro-3-chloromercuri-2-butene-1,4-diol, 63915-18-84.

References and Notes

(1) Part 11: R. C. Larock and J. C. Bernhardt, *J. Org. Chem.*, **42**, 1680 (1977).
(2) Preliminary communication: R. C. Larock and B. Riefling, *Tetrahedron Lett.*, 4661 (1976).
(3) DuPont Young Faculty Scholar, 1975–1976.
(4) Alfred P. Sloan Foundation Fellow, 1977–1979.
(5) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds", Butterworths, London, 1963.
(6) L. J. Haynes, *Q. Rev., Chem. Soc.*, **2**, 46 (1948).
(7) L. J. Haynes and J. R. Plimmer, *Q. Rev., Chem. Soc.*, **14**, 292 (1960).
(8) T. K. Devon and A. I. Scott, "Handbook of Naturally Occuring Compounds", Vol. II, Academic Press, New York, N.Y., 1972, pp 79–175.
(9) P. G. Marshall in "Chemistry of Carbon Compounds", Vol. IID, E. H. Rodd, Ed., Elsevier, New York, N.Y., 1970, Chapter 17.
(10) F. J. Schmitz, K. W. Kraus, L. S. Ciereszko, D. H. Sifford, and A. J. Weinheimer, *Tetrahedron Lett.*, 97 (1966).
(11) G. Cimino, S. De Stefano, L. Minale, and E. Fattorusso, *Tetrahedron*, **28**, 333 (1972).
(12) F. Cafieri, E. Fattorusso, C. Santacroce, and L. Minale, *Tetrahedron*, **28**, 1579 (1972).
(13) D. J. Faulkner, *Tetrahedron Lett.*, 3821 (1973).
(14) I. Rothberg and P. Shubiak, *Tetrahedron Lett.*, 769 (1975).
(15) G. Cimino, S. De Stefano, A. Guerriero, and L. Minale, *Tetrahedron Lett.*, 1417 (1975).
(16) D. M. Kirpotin and K. L. Gladilin, *Priroda (Moscow)*, 108 (1969); *Chem. Abstr.*, **72**, 64115k (1970).
(17) T. Reichstein, *Cron. Chim.*, **15**, 3 (1967); *Chem. Abstr.*, **72**, 77821n (1970).
(18) J. B. Sidda l, U.S. Patent 3 700 694 (1972); *Chem. Abstr.*, **78**, 43254p (1973).
(19) T. L. Rebstock and H. M. Sell, *J. Am. Chem. Soc.*, **74**, 274 (1952).
(20) G. B. Payne, U.S. Patent 3 177 227 (1965); *Chem. Abstr.*, **63**, 6866e (1965).
(21) H. Veldstra and E. Havinga, *Recl. Trav. Chim. Pays-Bas.*, **62**, 841 (1943).
(22) Y. Iino, A. Tanaka, and K. Yamashita, *Agric. Biol. Chem.*, **36**, 2505 (1972).
(23) G. W. Perold, J.-C. Muller, and G. Ourisson, *Tetrahedron*, **28**, 5797 (1972).
(24) J. C. Mitchell, G. Dupuis, and T. A. Geissman, *Br. J. Dermatol.*, **87**, 235 (1972).
(25) C. J. Cavallito, in "Medicinal Chemistry", Vol. I, C. M. Suter, Ed., Wiley, New York, N.Y., 1951, pp 221–235.
(26) A. W. Ninenam and R. A. Raphael, *J. Chem. Soc.*, 118 (1949).
(27) K. Aoki, T. Tokuda, H. Hoshi, K. Satake, and S. Funayama, Japan Patent 73 28 646 (1973); *Chem. Abstr.*, **80**, P117147w (1974).
(28) A. Dal Pozzo, A. Dansi, and E. Meneghini, *Boll. Chim. Farm.*, 113 (1974).
(29) K. Sakurai, H. Matsumoto, and J. Adachi, *Yakugaku Zasshi*, **88**, 919 (1968); *Chem. Abstr.*, **69**, 94792j (1968).
(30) F. Dickens and H. E. H. Jones, *Br. J. Cancer*, **15**, 85 (1961); **17**, 100, 691 (1963).
(31) F. Dickens, *Br. Med. Bull.*, **20**, 96 (1964).
(32) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971).
(33) S. M. Kupchan, *Trans. N.Y. Acad. Sci.*, **32**, 85 (1970).
(34) Y. S. Rao, *Chem. Rev.*, **76**, 625 (1976).
(35) R. C. Larock, *J. Org. Chem.*, **40**, 3237 (1975).
(36) A. N. Nesmeyanov and N. K. Kochetkov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 76 (1949).
(37) Y. Y. Kharitonov, T. I. Beresneva, G. Y. Mazo, and A. V. Babaeva, *Russ. J. Inorg. Chem.*, **12**, 1373 (1967).
(38) Y. Y. Kharitonov, T. I. Beresneva, G. Y. Mazo, and A. V. Babaeva, *Russ. J. Inorg. Chem.*, **13**, 1129 (1968).
(39) R. Kazlauskas, P. T. Murphy, R. J. Quinn, and R. J. Wells, *Tetrahedron Lett.*, 37 (1977).
(40) J. A. Pettus, R. M. Wing, and J. J. Sims, *Tetrahedron Lett.*, 41 (1977).

Synthetic Applications and Mechanism Studies of the Decarbalkoxylations of Geminal Diesters and Related Systems Effected in Me_2SO by Water and/or by Water with Added Salts[1]

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The decarbalkoxylations of geminal diesters, β-keto esters, and α-cyano esters by water–Me_2SO and/or water–Me_2SO with added salts is a convenient preparative route, leading to esters, ketones, and nitriles, respectively. This type of reaction has been studied using a variety of substrates and diverse salts. The diesters $C_6H_5CH(CO_2CH_2CH_3)_2$, $C_6H_5CH_2(CO_2CH_2CH_3)_2$, and $CH_3CONHCH(CO_2CH_2CH_3)_2$ decarbethoxylate on being refluxed in wet Me_2SO. Monosubstituted β-keto esters also decarbethoxylate under these conditions. Diesters such as $CH_3CH_2CH(CO_2CH_2CH_3)_2$ and $CH_3CH_2CH(CO_2CH_3)_2$ undergo a much slower decarbalkoxylation in refluxing wet Me_2SO. Substrates such as $(CH_3)_2CHCH(CO_2CH_2CH_3)_2$ and the disubstituted diesters $(CH_3CH_2)_2C(CO_2CH_2CH_3)_2$, $C_6H_5C(CH_3)C(CO_2CH_2CH_3)_2$, and $(CH_3CH_2)_2C(CO_2CH_3)_2$ undergo no decarbalkoxylations on being heated for long periods in H_2O–Me_2SO. The addition of salts such as KCN, NaCl, or LiCl to the H_2O–Me_2SO dramatically enhances the decarbalkoxylation rates of these substrates. The CH_3CH_2CN–CH_3CH_2OH product ratios have been determined for several mono- and disubstituted geminal diesters using KCN–H_2O–Me_2SO. Relative rates of decarbalkoxylations have been determined for various substrates and salts. Comparative rate data have been obtained for several substrates in H_2O or D_2O in Me_2SO in the presence and absence of salts. Mechanistic interpretations which involve competitive $B_{AL}2$ and $B_{AC}2$ cleavages which are dependent on substrate structure are presented to rationalize the experimental data.

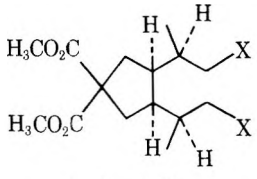
During the past several years we have reported studies of the synthetic applications of the decarbalkoxylations of malonate esters **1** to esters **2** (and the related β-keto esters and α-cyano esters) using NaCN in refluxing Me_2SO,[3] NaCl in wet Me_2SO,[4,5] and wet Me_2SO.[5,6]

$$R^1R^2C(CO_2R^3)_2 \rightarrow R^1R^2CHCO_2R^3$$
1 **2**

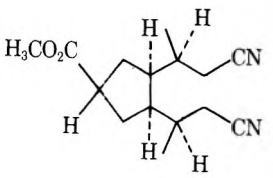
We now wish to report additional experimental data which further extends the synthetic utility of this extremely useful and versatile reaction and sheds some light on the mechanistic aspects.

Introduction

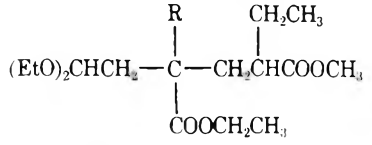
In an attempt to convert the ditosylate **3a** into the dinitrile **3b**, **3a** was treated with excess KCN in Me_2SO at 90 °C (12 h). Under these conditions, the tosylate groups were not only displaced, but a decarbomethoxylation occurred to produce **4** in a good yield.[7] Dinitrile **3b** could be prepared from **3a** if the KCN–Me_2SO (or NaCN) reaction mixture was maintained at room temperature (6 days). The application of the NaCN–Me_2SO reagent combination for effecting decarbalkoxylations was then studied by us utilizing several mono- and disubstituted malonate esters.[3] For example, treatment of $CH_3CH_2(CO_2CH_2CH_3)_2$ with 2 equiv of NaCN in Me_2SO (160 °C, 4 h) leads to ethyl butyrate (80%). Several advantages of this procedure include the facts that functional groups such as ketals or esters which are sensitive to acidic or basic conditions survive the reaction and isomerizations of double bonds do not occur.



3a, X = OTs
b, X = CN



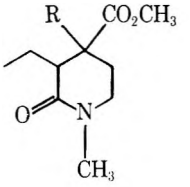
4



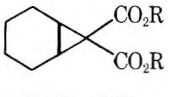
5a, R = $COOCH_2CH_3$
b, R = H

Since the introduction of this procedure, many applications of its synthetic utility to complex molecules have been reported.[8] The decarbethoxylation of **5a** yields **5b**.[8a]

Modifications of this procedure using cyanide salts, other substrates, and dipolar aprotic solvents have subsequently been reported.[9-12] DMF and NaCN have been used in the conversion of **6a** to **6b**.[9] Of mechanistic interest is the result that **7a** on treatment with 2 equiv of KCN in DMF yields **7b** (65%).[10]



6a, R = CO_2CH_3
b, R = H



7a, R = CH_3
b, R = H

Our further studies of this reaction showed that NaCl–H_2O–Me_2SO effected decarbalkoxylations of malonate esters, β-keto esters, and α-cyano esters.[4,5,6] Applications of this salt to effect decarbalkoxylations have appeared in other synthetic routes.[13,14]

Certain substrates undergo reaction when heated with wet Me_2SO without added salts.[5,6] Bernhard in 1894 had observed that hot water could effect decarbalkoxylations of doubly activated esters such as diethyl benzoylmalonate.[15] A recent application of this procedure reports that diethyl propionylmalonate with boiling water yields ethyl propionylacetate.[16] Meerwein[17] in 1913 reported that β-keto esters yield ketones on being treated with water in a sealed tube (200 °C, 0.5 h) and later reported the conversion of **8** to **9**.[18] The procedure failed for β-keto esters with no α hydrogens. A modification of this procedure using basic aluminum oxide in aqueous dioxane has recently been reported.[21,22]

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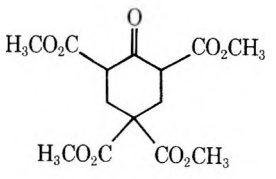
Table I. Decarbalkoxylations of Geminal Diesters by H_2O–Me_2SO

1			Registry	Heating	%
R^1	R^2	R^3	no.	period, h[a]	monoester
C_6H_5	H	CH_3CH_2[b]	83-13-6	3	90[c]
$C_6H_5CH_2$	H	CH_3CH_2[d]	607-81-8	4	61[e]
CH_3CONH	H	CH_3CH_2[f]	1068-90-2	3.5	70
CH_3	H	CH_3CH_2[g]	009-08-5	3	32[h]
CH_3CH_2	H	CH_3CH_2[d]	133-08-5	2	7[i,j]
CH_3CH_2	H	CH_3CH_2[k]		4.5	20[i]
CH_3CH_2	H	CH_3[l]	26717-67-9	2	32[i,m]
$(CH_3)_2CHCH_2$	H	CH_3CH_2[d]	10203-58-4	2.5	13[i]
$(CH_3)_2CH$	H	CH_3CH_2[d]	759-36-4	2	1[i]
c-C_6H_{11}	H	CH_3CH_2[d]	2163-44-2	2	1[i]
CH_3	CH_3	CH_3CH_2[n]	1619-62-1	2	1[i,o]
CH_3CH_2	CH_3CH_2	CH_3CH_2[n]	77-25-8	2	1[i]
CH_3CH_2	CH_3CH_2	CH_3[n]	27132-23-6	4.5	2[i]
C_6H_5	CH_3	CH_3CH_2[n]	34009-61-5	16	3[i]

[a] The total reaction time is the period beginning when heat was begun and when the refluxing mixture started to cool. All reactions were run in round-bottom flasks with magnetic stirring with a mantle. [b] Diester (0.03 mol) and water (0.06 mol) in 25 mL of Me_2SO. [c] The product was isolated by a water quench, extraction into pentane, and concentration of the pentane extract. Product identification was done by ^1H NMR, IR, and GLC comparisons. Yields are based on isolated products. [d] Substrate and water (0.03 mol each) in 50 mL of Me_2SO. [e] After 8 h and workup as in c, a 70% yield of ethyl phenylpropionate could be isolated (contained about 5% starting diester). [f] Substrate (0.01 mol) and water (0.02 mol) in 10 mL of Me_2SO. The product was isolated by distillation of the Me_2SO under water-aspirator pressure and the distillation of the ethyl acetamidoacetate under vacuum-pump pressure. [g] Diester (0.05 mol) and water (0.10 mol) in 50 mL of Me_2SO. [h] Low-boiling material was distilled from the reaction pot and washed with cold water, and the ester was isolated. [i] An aliquot was quenched with water, extracted with pentane and analyzed by VPC. [j] Fourteen percent monoester after 4 h of total heating. [k] As in *d*, except DMF as solvent. [l] Diester (0.003 mol) and water (0.03 mol) in 5 mL of Me_2SO. [m] Forty-two percent of ester after an additional hour of heating. [n] Substrate and water (0.015 mol each) in 25 mL of Me_2SO. [o] After 21 h of total heating, perhaps 3% reaction. Paraformaldehyde formed in the condenser.



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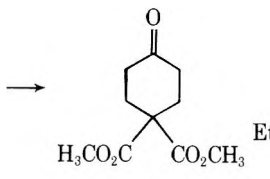

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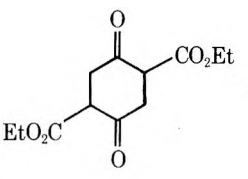

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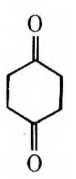

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Halolytic decarbalkoxylations of activated esters have been reported with various iodide salts and dipolar aprotic or polar aprotic solvents.[24–31] The popular use of iodides in these types of reactions appears to be attributable to their prior applications to cleavages of methyl esters.[11d,32]

Many other halide salts have found use in decarbalkoxylation procedures.[12a,33,34] Internal alkylative decarboxylations have been accomplished with salts such as NaCl, NaBr, KCl and tetramethylammonium bromide in solvents such as Me_2SO and HMPT.[29] External alkylative decarboxylations have been accomplished with LiCl in HMPT.[29b] The use of tetramethylammonium acetate in decarbalkoxylations in Me_2SO[8c] and HMPT[35] have recently appeared.

Decarbalkoxylations of activated esters with ethanolic sodium ethoxide have been reported by Thorpe,[36] Ingold,[37] and Cope and McElvain.[38] Amines in refluxing xylene[14d,39,40] or toluene[41] have also found use in these types of reactions.

Results and Discussion

Water–Me_2SO Studies. Experiments were performed on a variety of geminal diesters to ascertain the limitations of the decarbalkoxylation process using water in Me_2SO (and in one case DMF). The results are tabulated in Table I.

An examination of the data presented in Table I reveals the following pertinent points: (1) substrates with electron-withdrawing substituents such as diethyl phenylmalonate, diethyl benzylmalonate, and diethyl acetamidomalonate undergo decarbethoxylations fairly readily in H_2O–Me_2SO; (2) *n*-alkyl-substituted diethyl malonates and diethyl isobutylmalonate undergo slow decarbalkoxylations, while dimethyl ethylmalonate proceeds about four times faster than the corresponding diethyl ester; (3) substrates such as diethyl isopropylmalonate and diethyl cyclohexylmalonate show little tendency to decarbethoxylate (substituents adjacent to the carbon bearing the geminal diester groups presumably sterically inhibit water attack at one of the ester carbonyl groups); and (4) diethyl and dimethyl disubstituted malonates undergo practically no decarbalkoxylations when heated in H_2O–Me_2SO.[42]

Data has also been obtained for decarbalkoxylations of β-keto esters in H_2O–Me_2SO and these data are summarized in Table II.

The data in Table II reveal that many β-keto esters which contain an α hydrogen undergo rapid decarbalkoxylations in wet Me_2SO. Other dipolar aprotic solvents such as DMF can also be utilized.[5]

Salt Effect Studies. In those geminal diesters which undergo slow decarbalkoxylations in H_2O–Me_2SO (Table I), the addition of salts such as KCN or NaCl accelerates ester formation.[4,5] To more fully probe into the nature of the accelerating effect of salts, various substrates were studied using a variety of salts and conditions. Individual diesters are tabulated in the following tables.

The experimental data for the decarbalkoxylation of diethyl ethylmalonate are summarized in Table III.

It can be seen from the data in Table III that the addition of 2 equiv of NaCl or 1 or 2 equiv of LiCl dramatically increases the rate of ester formation. The different effect seen for LiCl and NaCl is probably due to the greater solubility of LiCl in Me_2SO in comparison to NaCl (heterogeneous). With this particular malonate ester the reaction also proceeds rapidly in DMF as solvent when 1 or 2 equiv of LiCl are

Table II. Decarbalkoxylations of β-Keto Esters Using Water–Me_2SO

Substrate[a]	Registry no.	Ketone, %[c]
2-Carbalkoxycyclohexanone[b]		87
2-Carbethoxycyclooctanone	4017-56-5	70
2-Carbethoxycyclododecanone	4017-60-1	85
2,5-Dicarbomethoxy-1,4-cyclohexanedione	6289-46-9	60 (dione)
$C_6H_5COCH_2COOCH_2CH_3$	94-02-0	70
$CH_3COCH(CH_3)COOCH_2CH_3$	609-14-3	70[d]
$CH_3COC(CH_3)_2COOCH_2CH_3$	597-04-6	*e*

[a] Substrate (0.03 mol) and water (0.06 mol) in 25 mL of Me_2SO which was heated for 4 h except in entries 1 and 2 which were heated for 3 h. [b] Thirty-five percent methyl ester and 65% ethyl ester. [c] Quenched with water, extracted with pentane, and isolated. [d] Yield calculated from ^1H NMR of crude product. [e] Only starting material recovered in higher than 90% yield.

Table III. Decarbethoxylations of Diethyl Ethylmalonate

Salt, equiv[a]	Heating period, h	% monoester[b]
None	0.5	2
None[c]	4.5	20
1 LiCl	1	84
2 LiCl	0.5	60
	2.0	92
	4.0	99[d]
2 LiCl[e]	0.5	45
2 NaCl	0.5	40
	2.0	72
	4.5	99[d]
2 KCN	1.5	94[f]
1 LiCl[c]	4.5	70
2 LiCl[c]	4.5	83

[a] Diester and water (0.03 mol each) in 50 mL of Me_2SO (0.6 M in substrate). [b] Aliquot quenched with cold water, saturated with NaCl, extracted with pentane, and analyzed by GLC. [c] As in *a*, except 50 mL of DMF as solvent. [d] Distilled low-boiling materials from the reaction pot and quenched with water, and the ester separated (about 90% isolated yields). [e] As in *a*, except 5 equiv of H_2O. [f] Distilled material which showed no starting material (90%).

present. Lithium chloride is an excellent salt for use in preparative decarbalkoxylations.

The decarbomethoxylation of dimethyl ethylmalonate also proceeds rapidly in water–Me_2SO–LiCl. In 0.5 h, 98% decarbomethoxylation occurs (0.6 M substrate, water, and LiCl), while only 32% monoester forms in 2 h (0.6 M substrate and water).

Other monosubstituted malonate esters which undergo slow decarbethoxylations in H_2O–Me_2SO proceed rapidly and in excellent yields when 2 equiv of LiCl or NaCl are present. Some malonate ester decarbethoxylations of this type are summarized in Table IV.

Since the decarbalkoxylations of the dimethyl and diethyl disubstituted malonates barely proceed on heating in H_2O–Me_2SO, several substrates were studied to optimize the rates and yields of the esters which are produced. Data for dimethyl diethylmalonate using a variety of salts and solvents are listed in Table V.

From the data tabulated in Table V it can be seen that the decarbomethoxylation of this particular diester proceeds readily in H_2O–Me_2SO with NaCl, LiCl, or KCN, and also with LiCl in DMF–H_2O. As the reaction proceeds with LiCl as the salt, Li_2CO_3 precipitates during the reaction and can

Table IV. Monosubstituted Malonates with Added Salts

1			Equiv	Heating	
R^1	R^2	R^{3a}	of salt	period, h	% ester[b]
$(CH_3)_2CHCH_2$	H	CH_3CH_2	None	2.5	13
			2 LiCl	4.0	99[c]
$(CH_3)_2CH$	H	CH_3CH_2	None	2.0	1
			2 LiCl	4.0	96[c]
c-C_6H_{11}	H	CH_3CH_2	None	2.0	1
			2 NaCl	3.0	91
				4.0	99[c]

[a] Diester (0.015 mol) and water (0.015 mol) in 25 mL of Me_2SO. [b] GLC analysis of a pentane extract after quenching an aliquot with water and pentane extraction. [c] Distillation from the reaction mixture and washing with water led to about 90% yields of isolated pure ester.

Table V. Decarbomethoxylations of Dimethyl Diethylmalonate

Equiv of salt	Heating period, h	% monoester
None[a]	4.5	2[b]
2 NaCl[a]	4.5	98[c]
2 LiCl[d]	4.0	99[c,e]
2 LiCl[d]	0.5	90[b]
2 KCN[d]	0.5	99[b]
2 LiCl[f]	4.2	98[b]
1 Li_2CO_3[f]	16	6[b]
2 LiOAc·$2H_2O$[f]	4.0	6[b]
1 $MgCl_2$·$6H_2O$[f]	4.0	30[b]
2 LiF[f]	4.0	1[b]
1 LiI·H_2O[f]	4.0	*g*

[a] Diester and water (0.015 mol each) in 25 mL of Me_2SO. [b] GLC analysis of a quenched aliquot. [c] Distilled from the reaction, water washed, and dried (90% isolated yields). [d] Diester and water (0.03 mol each) in 50 mL of Me_2SO. [e] Li_2CO_3 (35%) was also isolated. On distillation, an 80% yield of ester was obtained. [f] Diester and water (0.03 mol each) in 50 mL of DMF. [g] GLC and ^1H NMR of material collected in a Dean–Stark trap indicated the presence of about 30% CH_3I. A 40% yield of Li_2CO_3 could also be isolated.

be isolated from the mixture in 30–40% yields.[43] The remainder of CO_2 is evolved [trapped via $BaCO_3$ with a $Ba(OH)_2$ trap]. Li_2CO_3 exhibits little effect on the rate of decarbomethoxylation in H_2O–DMF (Table V, entry 7). The salt LiF (perhaps present as tight ion pairs) exerts no accelerating effect. Lithium acetate is somewhat effective and $MgCl_2$ is reasonably effective. In the case of LiI·H_2O in DMF, the isolation of CH_3I is mechanistically significant (vide supra).

Comparative data for decarbethoxylations of diethyl diethylmalonate are tabulated in Table VI. Substrates of this type (disubstituted) are the most difficult to decarbethoxylate.

The data in Table VI indicate that the most effective decarbethoxylation combination for this substrate is the H_2O–Me_2SO medium with addition of 2 equiv of KCN or LiCl. Sodium chloride is not as effective as LiCl, since longer heating periods are necessary with the former. Since 0.5 equiv of LiCl in entry 4 leads to 60% reaction after 8 h, Cl^- must be regenerated or a pathway not using Cl^- is competitive. The rate depends on the LiCl concentration, as a fourfold concentration increase doubles the product yield (vide supra for mechanistic data bearing on this point). Once again Li_2CO_3 can be isolated in 35–40% yields in the runs using LiCl, and the remaining CO_2 is lost as the gas.

The decarbethoxylations of diethyl dimethylmalonate and

Table VI. Decarbethoxylations of Diethyl Diethylmalonate

Equiv of salt[a]	% monoester
None	1[b]
2 LiCl	80[c]
2 LiCl	98[d]
0.5 LiCl	40[e]
2 LiCl[f]	23[b]
2 NaCl	30[b,g]
2KCN	43[b,h]

[a] Substrate and water (0.03 mol each) in 50 mL of Me_2SO. Entries 2, 4, 5, and 6 were heated for 4 h; entry 1, 2 h; entry 3, 6 h; and entry 7, 1 h. [b] GLC analysis of a water-quenched aliquot and extracted into pentane. [c] Distillation of the ester from the reaction followed by addition of water and separation of the ester layer. An 85% yield of monoester was obtained which contained only a trace of starting material. A 35% yield of Li_2CO_3 was isolated by filtration of the residue after distillation. [d] Isolated yield after distillation and washing with water. A 30% yield of Li_2CO_3 was isolated. [e] After 8 h total heating, about 60% monoester. [f] As in *a*, except 50 mL of DMF. [g] After 22 h a quenched aliquot showed 85% monoester. This reaction mixture is homogeneous. [h] After 5-h total heating, no starting material is present.

Table VII. Decarbethoxylations of Diethyl Dimethylmalonate

Equiv of salt	% monoester
None[a]	1[b]; 3 (21 h)
1 Na_2SO_4[a]	3[b]
1 HOAc[a]	1[b,c]
1 NaOAc[a]	60[b]
1.5 LiOAc·$2H_2O$[a]	60[b]
1 LiCl[d]	70[b,e]
2 LiCl[d]	97[f]
1 KF·$2H_2O$[d]	18[b]; 56 (20 h)
0.2 Na_3PO_4·$12H_2O$[g]	30[b]; 75 (22 h)
1 KI[a]	22[b]; 50 (20 h)
1 KBr[a]	40[b]; 67 (20 h)
1 KCl[a]	40[b,h]; 72 (20 h)
1 NaCl[a]	40[b,h]; 70 (20 h)
1 KCN[a]	98[b,e]

[a] Diester (0.015 mol) and H_2O (0.03 mol) in 25 mL of Me_2SO. All reactions were run for 4 h except entry 1 (2 h) and entry 7 (5 h). [b] GLC analysis of a quenched aliquot. [c] Also paraformaldehyde from Me_2SO decomposition. [d] As in *a*, except 0.015 mol of H_2O. [e] Eighty percent yields of ester on distillation (99% purity). [f] Ninety percent yield on distillation. [g] No water added. [h] Heterogeneous at start of reaction.

diethyl 1,1-cyclobutanedicarboxylate were also studied using a variety of salts and conditions. The pertinent experimental findings for the former substrate are listed in Table VII.

The data for the cyclobutyl diester is summarized in Table VIII.

As can be noted from the data in Tables VII and VIII, the decarbethoxylations of these substrates can be accomplished by a wide variety of salts. Only Na_2SO_4 (insoluble in the medium) and LiF fail to accelerate the reaction. Acetates (lithium and sodium) are effective but the reaction is not catalyzed by acetic acid. Lithium halides are more effective than the corresponding potassium or sodium halides (except for LiF where KF appears to work more effectively). For the data tabulated in Table VIII, the best decarbethoxylating agent appears to be LiCl, with LiI or LiBr somewhat less effective.

The decarbethoxylation of diethyl dimethylmalonate by Na_3PO_4·$12H_2O$ is of interest. It appears that the effectiveness of this salt may be due to the high pH of its aqueous solutions

Table VIII. Decarbethoxylations of Diethyl 1,1-Cyclobutanedicarboxylate

Equiv of salt	% monoester
0.5 LiOAc·$2H_2O$[a]	80[b]; 85 (6.5 h)
1 LiI·$2H_2O$[a]	93[b,c]
2 LiF[d]	1[b]
2 LiBr[a]	92[b,e]
2 NaCl[d]	60[b]
2 LiCl[d]	99[b,f]

[a] Diester (0.015 mol) and Me_2SO (25 mL) heated for 3 h. [b] GLC analysis of an aqueous quench. [c] Distillation and workup gave pure ester (80%). [d] Diester (0.015 mol) and water (0.03 mol) in 25 mL of Me_2SO heated for 3 h. [e] Distillation and workup gave ester (90% yield, 98% purity). [f] Distillation and workup gave pure ester (85%).

and perhaps a catalysis of the decarbethoxylation by a hydrolysis–decarboxylation pathway.

Several other substrates were also investigated for preparative purposes using LiCl in Me_2SO and the results are listed in Table IX.

Mechanism Studies: (a) H_2O and D_2O Isotope Effects in the Presence and Absence of Salts. The fact that certain β-keto esters and geminal diesters which possess electron-withdrawing groups on the α carbon undergo decarbalkoxylations in H_2O–Me_2SO indicates that a neutral water hydrolysis is occurring. The deuterium isotope effects were studied by comparison of the rates of decarbalkoxylations in H_2O–Me_2SO and D_2O–Me_2SO in the presence and absence of salts. The data are summarized in Table X.

The data in Table X reveal a k_{H_2O}/k_{D_2O} of 2.7 for diethyl phenylmalonate and 2.2 for dimethyl ethylmalonate (no added salts). However, in the presence of the salts LiCl or KCN the k_{H_2O}/k_{D_2O} values are close to unity. In the absence of salts it would appear that the mechanism is of a water-catalyzed nucleophilic attack by water (or a kinetic equivalent) at the ester carbonyl ($B_{AC}2$) similar to the mechanism proposed for neutral (water-catalyzed) hydrolysis of other acyl activated esters.[44] The salts do not appear to be functioning as general base catalysts.[45] In those substrates which do not react with H_2O–Me_2SO, steric factors may prevent water attack at the ester carbonyl.

The absence of a significant isotope effect in the presence of LiCl or KCN is consistent with a nucleophilic catalysis mechanism ($B_{AC}2$ route via a tetrahedral intermediate) involving the nucleophile, or a $B_{AL}2$ route involving the nucleophile.[46,47,48] Of course the total mechanistic route could proceed via the simultaneous occurrence of both routes.

The decarbalkoxylation procedure in D_2O–Me_2SO is a useful preparative route to α-deuterated esters.[49]

(b) CH_3CH_2CN: Alcohol Ratios Using KCN–H_2O–Me_2SO and Various Diesters. Since the most effective decarbalkoxylation reagent system studied by us is the KCN–H_2O–Me_2SO combination, it was of interest to determine the nitrile/alcohol ratios for various substrate structures from the mechanistic point of view. The experimental data for several malonate esters are tabulated in Table XI.

It might also be noted at this point that K_2CO_3 could be isolated in ca. 40% yields from several of the runs listed in Table XI and CO_2 was also evolved as evidenced by trapping as $BaCO_3$. The data presented in Table XI clearly indicate that the mechanistic pathway is dependent on substrate structure. The formation of CH_3CN (from the disubstituted dimethyl ester) and CH_3CH_2CN (from the diethyl esters) can only arise from a $B_{AL}2$ cleavage as depicted in Scheme I.[47]

A concerted decarbalkoxylation to directly yield carbanion **13** must also be considered. It would appear that this process

Table IX. Preparative Decarbethoxylations Using LiCl–Water–Me_2SO

1			Registry	
R^1	R^2	R^3	no.	% monoester
$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	CH_3CH_2	596-75-8	90[b]
CH_3CH_2	C_6H_5	CH_3CH_2	76-67-5	80[b,c]
$CH_3(CH_2)_2CH_2$	H	CH_3CH_2	133-08-4	75[d]; 95 (3 h)[b]

[a] Substrate and water (0.03 mol each) and LiCl (0.06 mol) in 50 mL of Me_2SO. Entries 1 and 2 were isolated by a water quench and extraction with pentane. The heating times were: entry 1, 6 h; entry 2, 4 h; and entry 3, 0.5 h. [b] Isolated yields with less than 1% starting material. [c] A 60% yield of monoester was found by GLC of a quenched aliquot if 50 mL of DMF was used as the solvent. [d] GLC analysis of a quenched aliquot.

Table X. Decarbalkoxylations in Me_2SO with D_2O or H_2O

1			k_{H_2O}/k_{D_2O}[b]		
R^1	R^2	R^3[a]	1 equiv of LiCl	1 equiv of KCN	No salt
C_6H_5	H	CH_3CH_2	1.09	1.10	2.7
CH_3CH_2	H	CH_3CH_2	0.96	1.08	
CH_3CH_2	H	CH_3			2.2
CH_3CH_2	CH_3CH_2	CH_3CH_2	1.0	1.0	No rxn

[a] Three millimole each of malonate ester, H_2O or D_2O, and salt (if any) in 10 mL of dry Me_2SO. [b] Average values for duplicate or triplicate determinations.

would be energetically favorable for those substrates with electron-withdrawing groups that could stabilize the developing carbanionic center. The previous study of Asoaka et al.[29b] indicates that the intermediate **12** ($R^1 = R^2 = CH_3$) can be trapped if the reaction is performed in HMPT with LiCl in the presence of benzyl bromide to yield the monobenzyl diester **14** (30%). An 18% yield of the dibenzyl ester was also isolated. In other cases, the carbanion **13** can be trapped in the presence of benzyl bromide. The formation of acylcyclopropanes by treatment of α-acyl-γ-butyrolactones with various nucleophiles are examples of $B_{AL}2$ cleavages followed by decarboxylations and intramolecular cyclizations of the carbanions which are formed.[29] The conversion of **7a** to **7b** leads to intermediate **15** which is energetically difficult to decarboxylate, and it undergoes a further conversion to the diacid.[10]

The pathway outlined in Scheme I appears to be the dominant mechanistic route for disubstituted malonate esters. The higher nitrile/alcohol ratios seen for the diethyl- vs. the dimethyl-substituted diethylmalonate points to a steric hindrance to attack of the nucleophile at one of the ester carbonyl groups. However, in all cases (except for the dimethyl ester listed) the isolation of ethanol indicates that the $B_{AC}2$ mechanism is competitive. Scheme II presents the mechanism for this route.

Scheme I

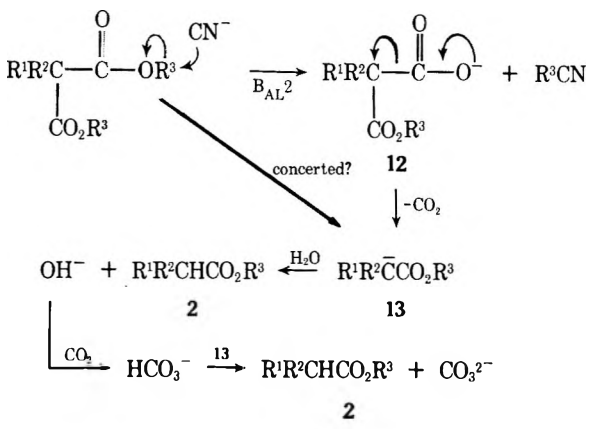
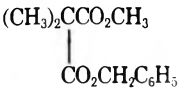


Table XI. Nitrile/Alcohol Ratios from Decarbalkoxylations with NaCN

1			CH_3CH_2CN/
R^1	R^2	R^3	Alcohol[a]
CH_3CH_2	H	CH_3CH_2[b]	0.4[c]
CH_3	H	CH_3CH_2[d]	0.5
CH_3	CH_3	CH_3CH_2[d]	1.4
CH_3CH_2	CH_3CH_2	CH_3CH_2[b]	4.3
CH_3CH_2	CH_3CH_2	CH_3[b]	c,e

[a] GLC analysis of low-boiling material distilled from the reaction after the specified heating period. [b] Substrate (0.03 mol), KCN (0.06 mol), and H_2O (0.03 mol) in 50 mL of Me_2SO. Heating periods for each tabular entry: 1, 1.5 h; 2 and 3, 8 h; 4, 5 h; and 6, 0.5 h. [c] No starting material was detectable. [d] Substrate (0.03 mol), KCN (0.045 mol), and H_2O (0.03 mol) in 50 mL of Me_2SO. [e] Only CH_3CN was detectable. No CH_3OH could be detected by GLC.

Intermediates such as ethyl cyanoformate would be expected to undergo rapid hydrolysis in H_2O–Me_2SO.[50] It might



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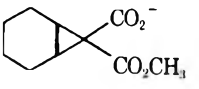

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be pointed out that ester exchanges appear to be catalyzed by KCN in alcohols.[51]

Most simple esters hydrolyze with acyl–oxygen cleavages ($B_{AC}2$) via presumed tetrahedral intermediates. However, in hindered esters the $B_{AL}2$ route can eclipse the usual $B_{AC}2$ pathway.[52] In symmetrical transesterifications such as the treatment of methyl benzoate with sodium methoxide in methanol, good yields of dimethyl ether can be obtained.[52c] Under certain conditions the E1cB mechanism via a ketene intermediate must be considered for those substrates with at least one α hydrogen.[53] Variations in the alkoxyl group of the

Scheme II

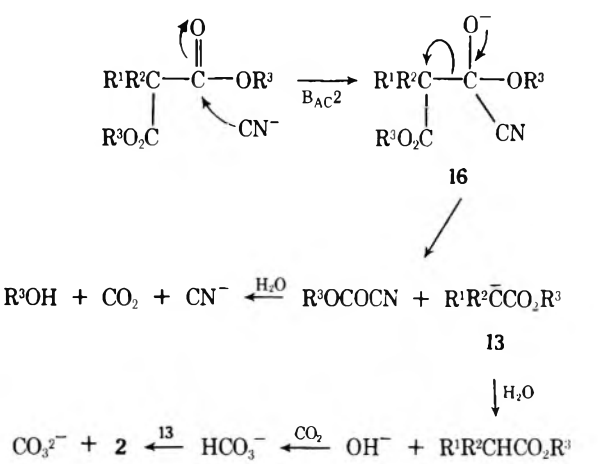

Table XII. LiCl Concentration Variation Study

Equiv of LiCl[a]	k_{rel}[b]
1	1
2	1.6
3	2.2
4	2.6
5	3.3
6	3.6
7	3.7
8	4.0
9	4.1
10	4.3

[a] Three millimole each of diethyl diethylmalonate, water, and LiCl (or multiple thereof) in 10 mL of dry Me_2SO. [b] $k_{rel} = k_{conc}/k_{1equiv}$ (see Experimental Section).

ester have less effect on the $B_{AC}2$ route than the $B_{AL}2$ route.[47] The nucleophilic species must also play a role in the mechanistic pathway.[54]

The observation that methanol could not be detected in the decarbomethoxylation of dimethyl diethylmalonate by KCN–H_2O–Me_2SO indicates that this substrate reacts via the $B_{AL}2$ pathway outlined in Scheme I. The other diesters listed in Table XI exhibit dual pathways in which disubstituted malonates react predominantly via the $B_{AL}2$ route, while monosubstituted malonates react predominantly via the $B_{AC}2$ route.[55]

(c) LiCl Concentration Variations. In order to assess the kinetic effect of the nucleophile, the decarbethoxylation of diethyl diethylmalonate was studied using LiCl–H_2O–Me_2SO. This substrate was chosen since it was anticipated that the dominant route would be of the $B_{AL}2$ type. The LiCl concentrations were varied over a range of 1 to 10 equiv per equivalent of diester, and the data are summarized in Table XII.

It can be seen from the data that the rate is dependent on the concentration of LiCl but does not exhibit a first-order dependency of LiCl concentration. The largest rate increase is seen up to the addition of 5 equiv of LiCl, and further concentration increase lead to much smaller enhancements of the decarbethoxylation rate. It is probable that ion pairing or association is playing a role in controlling the apparent nucleophilicity and observed rates.[56]

(d) Relative Rates with Various Salts. Relative rates of ester decarbethoxylation can give information on whether the $B_{AC}2$ mechanism is operative (alkoxyl group variations have small effects) or whether the $B_{AL}2$ route is operative (comparison to S_N2 routes).[47a] Competition experiments were performed on several methyl and ethyl diesters and the relative rate data are tabulated in Table XIII.

From the data presented in Table XIII, it is reasonable to conclude that monoalkyl-substituted malonates on treatment with LiCl–H_2O–Me_2SO are undergoing cleavages via a dominant $B_{AC}2$ attack of Cl^- on one of the ester carbonyl groups ($k_{CH_3}/k_{CH_3CH_2} = 4$).[47a,57] The relative rate of 30.5 found for the KCN–H_2O–Me_2SO reaction on diethyl ethylmalonate appears to be inconsistent with the nitrile/alcohol ratio data in Table XI and is anomalous. Perhaps with KCN a more dominant role for the $B_{AL}2$ route is being exerted for the dimethyl ester and an enhanced value of the relative rate ratio is seen. The relative rates of 17.1 (LiCl) and 35.1 (KCN) for the decarbalkoxylations of the diethyl-substituted malonates are consistent with a dominant pathway for $B_{AL}2$ cleavages.[58,59]

(e) Salt Effects. It was of interest to examine a series of salts with a single diester under comparable reaction conditions to ascertain the best salt to be utilized for preparative purposes. The relative rates for various salts were studied in H_2O–Me_2SO using diethyl diethylmalonate (perhaps in each case undergoing a dominant $B_{AL}2$ cleavage). The relative rate data are tabulated in Table XIV.

Although the rate differences listed in Table XIV are small and the relative nucleophilicities can vary with solvation, nature of the cation, and nature of the transition state,[56d,60] it is tempting to attempt to rationalize the experimental data using HSAB principles[61] and symbiosis.[8c,61,62]

If one assumes that all nucleophiles are cleaving this malonate ester predominantly via a $B_{AL}2$ pathway (Scheme I), the order of rates with the cation Li^+ (hard) constant is $Cl^- > Br^- > I^-$, which is the order of decreasing hardness.[63] However, the position of OAc^- (hard) is out of order, as it might have been expected that OAc^- being harder than Cl^- would exert a larger symbiotic effect (in addition a symmetrical-like transition state with respect to entering and leaving group[8c]) than Cl^-. The relative position of CN^- (soft, and used as the K^+ salt which could alter the nucleophilicity somewhat) would be higher than Cl^- and thus constitutes an anomaly. Steric effects could play a role in hindering approach of a multiatomic anion such as OAc^- and comparison to halide anions may be unjustified. The question of loose and tight transitions states along with symbiotic effects might well have to be considered.[56d]

It can be seen from the data in Table XIV that little rate differences are found in the comparison of LiCl vs. $(CH_3)_4NCl$ and LiOAc and $(CH_3)_4NOAc$. The unreactivity of CuCl (soluble in Me_2SO) might simply be due to ion pairing or solution as Cu_2Cl_2 with reduced nucleophilicity of Cl^-. It would appear that LiCl should be used in preference to LiI in dipolar aprotic solvents to effect more rapid displacements.

Table XIII. Competition Experiments Using Various Malonate Esters

Ester pair[a]	Salt	$k_{CH_3}/k_{CH_3CH_2}$[b]
$CH_3CH_2CH(CO_2CH_3)_2$ $CH_3CH_2CH(CO_2CH_2CH_3)_2$	LiCl	3.9 ± 0.1[c]
$CH_3CH_2CH(CO_2CH_3)_2$ $CH_3CH_2CH(CO_2CH_2CH_3)_2$	KCN	30.5[d]
$(CH_3CH_3)_2C(CO_2CH_3)_2$ $(CH_3CH_2)_2C(CO_2CH_2CH_3)_2$	LiCl	17.1 ± 0.1[c]
$(CH_3CH_2)_2C(CO_2CH_3)_2$ $(CH_3CH_2)_2C(CO_2CH_2CH_3)_2$	KCN	35.1[d]

[a] Three millimole each of diesters, salt, and water in 10 mL of dry Me_2SO with refluxing for periods of 15, 6, 45, and 45 min, respectively. [b] Calculated from: $k_{CH_3}/k_{CH_3CH_2} = \log (x CH_3/x_0 CH_3)/\log (x CH_3CH_2/x_0 CH_3CH_2)$, where x = % unreacted diester (determined by GLC) and $x_0 = 100$ for the diesters. See, for example: P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, 78, 5430 (1956). [c] Average values for two runs and standard deviations. [d] Single determination.

Table XIV. Relative Rates of Salts in Decarbethoxylations

Salt[a]	k_{salt}/k_{LiCl}	k_{salt}/k_{LiI}
LiCl	1	3.1
$(CH_3)_4NCl$	0.75	2.3
CuCl[b]		
LiI	0.32	1
$(CH_3)_4NI$[c]		
LiBr	0.65	2.0
LiOAc	0.56	1.8
$(CH_3)_4NOAc$	0.34	1.0

[a] Performed in a common oil bath with one run containing 1 equiv of LiCl and the other 1 equiv of the listed salt. Substrate in all cases was diethyl diethylmalonate. Relative rates were determined as previously reported (see Table XIII and Experimental Section). [b] Soluble but no reaction after heating for 2 h. [c] Several side products and much decomposition. Not analyzed further.

Conclusions

Certain activated esters have been shown to undergo rapid decarbalkoxylations in wet Me_2SO while other substrates require the presence of salts. The data indicate that LiCl–H_2O–Me_2SO is an excellent salt for preparative decarbalkoxylations. The decarbalkoxylation mechanism is a blend of $B_{AL}2$ and $B_{AC}2$ pathways which are dependent on substrate structure and nucleophile type. A variety of salts can be effectively used in this process.

Experimental Section

All GLC analyses were performed using a DC-200 Chromosorb column with helium as the carrier gas and are corrected for any structural response change. The analyses were performed using a Gow-Mac 69-100 or an Aerograph A-90P chromatograph.

Materials. Me_2SO was kindly supplied by Crown-Zellerbach (Camas, Washington) or was purchased from Fisher Scientific Co. (certified grade) or Mallinckrodt (AR grade). The Me_2SO was dried by distillation from CaH_2 under reduced pressure and it was stored over molecular sieves. All salts (reagent grade) were used as received except for preliminary drying in a few cases. All malonate esters and most β-keto esters were commercially available from Aldrich, Eastman Organics, Pfaltz and Bauer, or ICN Life Sciences Group (K & K). The β-keto esters, 2-carbethoxycyclooctanone, and 2-carbethoxycyclododecanone were prepared according to the procedure described by Krapcho et al.[64] All ketones and esters which were prepared have been previously reported in the literature and compared favorably with the physical properties previously recorded and exhibited IR and NMR spectra consistent with their structures.

(A) Typical Preparative Runs. (a) 2, R^1 = H, R^2 = $(CH_3)_2CH$, R^3 = CH_3CH_2. In a 100-mL rb flask equipped with a magnetic spin bar and a reflux condenser are placed diethyl isopropylmalonate (6.1 g, 0.03 mol), Me_2SO (50 mL, Mallinckrodt AR, as received), water (0.5 mL), and LiCl (2.5 g, 0.06 mol). The solution is heated to refluxing using a mantle with stirring for 4 h. During this period, the mixture becomes turbid and pale yellow. A quenched aliquot and GLC analysis indicated only about 4% malonate ester. The mixture was distilled up to 185 °C to obtain about 10 g of distillate. Cold water was added to this distillate and the ester layer was removed by a pipet to yield 4.0 g of crude ester (GLC analysis showed less than 1% starting diester and trace amounts of low-boiling materials). Distillation (bp 129–132 °C, lit. bp 131–133 °C[65]) yielded 3.5 g of ester (90%).

(b) 2, R^1 = R^2 = R^3 = CH_3CH_2. Diethyl diethylmalonate (6.4 g, 0.03 mol), Me_2SO (50 mL, Fisher certified, as received), water (0.5 g, 0.03 mol), and LiCl (2.5 g, 0.06 mol) were placed in a 100-mL rb flask fitted with a gas-exit tube leading into a $Ba(OH)_2$ solution, a magnetic spin bar, and a heating mantle. The solution was heated at refluxing for a total period of 6 h. During this period, a turbidity appears and the mixture becomes yellow and the color then disappears. The mixture is then distilled up to 185 °C to yield about 7 g of distillate. The distillate is washed with ice water and the ester layer collected (4.1 g, 95%). GLC shows less than 1% starting diester and traces of short retention time materials (bp 148–151 °C, lit. bp 151 °C[65]). Filtration of the residue after the distillation of the ester from the reaction pot gave Li_2CO_3 (0.7 g, 30% of the CO_2 trapped as this salt) which was identified by an IR comparison to an authentic sample. Some CO_2 was also evolved as evidenced by much $BaCO_3$ formation in the $Ba(OH)_2$ during the course of the reaction.

Using procedures as in a and b above, ethyl cyclobutanecarboxylate, methyl 2-ethylbutyrate, ethyl cyclohexylacetate, ethyl isobutyrate, ethyl 4-methylvalerate, and ethyl hexanoate can be prepared.

(c) Ethyl 2-Phenylpropionate (2, R^1 = C_6H_5, R^2 = H, R^3 = CH_3CH_2). Diethyl phenylethylmalonate (7.9 g, 0.03 mol, Eastman practical grade), Me_2SO (50 mL, Mallinckrodt, AR), water (0.5 g, 0.03 mol), and LiCl (2.5 g, 0.06 mol) were placed in a 100-mL rb flask equipped with a magnetic stirrer and fitted with a condenser. The mixture was heated at refluxing for 4 h. At this point, a brown color had developed and suspended solid (Li_2CO_3) was evident. The mixture was poured into 200 mL of ice water and the aqueous layer was saturated with NaCl. The ester was extracted with 4 × 30 mL of pentane, and the yellow pentane extract was dried over Na_2SO_4 and concentrated to yield 4.6 g (80%) of ester which on GLC contained less than 0.5% starting material. Distillation under reduced pressure gave a bp of 120–125 °C/25 mm (lit. bp 123–124 °C/27 mm[65]). Ethyl hydrocinnamate and ethyl 2-*n*-butylhexanoate were isolated using a similar workup.

(B) Analytical Runs. All tabular data were obtained by quenching the reaction at a specified interval in cold water (usually a 2-mL aliquot), saturating the water with NaCl, extraction with pentane, and GLC analysis of the pentane extract.

(C) D_2O and H_2O Runs. Two runs were performed simultaneously in the same oil bath, and both reactions were quenched with water, extracted with pentane, and analyzed by GLC. In the water run, 3

Table XV. Decarbalkoxylations Using H_2O or D_2O in Me_2SO

1								
R^1	R^2	R^{3a}	Salt	Temp[b]	Rxn time, h	% diester[c] in H_2O	% diester[c] in D_2O	k_{H_2O}/k_{D_2O}[d]
C_6H_5	H	CH_3CH_2	None	177	0.75	20.9	51.2	2.4
			None	177	0.50	30.2	67.1	3.0
			LiCl	182	0.50	13.6	15.1	1.06
			LiCl	157	0.25	75.7	77.8	1.11
			KCN	157	0.25	17.9	20.8	1.10
CH_3CH_2	H	CH_3	None	185	4.0	39.6	66.5	2.27
			None	185	4.0	50.7	72.7	2.13
CH_3CH_2	H	CH_3CH_2	LiCl	175	0.50	66.5	66.6	1.00
			LiCl	180	0.50	67.2	67.1	0.99
			KCN	175	0.30	43.8	46.7	1.08
CH_3CH_2	CH_3CH_2	CH_3CH_2	LiCl	192	2.0	55.8	55.3	0.98
			LiCl	192	1.5	62.9	63.7	1.03
			KCN	192	2.0	16.7	19.2	1.08
			KCN	189	0.75	42.2	42.8	1.02

[a] In most cases, the pairs were run twice, sometimes for different periods of time. [b] Oil bath temperature, ±2 °C. [c] Average values for three GLC analyses with excellent agreement for each analysis. [d] k_{H_2O}/k_{D_2O} = log [% diester (H_2O)/100]/log [% diester (D_2O)/100].

Table XVI. Competition Experiments

Diester pairs, 1			Rxn[a]		% dimethyl[b]	% diethyl[b]	
R^1	R^2	R^3	time	Salt	remaining	remaining	$k_{CH_3}/k_{CH_3CH_2}$
CH_3CH_2	H	CH_3CH_2	0.3	LiCl	27.9	73.0	4.06
CH_3CH_2	H	CH_3	0.25	LiCl	18.6	64.5	3.84
			0.08	KCN	23.8	95.4	30.5
CH_3CH_2	CH_3CH_2	CH_3CH_2	0.75	LiCl	20.5	91.1	17.0
CH_3CH_2	CH_3CH_2	CH_3	0.50	LiCl	23.0	91.8	17.2
			0.75	KCN	7.0	92.7	35.1

[a] Timing starts with CO_2 evolution, in hours. [b] Average values for triplicate GLC analysis (agreements in all cases better than 2%).

Table XVII. LiCl Concentration Studies Using Diethyl Diethylmalonate

Rxn time,[a] h	% diester[b] Stdn, 1 equiv of LiCl	% diester[b] xLiCl	Ratio xLiCl/LiCl	k_{rel}[c]	Av k_{rel}
1.5	58.2	42.7	2	1.57	1.56
2.0	51.9	36.2	2	1.55	
1.5	61.0	32.7	3	2.26	2.21
2.0	54.8	27.4	3	2.15	
1.5	59.6	24.3	4	2.73	2.67
1.0	70.0	39.5	4	2.60	
0.9	75.9	40.2	5	3.30	3.30
1.0	71.7	33.2	5	3.31	
1.0	70.4	28.3	6	3.60	3.59
1.06	65.5	22.0	6	3.58	
1.0	71.2	28.6	7	3.69	3.66
0.75	78.1	40.9	7	3.62	
0.75	83.4	49.3	8	3.90	4.02
0.80	77.8	35.4	8	4.14	
0.75	77.9	35.1	9	4.16	4.14
0.80	78.9	37.7	9	4.12	
0.75	78.9	34.7	10	4.47	4.38
1.0	70.5	22.4	10	4.28	

[a] Heated in an oil bath at 190 ± 2 °C. [b] Average of duplicate GLC analysis with a precision of better than ±0.5%. [c] k_{rel} = log [% diester (xLiCl)/100]/log [% diester (1 equiv of LiCl)/100].

Table XVIII. Decarbethoxylations of Diethyl Diethylmalonate

Reaction time, h	Salt	% diester[a] in LiCl run	% diester[a] in salt run	k_{salt}/k_{LiCl}[b]	Av k_{rel}
1.5	$(CH_3)_4NCl$	78.7	82.3	0.77	0.74
2.0		69.9	77.4	0.71	
1.5	$LiI \cdot H_2O$	65.6	87.1	0.33	0.32
2.0		58.8	84.5	0.32	
1.5	LiBr	66.0	77.6	0.64	0.66
2.0		54.9	66.7	0.68	
1.5	LiOAc	63.5	76.5	0.59	0.57
2.0		58.3	74.3	0.55	
2.0	$(CH_3)_4NOAc$	57.7	83.2	0.33	0.34
2.5		52.9	80.7	0.34	

[a] Average values of duplicate GLC analysis. [b] k_{salt}/k_{LiCl} = log [% diester (salt)/100]/log [% diester (LiCl)/100].

mmol each of diester, H_2O, and salt (if present) was dissolved in Me_2SO (10 mL, dry) in a 25-mL rb flask equipped with a condenser and a magnetic stirrer. The D_2O run was prepared in an identical fashion, except that D_2O was used. Both runs were immersed in the oil bath and worked up in an identical fashion. A summary of the experimental data is listed in Table XV.

(D) Competition Experiments. Three millimoles of each diester, H_2O, and salt was dissolved in Me_2SO (10 mL, Mallinckrodt AR, as received) in a 25-mL rb flask equipped with a magnetic spin bar and a condenser. The mixture was then heated to refluxing for the specified period, quenched, and analyzed by GLC. The experimental results are listed in Table XVI.

(E) LiCl Concentration Effect Study. Duplicate runs were performed simultaneously in the same oil bath. In the standard com-

parison run diethyl diethylmalonate (3 mmol), LiCl (3 mmol), and H_2O (3 mmol) were dissolved in 10 mL of Me_2SO (dry). In the run to assess the salt effect the only variation was the amount of LiCl added. Both runs were heated for identical periods and analyzed as previously. The data are tabulated in Table XVII.

(F) Salt Effects. In a 25-mL rb flask was placed diethyl diethylmalonate (3 mmol), LiCl (3 mmol), H_2O (3 mmol), and 10 mL of Me_2SO (dry). Another run is prepared in similar fashion, except containing another salt (3 mmol). Both runs are simultaneously immersed in an oil bath preheated to 190 ± 2 °C. After the specified reaction period, the reactions are quenched in water and analyzed by VPC. These data are summarized in Table XVIII.

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Registry No.—Me_2SO, 67-68-5; 2-carbomethoxycyclohexanone, 41302-34-5; 2-carbethoxycyclohexanone, 01655-07-8; diethyl 1,1-cyclobutanedicarboxylate, 3779-29-1.

References and Notes

(1) Presented in part at the 172nd American Chemical Society National Meeting, San Francisco, Calif., Aug. 30–Sept. 3, 1976, ORGN Abstract 196.

(2) National Science Foundation Undergraduate Research Participant, Summer 1975.

(3) (a) A. P. Krapcho, G. A. Glynn, and B. J. Grenon, *Tetrahedron Lett.*, 215 (1967). (b) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis", Vol. 2, Wiley-Interscience, New York, N.Y., p 381 (1969).

(4) A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, 957 (1973).

(5) (a) A. P. Krapcho, E. G. E. Jahngen, Jr., A. J. Lovey, and F. W. Short, *Tetrahedron Lett.*, 1091 (1974). (b) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis", Vol. 5, Wiley-Interscience, New York, N.Y., p 265 (1975).

(6) C. L. Liotta and F. L. Cook, *Tetrahedron Lett.*, 1095 (1974). It is stated in this paper that "sodium chloride appears to be an unnecessary reagent".

(7) A. P. Krapcho and B. P. Mundy, *Tetrahedron* **26,** 5437 (1970).

(8) (a) J. Harley-Mason and Atta-ur-Rahman, *Chem. Ind. (London)*, 1845 (1968). (b) W. S. Johnson, C. A. Harbert, and R. D. Stipanovic, *J. Am. Chem. Soc.*, **90,** 5279 (1968). (c) W. S. Johnson, C. A. Harbert, B. E. Ratcliffe, and R. D. Stipanovic, *ibid.*, **98,** 6188 (1976). (d) F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 258 (1972). (e) E. J. Corey and H. A. Kirst, *J. Am. Chem. Soc.*, **94,** 667 (1972). (f) E. E. van Tamelen and R. J. Anderson, *ibid.*, **94,** 8225 (1972). (g) E. E. van Tamelen, M. P. Seiler, and W. Wierenga, *ibid.*, **94,** 8229 (1972). (h) F. Collonges and G. Descotes, *Tetrahedron Lett.*, 1117 (1973). (i) R. V. Venkateswaran, I. Gupta, and P. K. Ghoshal, *Indian J. Chem., Sect. B,* **14,** 243 (1976). (j) W. Kirmse, J. Knist, and H.-J. Ratajczak, *Chem. Ber.*, **109,** 2296 (1976).

(9) L. J. Dolby and H. Biere, *J. Org. Chem.*, **35,** 3843 (1970).

(10) B. W. Peace and D. S. Wulfman, *Synthesis*, 137 (1973).

(11) (a) B. M. Trost and T. J. Dietsche, *J. Am. Chem. Soc.*, **95,** 8200 (1973). (b) B. M. Trost, T. J. Dietsche, and T. J. Fullerton, *J. Org. Chem.*, **39,** 737 (1974). (c) B. M. Trost and L. Weber, *ibid.*, **40,** 3617 (1975). (d) J. E. McMurry and G. B. Wong, *Synth. Commun.*, **2,** 389 (1972).

(12) (a) P. Müller and B. Siegfried, *Tetrahedron Lett.*, 3565 (1973). (b) P. Müller and B. Siegfried, *Helv. Chim. Acta*, **57,** 987 (1974). (c) A. Greene and P. Crabbé, *Tetrahedron Lett.*, 2215 (1975).

(13) (a) O. P. Vig, S. S. Bari, O. P. Sood, and S. D. Sharma, *Indian J. Chem., Sect. B,* **14,** 438 (1976). (b) J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron Lett.*, 4035 (1975).

(14) (a) P. Goswani, R. V. Venkateswaran, and P. C. Dutta, *Indian J. Chem., Sect. B,* **14,** 299 (1976). (b) S. Torii, H. Tanaka, and T. Mandai, *J. Org. Chem.*, **40,** 2221 (1975). (c) P. M. McCurry and K. Abe, *Tetrahedron Lett.*, 1387 (1974). (d) B. S. Huang, E. J. Parish, and D. H. Miles, *J. Org. Chem.*, **39,** 2647 (1974). Certain substrates would probably decarbalkoxylate with H_2O–Me_2SO without added NaCl.

(15) (a) A. Bernhard, *Justus Liebigs Ann. Chem.*, **282,** 153 (1894). (b) D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Am. Chem. Soc.*, **66,** 1286 (1944). These authors claim that this reaction proceeds in a poor yield, but they also report the addition of a small amount of sulfuric acid which might have effected the further decarbethoxylation of the initially formed β-keto ester to acetophenone.

(16) J. B. Paine III, W. B. Kirshner, D. W. Moskowitz, and D. Dolphin, *J. Org. Chem.*, **41,** 3857 (1976), and references cited therein. The ethyl propionylacetate is contaminated with about 20% diethyl malonate (from acyl cleavage).

(17) H. Meerwein, *Justus Liebigs Ann. Chem.*, **398,** 242 (1913), reports that substrates such as 2-carbomethoxycyclopentanone and ethyl benzoylacetate yield ketones on treatment with water under these conditions. It was also reported that diethyl phenylmalonate on heating with water in a bomb at 250 °C undergoes a decarbethoxylation to yield ethyl phenylacetate, but this ester is partially hydrolyzed under the rigorous reaction conditions.

(18) H. Meerwein and W. Schürmann, *Justus Liebigs Ann. Chem.*, **398,** 196 (1913).

(19) (a) A. T. Nielsen and W. R. Carpenter, *Org. Synth.*, **5,** 288 (1973). (b) H. Musso and D. Döpp, *Chem. Ber.*, **97,** 1147 (1964).

(20) J. R. Vincent, A. F. Thompson, Jr., and L. I. Smith, *J. Org. Chem.*, **3,** 603 (1939). A few pieces of glass were added to the water.

(21) A. E. Greene, A. Cruz, and P. Crabbé, *Tetrahedron Lett.*, 2707 (1976). This method appears to proceed satisfactorily for cyclic β-keto esters with at least one α hydrogen. Long periods of heating are required for most compounds and this procedure would appear to offer no advantages to the method described in ref 5.

(22) Other related but nonaqueous decarbalkoxylations of β-keto esters include: J. M. Lalancette and A. Lahance, *Tetrahedron Lett.*, 3903 (1970), boric anhydride at 150 °C; P. A. Wehrli and V. Chu, *J. Org. Chem.*, **38,** 3436 (1973), boric acid at 150–170 °C.

(23) For examples, see: J. R. Johnson and F. D. Hager, *Org. Synth.*, **1,** 351 (1944).

(24) (a) F. Elsinger, *Org. Synth.*, **5,** 76 (1973), and references cited therein. (b) J. Kossanyi, B. Furth, and J. P. Morizur, *Tetrahedron Lett.*, 3459 (1973).

(25) (a) K. Kondo, T. Umemoto, Y. Takahatake, and D. Tunemoto, *Tetrahedron Lett.*, 113 (1977). (b) D. Tunemoto, N. Araki, and K. Kondo, *ibid.*, 109 (1977).

(26) (a) I. T. Harrison, V. R. Fletcher, and J. H. Fried, *Tetrahedron Lett.*, 2733 (1974). (b) K. Kondo, E. Hiro, and D. Tunemoto, *ibid.*, 4489 (1976).

(27) (a) D. Y. Chang, S. H. Lee, and H. C. Lee, *J. Org. Chem.*, **32,** 3716 (1967). (b) D. Y. Chang, C. F. Yam, S. Y. Chan, S. H. Lee, and H. C. Lee, *ibid.*, **31,** 3267 (1966).

(28) G. A. Smith and D. H. Williams, *J. Chem. Soc., Perkin Trans. 1,* 2811 (1972).

(29) (a) S. Takei and Y. Kawano, *Tetrahedron Lett.* 4389 (1975). (b) M. Asaoka, K. Miyake, and H. Takei, *Chemistry Lett.*, 1149 (1975).

(30) J. J. Wilczynski and H. W. Johnson, Jr., *J. Org. Chem.*, **39,** 1909 (1974), obtained methyl acetate in a 35% yield.

(31) E. S. Behare and R. B. Miller, *J. Chem. Soc. D,* 402 (1970).

(32) (a) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43,** 113 (1960), and references cited therein. (b) P. D. G. Dean, *J. Chem. Soc.*, 6655 (1965). (c) P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970).

(33) P. Ykman and H. K. Hall, Jr., *Tetrahedron Lett.*, 2429 (1975).

(34) N. Ono, H. Eto, R. Tamura, and J. Hayami, *Chem. Lett.*, 757 (1976).

(35) (a) B. M. Trost and T. R. Verhoeven, *J. Org. Chem.*, **41,** 3215 (1976). (b) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 98, 630 (1976).

(36) F. B. Thole and J. F. Thorpe, *J. Chem. Soc.*, **99,** 2183, 2187 (1911).

(37) C. K. Ingold and J. F. Thorpe, *J. Chem. Soc.*, **115,** 143 (1919).

(38) A. C. Cope and S. M. McElvain, *J. Am. Chem. Soc.*, **54,** 4311, 4319 (1932).

(39) D. H. Miles and B. S. Huang, *J. Org. Chem.*, **41,** 208 (1976), and references cited therein. Side reactions and poor conversions in certain disubstituted systems render these processes less useful.

(40) E. J. Parish, B. S. Huang, and D. H. Miles, *Synth. Commun.*, **5,** 341 (1975).

(41) F. Texier, E. Marchand, and R. Carrié, *Tetrahedron*, **30,** 3185 (1974). Competitive amide formation except in a few methyl esters distracts from the preparative use of this method.

(42) T. M. Santosusso and D. Swern, *J. Org. Chem.*, **41,** 2762 (1976); acids generated in Me_2SO decomposition do not appear to catalyze this reaction.

(43) It is reported in ref 9 that in the conversion of **6a** to **6b** with KCN–DMF that only 13% of the calculated CO_2 is evolved. The white precipitate which was reported as being formed is probably K_2CO_3.

(44) (a) J. F. J. Engbersen and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **97,** 1563 (1975). (b) T. H. Fife and D. M. McMahon, *ibid.*, **91,** 7481 (1969).

(45) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **83,** 1743 (1961).

(46) For a compilation of solvent isotope effects, see: S. L. Johnson, "Advances in Physical Organic Chemistry", Vol. 5, V. Gold, Ed., Academic Press, New York, N.Y., 1967, p 281.

(47) (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2nd ed, Cornell University Press, Ithaca, N.Y., 1969, p 1131; for a review of ester hydrolysis mechanisms. (b) For reviews, see: A. J. Kirby, *Compr. Chem. Kinet.*, **10,** 57 (1972); R. E. J. Talbot, *ibid.*, 209 (1972).

(48) For data on Me_2SO, see: H. H. Szmant, "Dimethyl Sulfoxide", S. W. Jacob, E. E. Rosenbaum, and D. C. Wood, Ed., Marcel Dekker, New York, N.Y., 1971.

(49) For example, heating diethyl ethylmalonate with D_2O–Me_2SO leads to ethyl butyrate with an 80–90% incorporation of D at the α carbon. Further studies of the syntheses of other deuterated esters and ketones will be reported shortly.

(50) (a) D. H. R. Barton and C. P. Forbes, *J. Chem. Soc., Perkin Trans. 1,* 1614 (1975). (b) D. H. R. Barton, B. J. Garner, and R. H. Wightman, *J. Chem. Soc.*, 1855 (1964).

(51) K. Mori, M. Tominaga, T. Takigawa, and M. Matsui, *Synthesis*, 790 (1973). The conversion of methyl palmitate to ethyl palmitate in the presence of 0.65% KCN in ethanol occurs overnight. An acyl cyanide intermediate may be involved.

(52) (a) F. C. Chang and N. F. Wood, *Tetrahedron Lett.*, 2969 (1964). (b) L. R. C. Barclay, N. D. Hall, and G. A. Cooke, *Can. J. Chem.*, **40,** 1981 (1962). (c) J. F. Bunnett, M. M. Robison, and F. C. Pennington, *J. Am. Chem. Soc.*, **72,** 2378 (1950). (d) C. A. Bunton, A. E. Comyns, J. Graham, and J. R. Quayle, *J. Chem. Soc.*, 3817 (1955).

(53) (a) R. F. Pratt and T. C. Bruice, *J. Am. Chem. Soc.*, **92,** 5956 (1970). (b) B. Holmquist and T. C. Bruice, *ibid.*, **91,** 2993, 3003 (1969); hydrolysis of malonate esters are reported.

(54) E. W. Thomas and T. I. Crowell, *J. Org. Chem.*, **37,** 744 (1972).

(55) In ref 27a, the decarbethoxylations of $CH_3COOR^1R^2CO_2Et$ with $CaI_2 \cdot 2H_2O$ for $R^1 = R^2 = H$ and $R^1 = H$, $R^2 = CH_3$ gave EtI/EtOH ratios of 1.7 and 11.7, respectively. In the case of $R^1 = R^2 = CH_3$ only EtI was isolated in a 78% yield. These results are consistent with a dominant $B_{AL}2$ attack of I^- in the disubstituted case and a greater contribution of $B_{AC}2$ attack in the mono- and unsubstituted cases.

(56) (a) P. Müller and B. Siegfried, *Helv. Chim. Acta*, **55,** 2400, 2965 (1972). In HMPT, no linear dependence on LiCl concentration was found in the S_N2

displacement on ethyl tosylate. (b) J. F. Normant and H. Deshayes, *Bull. Soc. Chim. Fr.*, 1001 (1969). (c) S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens, and J. S. Gall, *Tetrahedron Lett.*, **9**, 24 (1960); solvents and nature of cation drastically effect apparent nucleophilicities. (d) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969); a review on protic–dipolar aprotic solvent effects on rates of bimolecular processes.

(57) Although media effects are important, the alkaline hydrolysis of methyl acetate vs. ethyl acetate exhibits a $k_{CH_3}/k_{CH_3CH_2}$ of about 2 (ref 47a).

(58) The $k_{CH_3}/k_{CH_3CH_2}$ for a simple ester with $B_{AL}2$ cleavage has been reported as 49 using molten thiocyanate salts (ref 54).

(59) (a) A. J. Streitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962, p 73; average values for a series of S_N2 displacements of about 30. (b) A $k_{CH_3}/k_{CH_3CH_2}$ of 17 was reported for the alkylative decarbalkoxylation of a *N*-carbalkoxypyrazole with Cl^- (ref 30). (c) A $k_{CH_3}/k_{CH_3CH_2}$ of 72 was reported for the decarbalkoxylation of 2-benzyl-2-carboalkoxycyclopentanone with NaCN–HMPT (ref 12a).

(60) C. L. Liotta and E. E. Grisdale, *Tetrahedron Lett.*, 4205 (1975), and references cited therein.

(61) (a) A volume containing reprints of important papers in this area has recently been published: R. G. Pearson, Ed., "Hard and Soft Acids and Bases", Dowden, Hutchinson, and Ross, Inc., Stroudsburg, Pa., 1973. (b) T. L. Ho, *Chem. Rev.*, **75**, 1 (1975). (c) J. F. Bunnett and J. D. Reinheimer, *J. Am. Chem. Soc.*, **84**, 3284 (1962), and references cited therein. (d) For a paper criticizing symbiotic effects, see: W. S. Trahanovsky and M. P. Doyle, *Chem. Commun.*, 1021 (1967). See also ref 56d.

(62) L. B. Engemyr and J. Songstad, *Acta Chem. Scand.*, **26**, 4179 (1972): symbiotic effects are greater for S_N2 displacements in dipolar aprotic solvents than in protic media.

(63) (a) In ref 12a for displacements of 2-benzyl-2-carbomethoxycyclopentanone in HMPT with LiCl or LiBr the relative reactivities are reported to be 2.4:1. (b) In ref 30 the alkylative decarboxylation of *N*-carbomethoxypyrazoles were studied in Me_2SO and the k_X-/k_{I^-} rate ratios are 5.1, 3.0, and 1.0 for Cl^-, Br^-, and I^-, respectively. (c) R. Fuchs and K. Mahendran, *J. Org. Chem.*, **36**, 730 (1971); S_N2 reactions for unassociated X^- for primary alkyl *p*-toluene sulfonates are listed as $Cl^-/Br^-/I^-$ = 8:3:1 (Me_2SO) with the tetra-*n*-butylammonium cation.

(64) A. P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, *Org. Synth.*, **5**, 198 (1973).

(65) I. Heilbron, et al., Eds., "Dictionary of Organic Compounds", Oxford University Press, New York, N.Y., Vol. 1–5, 1965; all esters are listed except **2** ($R^1 = R^2 = n$-butyl, R^3 = ethyl) which is reported in M. Rouchi-Laridjani and M. Vilkas, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **254**, 1090 (1962), and ester **2** (R^1 = phenyl, R^2 = H, and R^3 = ethyl) which is reported in H. Laatc and R. Isotalo, *Acta Chem. Scand.*, **21**, 2119 (1967).

Vinyllithium Reagents from Arenesulfonylhydrazones

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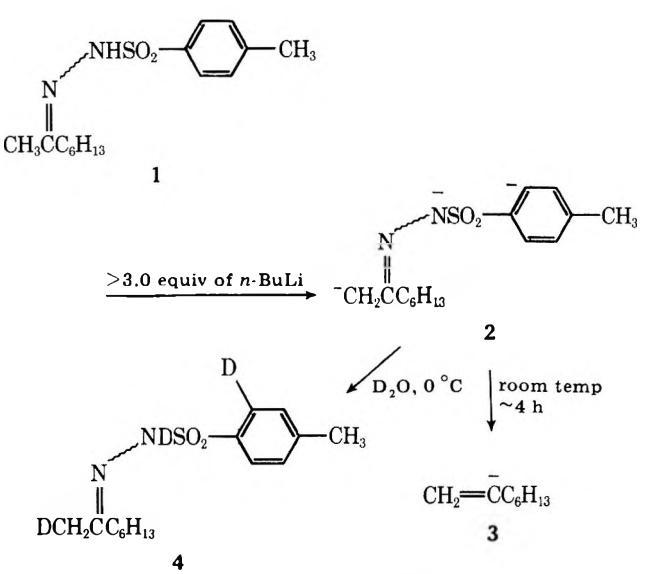
2,4,6-Triisopropylbenzenesulfonylhydrazones of a wide range of ketones serve as a convenient source of vinyllithium reagents. Treatment with 2.0–3.0 equiv of alkyllithium reagent at −78 °C in TMEDA–hexane followed by warming to 0 °C rapidly generates the vinyl anions in most cases. The reagents so formed can be trapped with a variety of electrophiles. This procedure leads to a convenient synthesis of allylic alcohols, di-, tri-, and tetrasubstituted olefins, acrylic acids, acrylic aldehydes, vinylsilanes, and vinyl bromides.

Organolithium reagents have become increasingly important in synthetic organic chemistry.[1] We report here an extremely facile method for generation of a variety of vinyllithium derivatives and trapping of them with an assortment of electrophilic reagents. Our initial studies, portions of which have been reported in preliminary form,[2,3] used the reaction of tosylhydrazones with excess *n*-butyllithium in TMEDA–hexane solvent systems for generation of vinyllithium reagents. This procedure represented a modification of the valuable and widely used Shapiro olefin synthesis[4] by allowing the vinyl anion intermediate[5] to be trapped by externally added electrophiles.

The procedure is illustrated in Scheme I for the tosylhydrazone (**1**) of 2-octanone. Treatment of **1** with excess base generates almost exclusively the 1-octenyl anion (**3**). In solvents (hexane or ether) normally used for the olefin synthesis, **3** is protonated either by solvent[4,6] or, in the case of hexane where the reaction is heterogeneous, by the tosylhydrazone.[7] Use of TMEDA as solvent overcomes this problem, but requires the use of 3 equiv or more of alkyllithium reagent if workup is to produce the desired product. This is shown in Table I for D_2O workup of the reaction. The yield of olefin is invariably high, but deuterium incorporation on workup clearly requires excess base beyond the 2 equiv needed for stoichiometric dianion formation.

Scheme I



The source of this problem has now been shown to be an o-aryl hydrogen of the tosyl group.[3,8] Specifically, treatment of **1** at −78 °C with >3.0 equiv of *n*-butyllithium in TMEDA–hexane, followed by D_2O quench, results in the incorporation of two deuterium atoms, one on nitrogen (washed out on workup) and one on the α-methyl group. If, however, the reaction mixture is warmed to 0 °C and then quenched before decomposition to **3** becomes significant, trideuterated tosylhydrazone **4** is obtained. NMR examination of the recovered tosylhydrazone shows that metalation[9] has occurred in the ortho position. A similar directed ortho metalation by an SO_2NHCH_3 group has been reported.[10] Such metalation is facilitated by the use of the strongly basic *n*-butyllithium/TMEDA solvent system and is necessary if **3** is to be trapped by externally added electrophiles. Otherwise, the vinyl anion **3** metalates the remaining dianion, giving 1-octene. Excess *n*-butyllithium (typically 3.5–4.5 equiv) must therefore be used with tosylhydrazones, and this in turn necessitates the use of excess electrophile and the separation of side products which result from attack of the *n*-butyllithium on the electrophile.

These problems can be overcome and the reaction greatly facilitated by the use of easily prepared[11] 2,4,6-triisopropyl-

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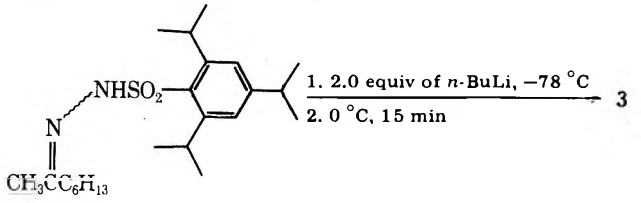
Table I. Deuterium Incorporation As a Function of the Number of Equivalents of *n*-Butyllithium Used to Decompose 1

Equiv of *n*-BuLi	% yield of 1-octene[a]	% d_1[b]
2.0	95–97	<1
2.5	95–97	<1
3.0	95–97	59
4.0	95–97	85
4.5	95–97	95

[a] Determined by GLC. [b] Determined by mass spectrometry.

benzenesulfonylhydrazones (trisylhydrazones) such as **5**. With these derivatives the desired dianion can be formed at −78 °C, except for examples which involve removal of tertiary α-hydrogens, a procedure for which is described later. There is



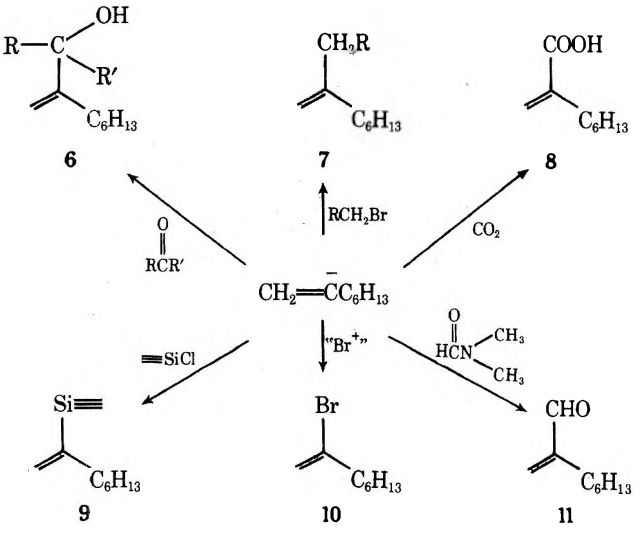
5

no evidence for benzylic metalation even with excess base, and there is an important added advantage in that dianion decomposition to vinyl anion is accelerated relative to the analogous tosylhydrazone. The latter typically requires 1–8 h at room temperature, whereas the dianion from **5** forms **3** rapidly and conveniently at 0 °C. Only 1.0–1.2 equiv of electrophile is then required, and is routinely added as soon as nitrogen evolution ceases. A possible explanation for the enhanced rate of decomposition is discussed in an accompanying note[12] which also demonstrates the utility of trisylhydrazones in carbene generation.

The vinyllithium reagents so generated have been trapped with a variety of electrophiles as shown in Scheme II. The reactions are illustrated for the 1-octenyl anion (**3**), but can be applied to a variety of other reagents, generated as described below.

In our initial studies we reported trapping of **3** (generated from the tosylhydrazone) with D_2O,[2,6] with ketones and aldehydes,[3] with alkyl halides,[3,6] and with carbon dioxide.[3] In the meantime, we[13] and others[14,15] have used chlorotrimethylsilane to generate synthetically useful vinylsilanes such as **9**, and in another application the reaction of organolithium reagents with *N,N*-dimethylformamide[16] has been used on

Scheme II

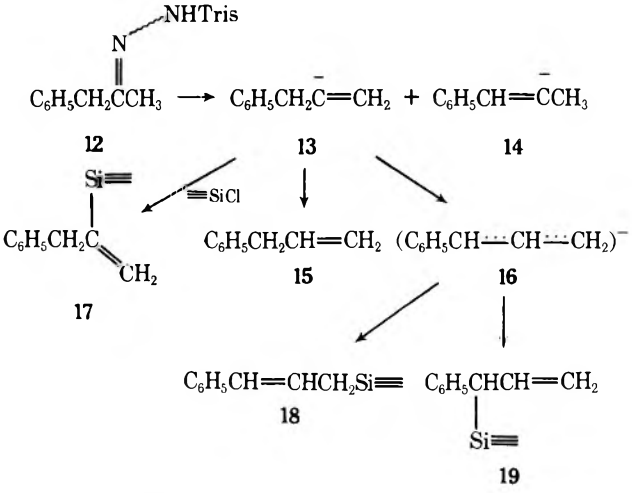


tosylhydrazone derived reagents to give α,β-unsaturated aldehydes such as **11**.[17] All of these reactions are much more conveniently run using trisylhydrazone precursors and yields are often higher. In virtually every case examined, isolated yields of 50–70% have been obtained in small-scale reactions with no more than standard bench top precautions for protection from moisture. Allylic alcohols **6**[18] and alkylated olefins such as **7**[19] are particularly useful products of this sequence.

All of the reactions illustrated in Scheme II can be run, of course, on vinyllithium reagents generated in other ways. The standard route[1] for the preparation of reagents such as **3**[20] involves metal–halogen exchange[21] on a suitable vinyl halide such as **10**.[22] The problem with this method, as noted before,[23] is that regiospecific preparation of vinyl halides is often cumbersome. We believe that the preferred route to **10**[22a] and similar vinyl bromides is actually via trisylhydrazone derived vinyl anion **3**, which gives **10** with either allyl bromide or 1,2-dibromoethane.[24]

The optimum conditions for generation of the vinyllithium reagent depend on the nature of the α-hydrogen removed and follow the expected order of acidity primary > secondary > tertiary. Conditions for each type are discussed below. Only representative electrophiles are given, as with few exceptions we have been able to use all of the electrophiles shown in Scheme II with all ketone precursors. Alkyl halides appear to be the least reactive, as discussed in the next section.

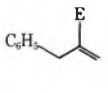
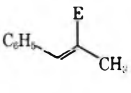
Trisylhydrazones such as **5**, in which an α-methyl proton is removed, require 2.0 equiv of *n*-BuLi at −78 °C for 20 min, followed by warming to 0 °C to generate **3**. Regioselectivity toward C-1 is as high as that observed with tosylhydrazones.[4] The derivative **12** of benzyl methyl ketone is an interesting



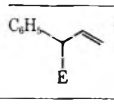
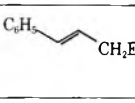
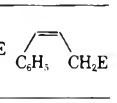
system in which the trisylhydrazone offers special advantages. Shapiro et al.[6] have proposed that the less substituted nonconjugated vinyl anion **13** is formed initially in the tosylhydrazone reaction. Indeed, allylbenzene (**15**) is the sole product of the olefin reaction (methyllithium–ether), and its dianion precursor could be quenched at the methyl position with a variety of electrophiles. When **13** was generated from the tosylhydrazone using *n*-butyllithium in hexane/TMEDA, however, only alkylation products derived from the rearranged 1-phenylallyl anion (**16**) could be obtained. We have found that decomposition of the dianion of trisylhydrazone **12** is much faster and that unrearranged anions **13** and **14** (ratio ca. 9:1) can be trapped by rapid quench using reactive electrophiles. For example, when the anion **13** is quenched with trimethylsilyl chloride after only 5 min at 0 °C, **17** is the major product, whereas after 30 min allylic isomers **18** and **19** predominate as shown in Table II. Alkylation, unfortunately, is too slow at 0 °C to trap **13**, and with this electrophile the re-

Table II. Products Derived from Trisylhydrazone 12

A. Vinyl Anion Quench after 5 min at 0 °C

Electrophile	E	% yield[a,b]		
				
D_2O	D-	74	5	3
$(CH_3)_3SiCl$	$(CH_3)_3Si$-	51	5	2
C_6H_5CHO	C_6H_5CHOH-	60	<5	<5

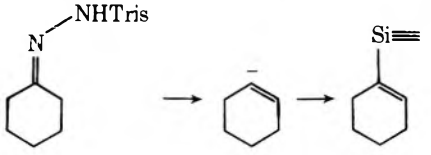
B. Vinyl Anion Quench after 30 min at 0 °C

Electrophile	E	% yield[a,c]		
				
D_2O	D-	20	52	8
$(CH_3)_3SiCl$	$(CH_3)_3Si$-	10	54	5
$CH_3(CH_2)_2CH_2Br$	*n*-Bu-	50	8	2

[a] Yields determined by calibrated GLC. Products characterized by IR and NMR. [b] Products arising from phenylallyl anion 16 were not detected by GC or NMR. [c] Products arising from vinyl anion 13 were not detected by GC or NMR.

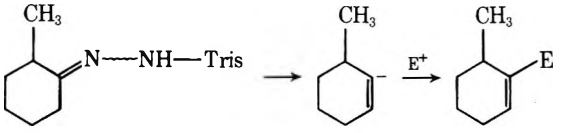
sults of Shapiro et al. are confirmed with the trisylhydrazone.

In cases where dianion formation requires the removal of a secondary α-hydrogen, we have used either 2.0 equiv of the stronger base[25] *sec*-butyllithium, at −78 °C for 2 h, or excess (3.0 equiv) *n*-butyllithium at the same temperature for 30 min. Removal of the secondary α-hydrogen under these conditions is accelerated by this excess base which, however, is not consumed. Thus, cyclohexanone trisylhydrazone (**20**) can be converted in 83% yield to vinylsilane **21**.[14,15,26]



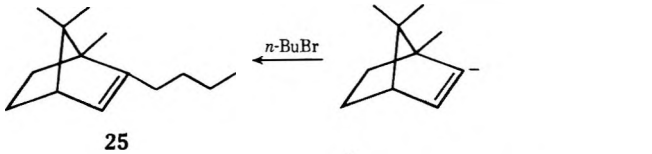
20 **21**

More interesting examples involve unsymmetrical ketones, more hindered ketones, or ketones which can give rise to geometrically isomeric vinyllithium reagents. As an example of the first type, the derivative **22** of 2-methylcyclohexanone behaves similarly to the corresponding tosylhydrazone[3] and gives good yields of **23** containing only trace amounts of the



22 **23**

more highly substituted product. Camphor trisylhydrazone (**24**) (easily prepared; see Experimental Section) is best con-



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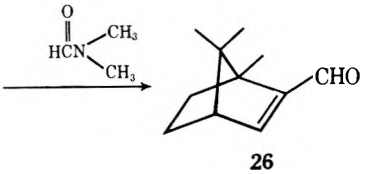

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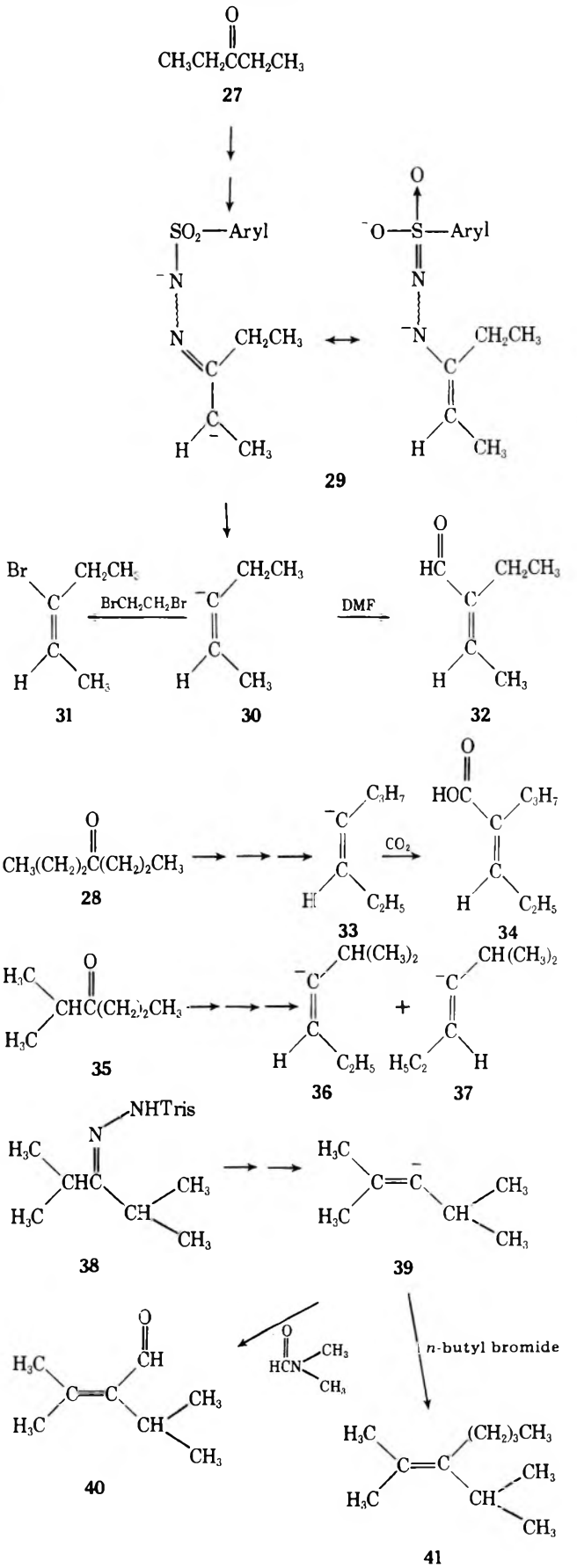
verted into its dianion by treatment with 2.0 equiv of *sec*-butyllithium at approximately −50 °C for 2 h. The solution is then warmed to 0 °C until nitrogen evolution ceases (~20 min), and the electrophile is added. In this way, **25** and **26**[17]

Scheme III

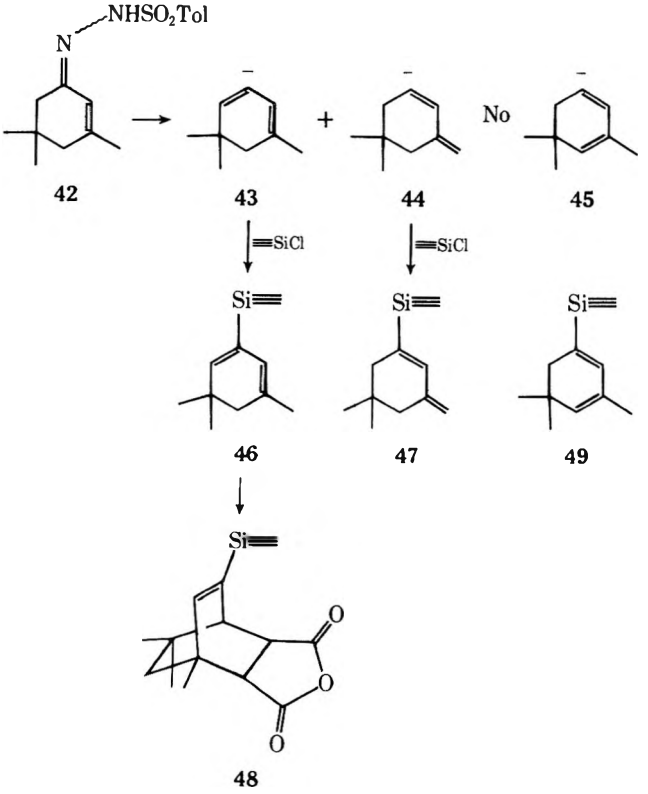


were obtained in isolated yields of about 60%. The tosylhydrazone route to **26** is far less satisfactory.[17]

Symmetrical ketones 3-pentanone (**27**) and 4-heptanone (**28**) are converted exclusively into their *cis*-vinyllithium reagents as shown in Scheme III. The dianion **29** from **27** controls the stereochemistry of the sequence and generates the configurationally stable **30**. This vinyllithium reagent was trapped with 1,2-dibromoethane to give **31** and with dimethylformamide to give **32**. Vinyl bromide **31** has spectroscopic properties consistent with the assigned stereochemistry.[27,28] Aldehyde **32** was assigned the *E* geometry based on the chemical shift of the aldehyde proton at 9.37 ppm. This resonance is characteristically found at about 9.3 ppm for *E*-trisubstituted α,β-unsaturated aldehydes of this type and at about 10 ppm for the corresponding *Z* isomers.[29,30] Likewise, 4-heptanone (**28**) was converted into **33** and carboxylated to the known[30] acid **34**. With 2-methyl-3-hexanone (**35**) the stereoselectivity is lost, however, as a mixture of products derived from **36** and **37** was obtained.

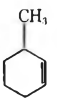
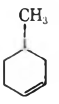
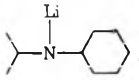
Formation of dianion by removal of a tertiary α-hydrogen is fairly difficult,[6] as substitution[31] competes. We have investigated one trisylhydrazone of this type (**38**), and have found that treatment with 3.0 equiv of *sec*-butyllithium at room temperature for 90 min generates **39** in reasonable yield, as shown by trapping with dimethylformamide to give **40** or with *n*-butyl bromide to yield **41**. Some metalation of TMEDA[32] is observed under these conditions, but separation of the basic side products so obtained is not difficult. Substitution products were not detected.

The use of tosylhydrazones of α,β-unsaturated ketones in the Shapiro reaction has become a valuable route to 1,3-dienes.[33] In our preliminary report[3] we showed that isophorone tosylhydrazone (**42**) could be converted into **43** and



trapped with CO_2 to give derived acid. We have since found, using chlorotrimethylsilane as the electrophile, that both **43** and **44** are formed in approximately a 9:1 ratio. The major product **46** was purified and shown to have the assigned structure rather than **49** by Diels–Alder reaction with maleic anhydride to give a single adduct **48**, the NMR of which clearly

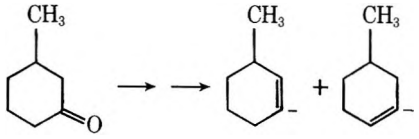
Table III. Relative Olefin Composition from Decomposition of 3-Methylcyclohexanone Tosylhydrazone with Various Bases

	% product ratio[a]	
		
Conditions	53	54
n-BuLi/hexane	29	71
tert-BuLi/pentane	33	65
CH_3Li/ether[b]	32	68
n-BuLi/TMEDA-hexane	50	50
t-BuLi/TMEDA-hexane	50	50
 /hexane	52	48

[a] Product composition was determined by integration of the vinyl and methyl signals in the NMR spectrum of the product. Figures given are the average of three runs and are accurate within ±5%, as determined using authentic mixtures of known composition. [b] A mixture of 1,3-dimethylcyclohexanes was a major impurity in this reaction.

distinguishes it from the product derivable from **49**. The trisylhydrazone of isophorone, however, gives a different ratio, approximately 1:1, of **43** to **44**. This is the only example we have encountered of a difference in product distribution between a tosyl and trisyl decomposition. It is clear from the work of Dauben, Yang, et al.[34] that the syn-anti stereochemistry of the arenesulfonylhydrazone is a factor in determining the directionality of vinyl anion formation from α,β-unsaturated derivatives. This appears to be the case here, although it is not clear why this should be so with a rigid transoid derivative compared with the cisoidal examples reported previously.

The only other type of ketone which does not lend itself readily to the synthetic methods discussed in this paper is an α,α'-dimethylene system such as derivatives of 3-methylcyclohexanone (**50**). Products are obtained from both isomeric



vinyl anions **51** and **52**. We have examined the effect of base on the olefin forming reaction, as shown in Table III. Tosylhydrazones were used in this study and the product ratio was determined by NMR spectroscopy as the GLC separation of 3- and 4-methylcyclohexene proved difficult.[35] The same starting material, approximately a 1:1 mixture of syn and anti isomers which could not be separated, was used in each reaction. It is clear from the data in Table III that bulky aggregated[1] alkyllithium bases give a slight preference for attack at the less hindered methylene position. With RLi/TMEDA systems this preference disappears. There is thus a small base effect in the directionality of this olefin-forming reaction.

In conclusion, trisylhydrazones offer distinct advantages over tosylhydrazones for vinyl anion generation in TMEDA. With the exception of α,β-unsaturated derivatives discussed above, there appears to be no variation in product composition. Tosylhydrazones, however, require an excess of alkyllithium reagent, typically 3.5–4.5 equiv, and a corresponding excess of electrophile. In addition, side products resulting from attack of the alkyllithium reagent on the electrophile are encountered, and these can be difficult to separate. Often, me-

talation of TMEDA[32] occurs, giving further side products upon reaction with the electrophile. The faster decomposition of the dianions from trisylhydrazones makes generation of the vinyllithium reagents more rapid and convenient. With tosylhydrazones, the dianion decomposition typically requires 1–8 h at room temperature and is difficult to monitor. For the Shapiro olefin formation trisylhydrazones offer no real advantage, since protonation during the reaction is desired and *n*-butane is easily removed. For trapping with external electrophiles, however, trisylhydrazones are clearly the reagents of choice.[36] The derived vinyllithium reagents have been trapped with a wide variety of electrophiles and can be converted into vinyl cuprates as well.[37] We are studying further use of these reactions, their application in natural products synthesis, and the utility of the derived alkenes.

Experimental Section[38]

Preparation of Trisylhydrazones. Trisylhydrazones were prepared by one of two methods. Unhindered ketones are illustrated by method A for cyclohexanone. More hindered ketones were treated as described for camphor in method B, which prevented decomposition[11] of the trisylhydrazide. Detailed spectral data are reported only for these two derivatives; all others had properties consistent with the assigned structure, allowing for the possibility of syn-anti isomerism.

A. Cyclohexanone 2,4,6-Triisopropylbenzenesulfonylhydrazone (20). To a stirred suspension of 29.8 g (0.10 mol) of finely ground[39] 2,4,6-triisopropylbenzenesulfonylhydrazide[11] in 100 mL of methanol was added 9.82 g (0.10 mol) of freshly distilled cyclohexanone. The addition of 1 mL of concentrated hydrochloric acid caused the mixture to clear rapidly, after which a fine granular product began to crystallize. The reaction mixture was chilled overnight and filtered. The product was washed with cold methanol and dried at room temperature at 0.5 Torr to yield 30.8 g (81%) of white crystals, mp 123–124 °C dec.

The IR spectrum shows 3240, 2945, 2880, 1640, 1168, 1155, 1010, and 650 cm^{-1}. The NMR spectrum shows δ 1.25 (d, J = 7 Hz, 18 H), 1.57 (br s, 6 H), 2.30 (br s, 4 H), 2.90 (septet, J = 7 Hz, 1 H), 4.26 (septet, J = 7 Hz, 2 H), 7.18 (2 overlapping s; 3 H (aryl and NH)).

Anal. Calcd for $C_{21}H_{34}N_2O_2S$: C, 66.64; H, 9.05. Found: C, 66.85; H, 8.89.

B. Camphor 2,4,6-Triisopropylbenzenesulfonylhydrazone (24). To a solution of 33.0 g (0.11 mol) of 2,4,6-triisopropylbenzenesulfonylhydrazide in 100 mL of acetonitrile was added 15.2 g (0.10 mol) of camphor and 10 mL[40] of concentrated hydrochloric acid. The solution was stirred overnight at room temperature and cooled at 0 °C for 4 h, and the resulting white solid was collected. The crude product was taken up in a minimum amount of chloroform, filtered, concentrated in vacuo, and dried at 0.5 Torr to give 30.3 g (70%) of a white solid, mp 197–199 °C dec.

The NMR spectrum shows δ 0.60 (s, 3 H), 0.80 (s, 6 H), 1.25 (2 overlapping d, J = 7 Hz, 18 H), 1.4–2.4 (m, 7 H), 2.88 (septet, J = 7 Hz, 1 H), 4.23 (septet, J = 7 Hz, 2 H), 7.15 (s, 2 H), 7.45 (br s, 1 H).

Anal. Calcd for $C_{25}H_{40}N_2O_2S$: C, 69.40; H, 9.32. Found: C, 69.28; H, 9.30.

Other trisylhydrazones were prepared as indicated.

2-Octanone 2,4,6-triisopropylbenzenesulfonylhydrazone (5): method A, mp 87–88 °C dec, yield 92%.

1-Phenyl-2-propanone 2,4,6-triisopropylbenzenesulfonylhydrazone (12): method A, mp 122–124 °C dec, yield 98%.

2-Methylcyclohexanone 2,4,6-triisopropylbenzenesulfonylhydrazone (22): method A, mp 107–109 °C dec, yield 94%.

3-Pentanone 2,4,6-triisopropylbenzenesulfonylhydrazone: method A, mp 115–116 °C dec, yield 79%.

4-Heptanone 2,4,6-triisopropylbenzenesulfonylhydrazone: method A, mp 92–95 °C dec, yield 64%.

2,4-Dimethyl-3-pentanone 2,4,6-triisopropylbenzenesulfonylhydrazone (38): method B, mp 116–122 °C dec, yield 73%.

2-Methyl-3-hexanone 2,4,6-triisopropylbenzenesulfonylhydrazone: method A, mp 103–105 °C dec, yield 72%.

Deuterium Incorporation Studies. A. −78 °C Quench. To a stirred solution of 0.296 g (1.0 mmol) of 1 in 5 mL of TMEDA at approximately −55 °C was added 2.25 mL (4.5 mmol) of 2.0 M *n*-butyllithium in hexane. After stirring for 10 min while cooling with a −78 °C bath, D_2O (1 mL) was added. The reaction mixture was poured into 1 N HCl and the tosylhydrazone recovered quantitatively by ether extraction. The NMR spectrum of recovered tosylhydrazone[41] was identical with that of starting material except for the C-1 methyl singlets at δ 1.74 and 1.88 (from anti and syn isomers), which are broadened and reduced to an area equivalent to 2.0 H.

B. 0 °C Quench. Experiment A was repeated under the above conditions except that the solution was warmed to 0 °C and stirred for 10 min before D_2O quench. Tosylhydrazone was recovered as before. The upfield portion of the NMR spectrum[41] of this material is identical with that described above. In the low-field region the AA'BB' pattern in the aromatic region was changed dramatically. The "doublet" at δ 7.84 is reduced to an area of 1.09 H, and a new singlet bisects the reduced doublet at δ 7.29 (total area 2.0 H).

2-Lithio-1-octene (3). General Procedure. The 2-octanone trisylhydrazone **5** was placed in a flame-dried flask flushed with nitrogen. A solution (10 mL/g of trisylhydrazone) of 10% TMEDA in hexane was added, stirring was begun, and the flask was cooled in a dry ice–acetone bath to −78 °C. *n*-Butyllithium in hexane (2 M, 2.0–2.2 equiv) was then added dropwise, either from a dropping funnel or through a septum via syringe, causing the solution to turn dark orange-red. After stirring at −78 °C for 15 min, the solution was allowed to warm to ~0 °C, during which time it turned light yellow. The reaction flask was then cooled in an ice bath until nitrogen evolution ceased (~10 min), followed by addition of electrophile as described below.

2-*n*-Hexyl-1-phenyl-2-propenol (6, R = Ph, R' = H). A solution of **3** was prepared as described above from 10.0 g (0.0245 mol) of **5** and 25.7 mL (0.0514 mol) of 2.0 M *n*-butyllithium. The solution was treated with stirring at 0 °C with 3.12 g (0.0294 mol) of freshly distilled benzaldehyde. The reaction was stirred for 1 h at room temperature and worked up in the standard manner. GLC analysis (column A at 200 °C) of the crude product showed a single peak in 84% yield, using purified product as standard. Short-path distillation afforded 3.31 g (62%) of **6** as a colorless liquid, bp 135–138 °C (1.0 Torr).

The NMR spectrum shows δ 0.83 (t, J = 6 Hz, 3 H), 1.0–1.5 (m, 8 H), 1.85 (m, 2 H), 2.57 (s, 1 H), 4.90 (s, 1 H), 5.03 (s, 1 H), 5.18 (s, 1 H), and 7.28 (s, 5 H). The mass spectrum shows peaks at *m/e* 133 (base) and 218 (parent).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.57; H, 10.18.

2-*n*-Butyl-1-octene (7, R = *n*-Pr). A solution of 2-lithio-1-octene was prepared as described for **6** above, but treated with 4.03 g (0.0294 mol) of *n*-butyl bromide. After stirring at room temperature for 4 h the reaction was worked up in the usual manner (GLC yield 72%, column A at 135 °C). Distillation through a 4-in. Vigreux column afforded 2.39 g (58%) of **7** as a clear liquid, bp 87–89 °C (28 Torr) [lit.[42] bp 83–84 °C (9 Torr)].

The mass spectrum shows *m/e* 168 (parent) and 56 (base). The NMR spectrum has δ 0.88 (t, J = 6 Hz, 6 H), 1.0–1.7 (m, 12 H), 2.00 (t, J = 6 Hz, 4 H), and 4.70 (s, 2 H).

2-Trimethylsilyl-1-octene (9). A solution of 2-lithio-1-octene was prepared as described above and treated at 0 °C with 3.18 g (0.0294 mol) of chlorotrimethylsilane. After stirring for 1 h at room temperature the reaction mixture was worked up in the standard method. GLC analysis showed 1-octene (5%) and **9** (71%). The crude material was subjected to short-path distillation, affording 2.50 g (55%) of clear liquid, bp 78–80 °C (14 Torr).

The NMR spectrum shows δ 0.00 (s, 9 H), 0.80 (t, J = 6 Hz, 3 H), 1.0–1.7 (m, 8 H), 2.05 (m, 2 H), 5.25 (m, 1 H), and 5.45 (m, 1 H). The mass spectrum shows *m/e* 184 (parent) and 73 (base). Careful GLC–mass spectral analysis shows ~1% of an isomeric product.

Anal. Calcd for $C_{11}H_{24}Si$: C, 71.65; H, 13.12. Found: C, 71.62; H, 12.97.

2-Bromo-1-octene (10).[22a] A solution of 2-lithio-1-octene was prepared as described above from 4.1 g of **5** (0.010 mol) and 10.0 mL (0.020 mol) of 2.0 M *n*-butyllithium in hexane. The solution was treated at 0 °C with 2.00 g (0.0106 mol) of 1,2-dibromoethane and stirred until gas evolution ceased. Standard workup followed by short-path distillation afforded 0.83 g (43%) of **10**, bp 70–72 °C (18 Torr).

The NMR spectrum shows δ 0.88 (t, J = 6 Hz, 3 H), 1.29 (m, 8 H), 2.41 (br t, J = 7 Hz, 2 H), 5.37 (d, J = 1.3 Hz, 1 H), and 5.52 (q, J = 1.3 Hz, 1 H).

2-Lithio-3-phenylpropene (13). A solution of **13** was prepared as described in the general procedure for **3** by treating 0.415 g (1.0 mmol) of **12** with 1.1 mL (2.2 mmol) of 2.0 M *n*-butyllithium at −78 °C for 15 min. The −78 °C bath was replaced with a 0 °C bath and after 5 min of stirring the solution was treated with electrophiles as described below.

A. D_2O Quench. D_2O quench of the reaction mixture followed by standard workup gave, as shown in Table II, a 74% yield (GLC, column A at 95 °C) of 3-phenyl-1-propene, a 5% yield of (*E*)-1-phenylpropene, and a 3% yield of (*Z*)-1-phenylpropene. The major product, isolated

by preparative GLC, shows virtually quantitative deuterium incorporation at C-2. The NMR spectrum shows δ 3.38 (s, 2.0 H), 5.07 (s, 2.0 H), and 7.22 (s, 5.0 H).

B. Chlorotrimethylsilane Quench. Addition of 0.130 g (1.2 mmol) of chlorotrimethylsilane to a solution prepared as above and standard workup gave a mixture of products as shown in Table II. Preparative GLC collection of the major peak afforded 2-trimethylsilyl-3-phenylpropene (**17**). The NMR spectrum shows δ 0.00 (s, 9 H), 3.48 (s, 2 H), 5.45 (m, 2 H), and 7.2 (m, 5 H).

C. Benzaldehyde Quench. Similar quench of a solution prepared as above with 0.130 g (1.2 mmol) of benzaldehyde afforded, after standard workup, the mixture shown in Table II. The major product, 2-benzyl-1-phenyl-2-propen-1-ol, was isolated by column chromatography on silica gel. Its NMR spectrum shows δ 3.30 (q, 2 H), 4.90 (s, 1 H), 5.15 (s, 1 H (D_2O exchangeable)), 5.35 (s, 1 H), and 7.3 (m, 5 H).

D. Delayed Quenches. When the procedure described above was carried out exactly as above, but the reaction mixture was allowed to stir at 0 °C for 30 to 60 min, it became heterogeneous and intensely red, and products derived from **16** were obtained as shown in Table II. Chlorotrimethylsilane quench (0.130 g, 1.2 mmol) is typical and gave as the major product (54%) (*E*)-1-phenyl-3-trimethylsilylpropene. The NMR spectrum of the GLC collected product (column B at 180 °C) shows δ 0.00 (s, 9 H), 1.58 (dd, J = 5, 1.5 Hz, 2 H), 6.17 (m, 2 H), and 7.2 (m, 5 H).

1-Trimethylsilycyclohexene (21). To a stirred solution of 0.378 g (1.0 mmol) of **20** in 10 mL of 50% TMEDA–hexane at −78 °C was added 1.5 mL (3.0 mmol) of 2.0 M *n*-butyllithium in hexane. The solution was allowed to warm to 0 °C and then treated with 0.216 g (2.0 mmol) of chlorotrimethylsilane. After stirring for 1 h the solution was worked up in the normal manner to give **21** (GLC yield 83%, column A at 120 °C). The GLC collected product has properties as reported.[14,15]

If only 2.0 equiv of *n*-butyllithium was used above the GC yield dropped to 47% and butyltrimethylsilane was detected by GLC. This indicates incomplete dianion formation with stoichiometric quantities of base. With excess base trimethylsilylated TMEDA[32] was formed and detected in the basic products.

2-Lithio-3-methylcyclohexene. To a stirred solution of **22** in 50% TMEDA–hexane (10 mL/g) at −78 °C was slowly added 2.0 equiv of *sec*-butyllithium in cyclohexane or 3.0 equiv of *n*-butyllithium in hexane. After stirring at −78 °C for 2 h, the solution was allowed to warm to 0 °C, held there until gas evolution ceased (less than 5 min), and quenched.

A. 2-Deuterio-3-methylcyclohexene (23, E = D). To a solution prepared as above from 0.393 g (1.0 mmol) of **22** and 1.5 mL (3.0 mmol) of *n*-butyllithium was added 1.0 mL of D_2O. Standard workup gave (GLC, column A at 55 °C) 93% 3-methylcyclohexene and 1–2% 1-methycyclohexene. Integration of the NMR spectrum of the GLC collected major product showed only 1.12 olefinic protons, indicating 88% deuterium incorporation.

B. 2-*n*-Butyl-3-methylcyclohexene (23, E = *n*-Bu). A solution of 2-lithio-3-methylcyclohexene was prepared as above from 10.0 g (0.0255 mol) of **22** and 38.2 mL (0.0764 mol) of 2.0 M *n*-butyllithium. Quenching at 0 °C with 7.0 g (0.0511 mol) of n-butyl bromide and standard workup followed by short-path distillation gave 2.3 g (59%) of a clear liquid, bp 76–79 °C (18 Torr).

The NMR spectrum shows δ 1.0 (t, 3 H), 1.1 (d, 3 H), 1.2–2.5 (m, 13 H), and 5.5 (br s, 1 H). GC–mass spectral analysis shows the parent peak at *m/e* 152 and the base peak at *m/e* 95.

Anal. Calcd for $C_{11}H_{20}$: C, 86.76; H, 13.24. Found: C, 86.60; H, 13.38.

C. 3-Methylcyclohexene-2-carboxaldehyde (23, E = CH=O). A solution of vinyl anion was prepared by treating 10.0 g (0.255 mol) of **22** with 48.7 mL (0.0536 mol) of 1.1 M *sec*-butyllithium in hexane. After the solution had warmed to 0 °C and nitrogen evolution had ceased, 2.05 g (0.0280 mol) of *N,N*-dimethylformamide was added. After stirring for 1 h at room temperature the reaction was worked up in the standard manner. Short-path distillation afforded 1.99 g (63%) of colorless liquid, bp 88–90 °C (26 Torr).

The IR spectrum shows characteristic absorption at 2840, 2735, 1698, and 1650 cm^{-1}. The NMR spectrum has δ 1.07 (d, J = 7 Hz, 3 H), 1.6 (m, 4 H), 2.3 (m, 2 H), 2.67 (m, 1 H), 6.74 (t of d, J = 4, 0.7 Hz, 1 H), and 9.37 (s, 1 H).

2-*n*-Butylbornene (25). A solution of 2-lithiobornene was prepared by treatment of 10.0 g (0.023 mol) of **24** in 100 mL of 50% TMEDA–hexane with 46.2 mL (0.051 mol) of 1.1 M *sec*-butyllithium at ca. −55 °C for 2 h followed by stirring for 30 min at 0 °C. At this time, 3.80 g (0.02777 mol) of *n*-butyl bromide was added and the reaction was stirred overnight at room temperature. Standard workup (GLC yield 70%, column A at 145 °C) followed by short-path distillation afforded **25**, 2.26 g (51%), as a clear liquid, bp 57–59 °C (0.5 Torr).[43]

The mass spectrum shows the parent peak at *m/e* 192 and the base peak at *m/e* 121. The NMR spectrum shows three singlets at δ 0.73, 0.76, and 0.43 superimposed on a broad multiplet (total 16 H), δ 1.4 (m, 4 H), 1.9 (m, 2 H), 2.19 (t, 1 H), and 5.52 (m, 1 H).

Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.16; H, 12.38.

Bornene-2-carboxaldehyde (26). A solution of 2-lithiobornene was prepared exactly as above and quenched with 2.0 g (0.0277 mol) of *N,N*-dimethylformamide. After stirring for 30 min at room temperature the reaction was worked up by the standard method. GLC analysis (column A at 150 °C) showed a single peak in 79% yield. Vacuum sublimation gave 2.3 g (61%) of **26**.[17]

(*Z*)-3-Lithio-2-pentene (30). To a solution of 0.366 g (1.0 mmol) of 3-pentanone 2,4,6-triisopropylbenzenesulfonylhydrazone in 10 mL of 50% TMEDA–hexane at −78 °C was added 1.5 mL (3.0 mmol) of 2.0 M *n*-butyllithium, and the reaction was stirred for 30 min and warmed to 0 °C.

A. Addition of 0.146 g (2.0 mmol) of *N,N*-dimethylformamide and stirring at room temperature for 1 h was followed by standard workup to give a crude product (70% GC yield) which was shown to consist of 98% (*E*)-2-ethyl-2-butenal (**32**)[44] (aldehyde C–H proton at δ 9.37) and 2% of the *Z* isomer (aldehyde C–H proton at δ 9.90).

B. To a similarly prepared solution was added 0.376 g (2.0 mmol) of 1,2-dibromoethane. Standard workup after stirring at room temperature for 10 min gave a crude product (GLC yield 69%, column A at 55 °C). Preparative GLC (column B at 50 °C) afforded (*E*)-3-bromo-2-pentene (**31**).

The NMR spectrum shows δ 1.10 (t, 3 H), 1.65 (d, 3 H), 2.44 (q, 2 H), and 5.81 (q of t, 1 H).

(*E*)-2-Propyl-2-pentenoic Acid (34). A solution of (*Z*)-4-lithio-3-heptene (**33**) was prepared in the same manner as **30** from 1.00 g (2.54 mmol) of the trisylhydrazone and 5.0 mL (5.5 mmol) of 1.1 M *sec*-butyllithium in cyclohexane at −78 °C, followed by warming to 0 °C for 20 min. Carbon dioxide was sublimed into the stirred solution via cannula from a flask containing dry ice until gas absorption ceased. The mixture was poured into 1 N HCl, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated salt solution, dried, and concentrated in vacuo to give 1.0 g of a colorless oil which partially crystallized. The NMR spectrum of this product shows it to be a mixture of 2,4,6-triisopropylbenzenesulfinic acid and **34**: δ 0.90 (t, J = 7 Hz, 3 H), 1.05 (t, J = 7 Hz, 3 H), 1.40 (m, 2 H), 2.26 (m, J = 7 Hz, 4 H), 6.87 (t, J = 7 Hz, 1 H), and 10.08 (s, 1 H), in addition to signals from the sulfinic acid.[11] Attempted separation by distillation led to partial sulfinic acid isomerization of **34** to its *Z* isomer and the formation of 1,3,5-triisopropylbenzene.

3-Lithio-2,4-dimethyl-2-pentene (39). To a stirred solution of 10.0 g (0.0254 mol) of **38** in 100 mL of 50% TMEDA–hexane at −78 °C was added 70 ml)0.077 mol) of 1.1 M *sec*-butyllithium in cyclohexane. The reaction mixture was immersed in a room temperature bath and stirring was continued for 1.5 h.

3-Methyl-2-isopropyl-2-butenal (40). A solution of **39** prepared as above was treated with 3.70 g (0.051 mol) of *N,N*-dimethylformamide. After stirring for 1 h the reaction mixture was worked up in the standard manner to give **40** in a GC yield of 74%. Short-path distillation afforded 1.71 g (53%) of a clear liquid, bp 70–73 °C (25 Torr).

The IR spectrum shows 2810, 2780, 1680, and 1625 cm^{-1} characteristic bands. The NMR spectrum shows δ 1.15 (d, J = 7 Hz, 6 H), 1.97 (s, 3 H), 2.15 (s, 3 H), 2.9 (septet of d, J = 7, 1.5 Hz, 1 H), and 10.11 (d, J = 1.5 Hz, 1 H).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.25; H, 11.27.

2-Methyl-3-isopropyl-2-heptene (41). A solution of **39** was prepared as above and treated with 10.44 g (0.0762 mol) of *n*-butyl bromide overnight at room temperature. The reaction was worked up in the standard method to give product in a GC yield of 42% (column A, 120 °C). Short-path distillation afforded 1.2 g (31%) of **41** as a clear liquid, bp 79–80 °C (24 Torr).

The NMR spectrum shows δ 0.91 (d, J = 8 Hz, 9 H), 1.3 (m, 4 H), 1.91 (t, J = 7 Hz, 2 H), 2.62 (s, 6 H), and 2.83 (septet, J = 8 Hz, 1 H). A singlet at δ 6.90 indicates the presence of 3% of triisopropylbenzene.

Tosylhydrazone Decompositions. General Procedure. The tosylhydrazone (or benzenesulfonylhydrazone), typically 0.03 mol, was dissolved in TMEDA (10 mL/g) and the suspension stirred at −78 °C (TMEDA freezes at −55 °C, but melts upon addition of the alk-

yllithium solution) for 10 min, followed by addition of 3.5–4.5 equiv of alkyllithium in hexane over a 10–15-min period. The resulting deep red solution was warmed to room temperature. With tosylhydrazones the solution becomes yellow on reaching room temperature and gradually turns dark brown as vinyl anion is formed. With benzenesulfonylhydrazones a precipitate forms and gradually dissolves on stirring at room temperature. After stirring for 2–8 h at room temperature or 1–4 h at 35 °C, the solution was treated at 0 °C with 3–4.5 equiv of electrophile and the reaction worked up in the standard manner.

1,5,5-Trimethyl-3-trimethylsilylcyclohexa-1,3-diene (46). A solution of vinyl anion **43** was prepared by the above procedure from 10.0 g (0.033 mol) of **42** and 53 mL of 2.4 M *n*-butyllithium in 100 mL of TMEDA. After stirring for 4 h at room temperature the mixture was cooled to 0 °C and 11.0 g (0.10 mol) of chlorotrimethylsilane was added dropwise over a 10-min period. The solution was stirred at room temperature for 90 min and worked up in the standard fashion to give a crude product shown by GLC to consist of **46** and **47** in a 9:1 ratio. Short-path distillation afforded 3.21 g (50%) of the mixture, bp 90–92 °C (26 Torr). The isomers were separated by preparative GLC on column B at 100 °C. The major product, *m/e* 194, has an NMR spectrum consistent with structure **46:** δ 0.00 (s, 9 H), 0.85 (s, 6 H), 1.70 (s, 3 H), 1.88 (s, 2 H), 5.46 (br s, 1 H), 5.53 (br s, 1 H). The minor product, *m/e* 194, has an NMR spectrum with δ 0.0 (s, 9 H), 0.80 (s, 6 H), 1.88 (s, 2 H), 1.98 (s, 2 H), 4.70 (s, 1 H), 4.78 (s, 1 H), and 6.28 (s, 1 H) and is assigned structure **47.** Sturcture **49** was ruled out for the major product on the basis of the following experiment.

Reaction of 46 with Maleic Anhydride. A solution of 0.204 g (1.05 mmol) of GLC purified **46** and 0.200 g (2.0 mmol) of maleic anhydride in 5 mL of benzene was heated under reflux for 2 h. The cooled solution was washed with water and the aqueous extracts were backwashed with hexane. The combined organic layers were dried over magnesium sulfate, filtered, and evaporated to give 0.305 g (99%) of a colorless oil which showed a single peak on GLC (column A, 190 °C). The NMR spectrum, δ 0.00 (s, 9 H), 0.76 (s, 3 H), 1.0 (m, 5 H), 1.37 (s, 3 H), 2.65 (d, J = 9 Hz, 1 H), 2.76 (d, J = 3 Hz, 1 H), 3.41 (d of d, J = 3, 9 Hz, 1 H), and 6.14 (s, 1 H), is as expected for **48.**

Olefin Formation from 3-Methylcyclohexanone Tosylhydrazone. The tosylhydrazone of 3-methylcyclohexanone was prepared in the usual manner,[4] mp 108–110 °C dec. A solution of 3.0 g (0.01 mol) in 30 mL of solvent was treated at room temperature with 4.0 equiv of base as shown in Table III. After stirring for 3 h at room temperature the reaction was quenched with ice water. The organic layer was separted and dried over magnesium sulfate. After filtration, solvent was removed by distillation through a spinning band column and the olefinic mixture isolated by preparative GLC from a 12 ft × ¼ in. SE 30 column. The ratio of **53** to **54** was determined using integration of the vinyl and methyl regions of the 90-MHz NMR spectrum using a calibration curve established with mixtures of known composition which were subjected to the same isolation method.

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Registry No.—*syn*-**4,** 63904-78-9; *anti*-**4,** 63904-79-0; **5,** 63883-62-5; **6** (R = Ph, R′ = H), 61685-29-8; **7** (R = Pr), 5698-48-6; **9,** 63883-63-6; **10,** 13249-60-0; **12,** 63883-64-7; **17,** 63883-65-8; **18,** 40595-34-4; **20,** 61835-95-8; **22,** 63883-66-9; **23** (E = Bu), 61685-33-4; **23** (E = CHO), 41437-90-5; **24,** 63883-67-0; **25,** 61685-34-5; **30,** 63883068-1; **31,** 54653-28-0; (*E*)-**32,** 63883-69-2; (*Z*)-**32,** 63883-70-5; **33,** 63883-71-6; **34,** 33786-47-9; **38,** 63883-72-7; **39,** 63883-73-8; **40,** 63883-74-9; **41,** 63883-75-0; **42,** 21195-62-0; **43,** 63883-76-1; **46,** 63883-77-2; **47,** 63883-78-3; **48,** 63883-79-4; **50** tosylhydrazine, 63883-80-7; 2,4,6-triisopropylbenzenesulfonylhydrazide, 39085-59-1; cyclohexanone, 108-94-1; camphor, 76-22-2; 3-pentanone trisylhydrazone, 63883-81-8; 4-heptanone trisylhydrazone, 63883-82-9; 2-methyl-3-hexanone trisylhydrazone, 63883-83-0; 2-octanone, 111-13-7; 1-phenyl-2-propanone, 103-79-7; 2-methylcyclohexanone, 583-60-8; 3-pentanone, 96-22-0; 4-heptanone, 123-19-3; 2,4-dimethyl-3-pentanone, 565-80-0; 2-methyl-3-hexanone, 7379-12-6; butyllithium, 109-72-8; benzaldehyde, 100-52-7; butyl bromide, 109-65-9; chlorotrimethylsilane, 75-77-4; 1,2-dibromoethane, 106-93-4; 3-phenyl-2-deuterioprop-1-ene, 60468-24-8; 2-benzyl-1-phenyl-2-propen-1-ol, 63883-84-1; 2-lithio-3-methylcyclohexene, 63883-85-2; *N,N*-dimethylformamide, 68-12-2; 2-lithiobornene, 63883-86-3; *sec*-butyllithium, 598-30-1; maleic anhydride, 108-31-6; 2-lithio-1-octene, 63883-87-4; 2-octanone tosylhydrazone, 54798-76-4; 2-lithio-3-phenylpropene, 63883-88-5.

References and Notes

(1) (a) B. J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon Press, Oxford, 1974; (b) D. Seebach and K.-H. Geiss in "New Applications of Organometallic Reagents in Organic Synthesis", D. Seyferth, Ed., Elsevier, Amsterdam, 1976, p 1; (c) J. M. Brown, *Chem. Ind.* (*Ind.*), 454 (1972).
(2) J. E. Stemke and F. T. Bond, *Tetrahedron Lett.*, 1815 (1975).
(3) J. E. Stemke, A. R. Chamberlin, and F. T. Bond, *Tetrahedron Lett.*, 2947 (1976).
(4) R. H. Shapiro, *Org. React.*, **23,** 405 (1975).
(5) R. H. Shapiro and M. J. Heath, *J. Am. Chem. Soc.*, **89,** 5734 (1967); G. Kaufman, F. Cook, R. Shechter, J. Bayless, and L. Friedman, *ibid.*, **89,** 5737 (1967).
(6) R. H. Shapiro, M. F. Lipton, K. J. Kolonko, R. L. Buswell, and L. A. Capuan, *Tetrahedron Lett.*, 1811 (1975).
(7) R. H. Shapiro and E. C. Hornaman, *J. Org. Chem.*, **39,** 2302 (1974).
(8) The possibility of ring metalation was first suggested by E. Vedejs and R. P. Steiner, *J. Chem. Soc. D,* 599 (1973). The problem is *not* benzylic H abstraction as stated in ref 1b, p 60.
(9) (a) Reference 1a, p 28; (b) W. W. Langer, Ed., "Polyamine-Chelated Alkali Metal Compounds," American Chemical Society, Washington, D.C., 1974.
(10) D. W. Slocum and C. A. Jennings, *J. Org. Chem.*, **41,** 3653 (1976), and references cited therein.
(11) N. J. Cusack, C. B. Reese, A. C. Risius, and B. Roozpeikar, *Tetrahedron,* **32,** 2157 (1976).
(12) A. R. Chamberlin and F. T. Bond, *J. Org. Chem.*, following paper in this issue.
(13) J. E. Stemke, Ph.D. Thesis, University of California, San Diego, 1975; *Diss. Abstr.*, **36,** 5597 (1976).
(14) R. T. Taylor, C. R. Degenhart, W. P. Melega, and L. A. Paquette, *Tetrahedron Lett.*, 159 (1977).
(15) T. H. Chan, A. Baldassare, and D. Massuda, *Synthesis,* 801 (1976).
(16) Reference 1a, p 140.
(17) P. C. Traas, H. Boelens, and H. J. Takken, *Tetrahedron Lett.*, 2287 (1976).
(18) For recent alternative syntheses of allylic alcohols see: (a) P. Jacob III and H. C. Brown, *J. Org. Chem.*, **42,** 579 (1977); (b) H. J. Reich and S. K. Shaw, *J. Am. Chem. Soc.*, **97,** 3250 (1975); (c) W. G. Taylor and J. R. Dimmock, *Can. J. Chem.*, **42,** 2522 (1974); (d) W. Dumont, P. Bayet, and A. Kripf, *Angew. Chem., Int. Ed. Engl.*, **13,** 804 (1974); (e) D. Seebach and A. K. Beck, *ibid.*, **13,** 806 (1974).
(19) For recent references to alkylation of vinyllithium derivatives see: (a) J. Millon, R. Lorne, and G. Linstrumelle, *Synthesis,* 434 (1975); (b) A. P. Uijttewaal, F. L. Jonkers, and A. van der Gen, *Tetrahedron Lett.*, 1439 (1975); (c) G. Linstrumelle, *ibid.*, 3809 (1974); (d) F. Naf and P. Degen, *Helv. Chim. Acta,* **54,** 1939 (1971); (e) E. M. Schlosser and F. Hammer, *ibid.*, **57,** 2547 (1974).
(20) Reference 1a, p 62; E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2078, 2085 (1951).
(21) For selected recent examples, see: (a) G. Cahiez, D. Bernard, and J. F. Normant, *Synthesis,* 245 (1976); (b) D. Seebach and H. Neumann, *Chem. Ber.*, **107,** 847 (1974); (c) H. Neumann and D. Seebach, *Tetrahedron Lett.*, 4839 (1965); (d) B. M. Trost and J. L. Stanton, *J. Am. Chem. Soc.*, **97,** 4018 (1975); (e) D. A. Evans, R. C. Thomas, and J. A. Walker, *Tetrahedron Lett.*, 1427 (1976); (f) K. F. Bernady, J. F. Poletto, and M. J. Weiss, *ibid.*, 765 (1975); (g) P. A. Grieco, Y. Masaki, and D. Bowler, *J. Am. Chem. Soc.*, **97,** 159 (1975).
(22) For recent references to alternative routes, see: (a) R. K. Boeckman, Jr., and D. M. Blum, *J. Org. Chem.*, **39,** 3307 (1974); (b) J. Hartmann and M. Schlosser, *Helv. Chim. Acta,* **59,** 452 (1976); (c) J. F. Normant, C. Chint, G. Cahiez, and J. Villieras, *Synthesis,* 803 (1974).
(23) S. Baba, D. E. Van Horn, and E. Negishi, *Tetrahedron Lett.*, 1927 (1976).
(24) G. M. Whitesides, C. P. Casey, and J. K. Krieger, *J. Am. Chem. Soc.*, **93,** 1379 (1971).
(25) Reference 9b, p 10.
(26) U. F. Mironov, N. G. Maksimova, and U. V. Nepomniva, *Bull. Acad. Sci. USSR,* 313 (1967); *Chem. Abstr.*, **67,** 32719 (1967).
(27) R. Y. Tien and P. J. Abell, *J. Org. Chem.*, **35,** 956 (1970).
(28) For an incorrect assignment, see J.-P. Bianchini and E. M. Gaydon, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, **280,** 205 (1975).
(29) D. J. Faulkner, *Synthesis,* 175 (1971).
(30) K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.*, **33,** 3382 (1963).
(31) J. Meinwald and F. Uno, *J. Am. Chem. Soc.*, **90,** 800 (1968); J. Hertz and C. V. Ortiz, *J. Chem. Soc. C,* 2294 (1971); R. H. Shapiro and T. Gadek, *J. Org. Chem.*, **39,** 3418 (1974); E. Vedejs and W. T. Stolle, *Tetrahedron Lett.*, 135 (1977).
(32) D. J. Peterson *J. Organomet. Chem.*, **9,** 373 (1967).
(33) W. G. Dauben, M. E. Lorber, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan, and K. Tomer, *J. Am. Chem. Soc.*, **90,** 4762 (1968).
(34) W. G. Dauben, G. T. Rivers, W. T. Zimmerman, N. C. Yang, B. Kim, and J. Yang, *Tetrahedron Lett.*, 2951 (1976).
(35) The isomers are reported to be separable using a capillary column: G. Schomburg, *J. Chromatogr.*, **23,** 1 (1966).
(36) We have occasionally detected small amounts of 1,3,5-triisopropylbenzene, presumably formed from the sulfinate, in crude reaction products. Its separation in these cases can be effected by either distillation or chromatography.
(37) Work in progress with Mr. Sair Hagopian.

(38) Capillary melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were taker as neat films or $CHCl_3$ solutions on a Perkin-Elmer Infracord or Beckman IR-18 A-X. Proton magentic resonance (NMR) spectra were recorded in $CDCl_3$ or CCl_4 solution on a Varian T-60, EM-390, or HR-220 instrument. Chemical shifts are reported as parts per million (δ) downfield from tetramethylsilane. GLC–mass spectra were obtained on an LKB-9000 instrument using a $^1/_8$ in. × 6 ft Dexsil 300 column.
Reagent grade hexane was distilled from lithium aluminum hydride prior to use. Tetramethylethylenediamine (TMEDA) was distilled from lithium alum num hydride and could be stored, protected from moisture for several weeks. 2,4,6-Triisopropylbenzenesulfonylhydrazide was prepared as reported.[11] Alkyllithium reagents were obtained from Alfa-Ventron Corp. and stancardized prior to use.
"Standard workup" consisted of pouring the mixture into water, separating the crganic layer, and reextracting the aqueous layer with ether. The combined organic layers were washed to neutrality (removing TMEDA) with water and dried over magnesium sulfate. After concentration of the filtered solution in vacuo, it was diluted to known volume and an aliquot taken for GLC analysis. The aliquot was analyzed on a $^1/_8$ in. × 15 ft 6% SE-30 on Chromosorb W column (column A) using solutions of purified product as standard. Preparative GLC was done on a $^1/_4$ in. × 5 ft 20% SE-30 on Chromosorb W (column B). Microanalyses were performed by Galbraith Laboratories, Inc.
(39) Large particles tended to remain undissolved and were occluded in the product as it crystallized.
(40) Excess acid slows decomposition of the trisylhydrazide to diimide.
(41) This solution was treated with D_2O prior to recording the spectrum to ensure total N–H exchange.
(42) C. E. Griffen, *J. Org. Chem.*, **25**, 665 (1960).
(43) The forerun was 0.44 g of **25** contaminated with about 10% 1,3,5-triisopropylbenzene.
(44) S. Satsumabayashi, K. Nakajo, R. Soneda, and S. Motoko, *Bull. Chem. Soc. Jpn.*, **43**, 1586 (1970).

Notes

Leaving-Group Variation in Aprotic Bamford–Stevens Carbene Generation

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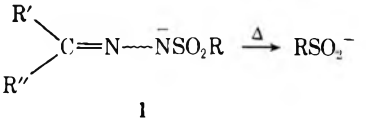
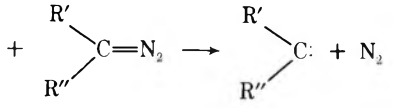
Thermal decomposition of the monoanions of tosylhydrazones **1** (R = *p*-tolyl) in aprotic solvents has become the standard method for generation of dialkyl carbenes.[1] The reaction is typically carried out at temperatures of 130 °C or higher, often in refluxing diglyme (161 °C). Carbenes can also be generated photochemically from **1**,[2] but the reaction is

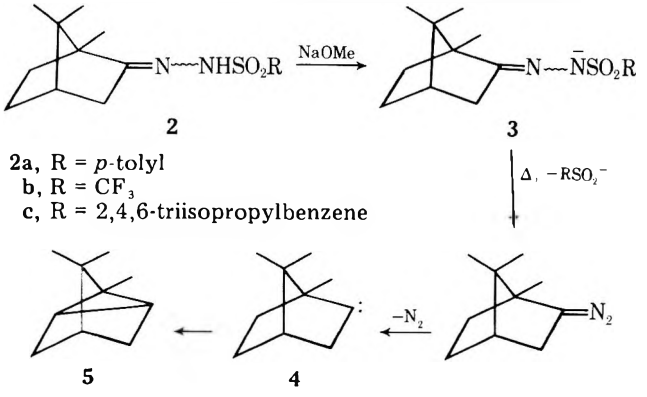


1



difficult to run on a large scale. In connection with another problem,[3] we had reason to investigate the variation of the R group in **1** and report here the results of that study which show that "trisylhydrazones" (**1**, R = 2,4,6-triisopropylbenzene) decompose at a much lower temperature in this aprotic Bamford–Stevens reaction.

We chose the camphor system **2** for our study, since exclusive formation of tricyclene **5** is a standard test[1] for the intermediacy of **4**. Camphene becomes an important product



2

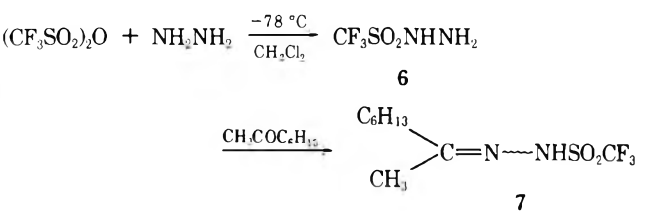
2a, R = *p*-tolyl
b, R = CF_3
c, R = 2,4,6-triisopropylbenzene

3

5 **4**

Under protic conditions, and bornylene is the product of Shapiro reaction[1b,4] conditions. Indeed, decomposition of **3a** at 161 °C produces **5** in essentially quantitative yield after 40 min.

In seeking a leaving group which would allow the reaction to proceed at a lower temperature, our attention was first directed toward trifylhydrazone **2b.** The enhanced leaving-group ability of the trifluoromethanesulfonate group[5] has been amply documented, particularly in the solvolytic generation of vinyl cations.[6] β eliminations of the trifluoromethylsulfinate group from nitrogen and carbon are also accelerated,[7] but the only reported α elimination, that of benzil monotrifylhydrazone, was merely reported to give the diazo ketone "quickly" at about 0 °C. Direct comparison with the tosylhydrazone was not made.[8] We initially attempted to prepare trifylhydrazide **6** as shown and were able to trap it in low yield at −78 °C with reactive ketones such as 2-octanone. All attempts at isolation of **6,** however, led to decomposition as first noted by Powell



6

7

and Whiting.[9] Less reactive ketones, including camphor, could not be trapped. Trifylhydrazone **2b** was therefore prepared by treatment of camphor hydrazone[10] with trifylanhydride in the presence of base.

Thermal decomposition of the sodium salt of **2b** at 161 °C does indeed produce **5** in a yield comparable with that obtained from **2a.** Unfortunately, the reaction is accelerated only slightly at best as shown in Table I for refluxing glyme (bp 85 °C). At this temperature both **3a** and **3b** decompose too slowly for practical purposes. We conclude that the increased leaving-group ability of the triflinate anion is about equally offset by increased stabilization of **3b,** making trifylhydrazones of little value for the aprotic Bamford–Stevens sequence.

We therefore sought an R group which might selectively destabilize the starting anion **3.** The report[11] that trisylhydrazide decomposes to diimide faster than tosylhydrazide prompted the study of decomposition of trisylhydrazone **2c.** The preparation of a wide variety of trisylhydrazones has been reported.[3,11] Indeed, thermal decomposition of the sodium salt **3c** is far faster than that of **3a** or **3b** as shown in Table I. In all

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Table I. Relative Rate of Decomposition of 3 in Refluxing Glyme (85 °C)

Hydrazone	% hydrazone remaining[a] t = 15 min	1 h	2 h	4 h
3a	94	87	*b*	60
3b	91	84	*b*	54
3c	49	15	0.4	<0.1

[a] Determined by HPLC as described in the Experimental Section. [b] Not determined.

three cases, **5** is formed with <2% camphene as an impurity. The reaction can be conveniently run in glyme or even THF, solvents much easier to purify and separate from product than diglyme. This dramatic decrease in reaction temperature should be of special value in the production of unstable carbene-derived products.[12] The enhanced rate of this elimination and those reported earlier[3,11] reflect steric destabilization of **3c** by the bulky ortho substituents.

Experimental Section[13]

Camphor Trifluoromethanesulfonylhydrazone (2b). Camphor hydrazone was prepared as described elsewhere[10] using 12.8 g (0.40 mol) of anhydrous hydrazine, 20 mL of ethanol, and 15.2 g (0.10 mol) of camphor. The concentrated crude product was not purified but simply dissolved in 100 mL of dichloromethane and 10.0 g (0.10 mol) of triethylamine. The temperature was lowered to −78 °C and 28.2 g (0.10 mol) of trifluoromethanesulfonic anhydride was added to the stirred solution. After addition was complete, the reaction mixture was allowed to warm to room temperature and then washed with 1 N HCl, water, and brine, dried over magnesium sulfate, and concentrated in vacuo. The resulting crude oil was taken up in 50 mL of heptane, heated on a steam bath, filtered hot, and allowed to crystallize in the refrigerator for 2 days. The prismatic crystals were washed with cold hexane and dried overnight to give 10.0 g (34%) of **2b**, mp 85–89 °C. One recrystallization from hexane raised the melting point to 88–90 °C: NMR δ 0.75, 0.95, 1.03 (3 s, 3 H each), 1.2–2.8 (m, 7 H), 7.95 (br s, 1 H); IR (cm^{-1}) 3320 (N–H), 1670 (C=N), 1410, 1135 ($-SO_2$), 1225, 1205, 1000.

Anal. Calcd for $C_{11}H_{17}F_3N_2O_2S$: C, 44.29; H, 5.74; N, 9.39. Found: C, 44.32; H, 5.82; N, 9.31.

Thermal Decomposition. General Procedure. The camphor sulfonylhydrazones **2** (1.0 mmol) were dissolved in 10 mL of freshly distilled solvent (diglyme, glyme, or THF). To the stirred solution was then added 4.0 mmol of sodium methoxide. The resulting milky mixture was heated under reflux for the appropriate time, as shown for the glyme experiments in Table I. The disappearance of **2** was conveniently followed by HPLC analysis on a Waters Associates 3.9 mm × 30 cm μ-Porsil column (hexane/chloroform/methanol solvent) using aliquots which were acidified with 1 N HCl and taken to known volume with ether. The results for glyme as solvent are shown in Table I. Product mixtures were worked up by extracting with 1 N NaOH and were analyzed by GLC on a ¼ in. × 10 ft 15% FFAP on Chromosorb W column at 120 °C, using o-xylene as internal standard. Tricyclene was the major product observed in all cases (75–95% yield), with camphene detected in trace quantity (≤2%).

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Registry No.—**2a** Na, 63866-11-5; **2b**, 63866-12-6; **2b** Na, 63866-13-7; **2c** Na, 63866-14-8; **5**, 508-32-7; camphor hydrazone, 770-53-6; trifluoromethanesulfonic anhydride, 358-23-6.

References and Notes

(1) (a) W. Kirmse, "Carbene Chemistry", 2nd ed, Academic Press, New York, N.Y., 1971; (b) R. H. Shapiro, *Org. React.*, **23**, 405 (1975).
(2) W. G. Dauben and F. G. Wiley, *J. Am. Chem. Soc.*, **84**, 1497 (1962).
(3) A. R. Chamberlin, J. E. Stemke, and F. T. Bond, *J. Org. Chem.*, preceding paper in this issue.
(4) Reference 1b; R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *J. Am. Chem. Soc.*, **89**, 1442 (1967).
(5) For a recent review, see R. D. Howells and J. D. McCown, *Chem. Rev.*, **77**, 69 (1977).
(6) M. Hanack, *Acc. Chem. Res.*, **3**, 209 (1970); P. J. Stang, *Prog. Phys. Org. Chem.*, **10**, 276 (1973).
(7) J. B. Hendrickson, A. Giga, and J. Wareing, *J. Am. Chem. Soc.*, **96**, 2275 (1974).
(8) J. B. Hendrickson, R. Bergeron, A. Giga, and D. Sternbach, *J. Am. Chem. Soc.*, **95**, 3412 (1973).
(9) J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959).
(10) D. H. R. Barton, J. F. McGhie, and P. J. Batten, *J. Chem. Soc. C*, 1033 (1970).
(11) N. J. Cusack, C. B. Reese, A. C. Risius, and B. Rodzpeikar, *Tetrahedron*, **32**, 2157 (1976).
(12) For examples where trisylhydrazones might have proven advantageous, see inter alia: (a) J. R. Neff and J. E. Nordlander, *J. Org. Chem.*, **41**, 2590 (1976); (b) F. T. Bond and L. Scerbo, *Tetrahedron Lett.*, 2789 (1968); (c) J. Meinwald, F. E. Samuelson, and M. Ikeda, *J. Am. Chem. Soc.*, **92**, 7604 (1970); (d) M. Oda, Y. Ito, and Y. Kitahara, *Tetrahedron Lett.*, 2587 (1975); (e) G. M. Kaufman, J. A. Smith, G. C. VanderStouw, and H. Shechter, *J. Am. Chem. Soc.*, **87**, 935 (1965).
(13) For general conditions see ref 3.

The Acetyl Function As a Protecting Group for Phenols

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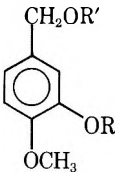
In the course of our current investigation of intramolecular phenolic coupling reactions[1] a number of diphenolic esters were required (e.g., **8** and **10**). While we were considering methods by which the phenolic groups could be protected during preparation of the ester linkages, our attention was drawn to a report concerning the reduction of phenyl esters.[2] In this study it was found that substituted phenyl esters of 3-phenylpropionic acid were reduced at least an order of magnitude more rapidly than the methyl ester. This observation suggested that the acetyl function might be useful as a protecting group for phenols. Although acetyls have been utilized for this purpose previously, they normally have been removed by treatment with aqueous acid or base.[3] The acid or base cleavage of phenols suffers from the disadvantage of not always being selective in the presence of other ester functional groups. A procedure for the selective removal of the acetyl group from phenols by reductive methods would greatly extend its utility as a protecting group.

The procedure was initially tested on the readily available diacetate **1**. Treatment of **1** with $NaBH_4$ in dimethoxyethane



1, R = R′ = C(O)CH_3
2, R = H; R′ = C(O)CH_3
3, R = C(O)CH_3; R′ = H

(DME) for 18 h at 40 °C afforded an 87% yield of the monoacetate **2**. The structure of **2** was assigned by comparison of its NMR spectrum with spectra of related compounds. The resonances due to the benzyl protons appear at δ 4.90 in the diacetate **1** and at δ 4.36 and 4.56 in alcohol **3** and isovanillin alcohol, respectively. Since the corresponding resonance occurs at δ 4.93 in **2**, **2** must be a benzyl acetate.

When *p*-acetoxybenzyl acetate (**4**)[4] was treated in the same manner, *p*-cresol was obtained in quantitative yield. No *p*-hydroxybenzyl acetate (**5**) could be isolated. Hayaski and Oka

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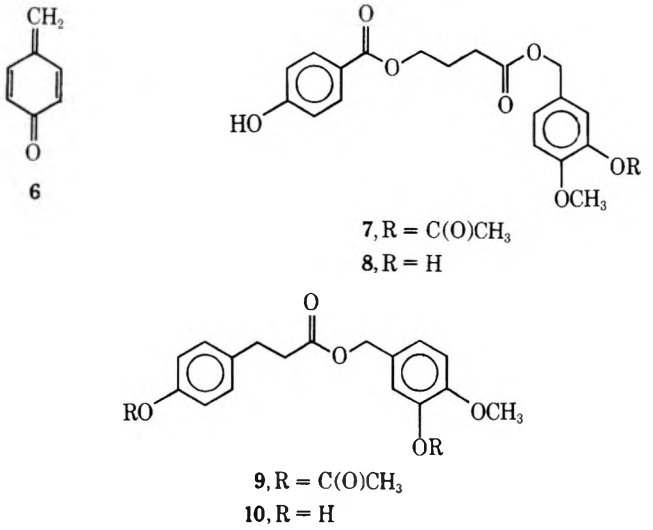
found that **4** gave good yields of *p*-hydroxybenzyl compounds when treated with nucleophiles.[5] Similar results were obtained with o-acetoxybenzyl acetate. The quinone methide (**6**) (or the ortho analogue) was postulated to be an intermediate in these reactions. Under the reduction conditions, **6** would be expected to be reduced to *p*-cresol. Since a quinone methide intermediate cannot be readily obtained from 3-acetoxybenzyl acetates, **2** would be expected to cleave without further reduction.

Monoacetate **3**, prepared by selective acetylation[6] of isovanillyl alcohol,[7] was converted into triester **7**.[8] Selective reduction of the triester with excess $NaBH_4$ produced the diphenol in 77% yield. Diacetate **9** was prepared from **3** by acylation with 3-(*p*-acetoxyphenyl)propionyl chloride.[9] Deacetylation of **9** afforded the diphenol **10** in 50% overall yield.



The procedure may be used to selectively cleave phenyl acetates in the presence of unsaturated esters. Thus, methyl *p*-acetoxycinnamate (**11**)[11] was converted to methyl *p*-hydroxycinnamate[11] in 90% yield.

These results indicate that a phenyl acetate may be reduced selectively in the presence of benzyl esters, benzoates, and cinnamates. Thus, $NaBH_4$ cleavage, in combination with selective acetylation, makes the acetyl group a very useful protecting group for phenols. Its utility in the hydroxybenzyl alcohol series is limited to those cases in which the hydroxyl group is in the 3 position.

Experimental Section

Representative examples of the acetate reduction and monoacetylation procedures are given here.

Reduction of Phenyl Acetates. 3-Hydroxy-4-methoxybenzyl Acetate (2). To a solution of 238 mg (1 mmol) of isovanillin alcohol diacetate (**1**)[4] in 5 mL of DME was added 200 mg (5.4 mmol) of sodium borohydride. The rapidly stirred suspension was heated at 45 °C for 18 h. After cooling in an ice–methanol bath, the reaction mixture was cautiously diluted with 5 mL of saturated aqueous NH_4Cl. The mixture was then diluted with 15 mL of ether and the organic layer was washed with saturated NH_4Cl (2 × 10 mL) and saturated NaCl (2 × 10 mL). After drying (Na_2SO_4) the organic layer was concentrated (in vacuo) to a pale yellow oil. Preparative TLC on silica gel (5% 2-propanol–benzene) afforded 171 mg (76% yield) of **2**: IR (film) 3420 (vb), 1750 (b), 1620 cm^{-1}; NMR ($CDCl_3$) δ 2.03 (s, 3 H, $-C(O)CH_3$), 3.80 (s, 3 H, $-OCH_3$), 4.93 (s, 2 H, $-CH_2Ar$), 5.73 (brs, 1 H, –OH), 6.7–6.9 (m, 3 H, aryl).

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.41; H, 6.25.

Monoacetylation. 3-Acetoxy-4-methoxybenzyl Alcohol (3). Isovanillin alcohol (4.6 g, 30 mmol) was dissolved in aqueous potassium hydroxide (7 mL, 45 mmol). To this vigorously stirred solution was added 15 g of ice followed by 3.84 g (37 mmol) of acetic anhydride.[12] After the temperature had risen to 20 °C, an additional 250 mL of water was added and the mixture stirred for 0.5 h. The aqueous solution was then extracted with ether (3 × 30 mL). The combined extracts were washed with water (2 × 20 mL) and 20 ml of aqueous NaCl, dried (Na_2SO_4), and concentrated (in vacuo) to a pale yellow oil. Distillation of this oil [195–196 °C (0.25 Torr)] afforded 4.9 g (85% yield) of **3** along with a small amount of **1**. Separation of **3** from **1** could also be achieved in 37% yield by formation of the hexane-insoluble complex of **3** with $CaCl_2$.[13]

An analytical sample of **3** was obtained by preparative TLC (silica gel; 10% ether–benzene) followed by bulb-to-bulb distillation (Kugelrohr). **3**: IR (film) 3395, 1765, 1620 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (s, 3 H, $-C(O)CH_3$), 3.40 (brs, 1 H, –OH), 3.70 (s, 3 H, $-OCH_3$), 4.36 (s, 2 H, $-CH_2Ar$), 6.8 (m, 3 H, aryl).

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.41; H, 6.01.

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Supplementary Material Available: Detailed procedures for the treatment of **4** with $NaBH_4$ and for the preparation of compounds **1**, **8**, and **10** (3 pages). Ordering information is given on any current masthead page.

Registry No.—**1**, 63866-99-9; **2**, 63867-04-9; **3**, 63867-05-0; **4**, 2937-64-6; **7**, 63867-01-6; **8**, 63867-02-7; **10**, 63876-03-8; isovanillin alcohol, 4383-06-6; acetic anhydride, 108-24-7; acetyl chloride, 75-36-5; 3-(*p*-acetoxyphenyl)propionyl chloride, 63867-00-5.

References and Notes

(1) K. Crelling and J. Quick, 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Aug 1976, Abstract No. ORGN-11.
(2) S. Takahashi and L. Cohen, *J. Org. Chem.*, **35**, 1505 (1970).
(3) E. Haslam in "Protective Groups in Organic Chemistry", J. McOmie, Ed., Plenum Press, New York, N.Y., 1973, p 172.
(4) B. Ruderman, *J. Soc. Chem. India*, **64**, 204 (1945).
(5) H. Hayashi and S. Oka, *Bull. Inst. Chem. Res., Kyoto Univ.*, **52**, 514 (1974).
(6) R. Grice and L. Owen, *J. Chem. Soc.*, 1947 (1963).
(7) H. Lock, *Ber.*, **62**, 1177 (1929).
(8) J. Quick and J. K. Crelling, manuscript in preparation.
(9) Prepared from 3-(*p*-acetoxyphenyl)propionic acid.[10]
(10) M. Winter, *Helv. Chim. Acta*, **44**, 2110 (1961).
(11) H. Stelmach and K. A. Conners, *J. Am. Chem. Soc.*, **92**, 863 (1970).
(12) F. Chattaway, *J. Chem. Soc.*, 2495 (1931).
(13) K. Sharpless, A. Chong, and J. Scott, *J. Org. Chem.*, **40**, 1252 (1975).

Triphase Catalysis. C-Alkylation of Nitriles

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In two recent papers[1,2] Regen introduced the new concept of triphase catalysis to describe a process of phase-transfer catalysis in which the ammonium salt was supported on a polymer insoluble in the reaction medium (e.g., anion-exchange resins). Two reactions were tested: the cyanide displacement on 1-bromooctane and 1-chlorooctane and the generation of dichlorocarbene from chloroform. In both cases, the reaction proceeds normally (e.g., as expected in two-phase catalysis[3-6]), but at higher temperatures and with longer reaction time. Also, almost at the same period anion-exchange resins were used in the synthesis of esters,[7] tetrahydropyrimidines,[8] and other reactions.[9-11]

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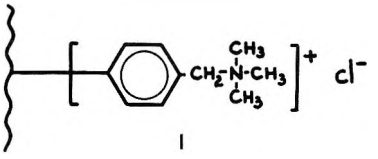
We wish to report in this note several results giving information on the reaction of C-alkylation catalyzed by anion-exchange resins (triphase catalysis). In this type of reaction it is important to point out the main differences in mechanism between the "true" phase-transfer catalysis and the "interfacial" catalysis, as both may be applied to triphase processes. In fact, in a reaction such as the alkylation of phenol or the cyanide displacement on 1-bromooctane using quaternary ammonium salt as catalyst, one of the reactants is transferred across the interface into the organic phase, where it exists in the form of an ion pair.

However, the situation seems to be rather different with substances containing labile hydrogens, for example, phenylacetonitrile (PAN). As Makosza[12,13] has shown, the alkylation of PAN can take place at the phase boundary. In such a reaction, carbanions seem to be formed at the interface upon the action of aqueous sodium hydroxide on PAN. These same carbanions then form organic phase soluble ion pairs (substrate$^-NR_4^+$) with cations supplied by the catalyst.

Now, in the case of triphase catalysis applied to the alkylation of PAN, the reaction mechanism will perhaps be more complicated, owing to the interference of carbanions coming from the phase boundary or from the hydrogen abstraction by hydroxide anion initially associated with the ammonium cations in the organic phase ($-NR_3^+OH^-$ belonging to the resin).

With a view to providing the best possible information we have determined the yield of the well-known reaction of PAN with *n*-butyl bromide using both classical phase-transfer catalysis (quaternary ammonium or phosphonium salts) and triphase catalysis. The resins used for this purpose were of the Dowex type: (a) Dowex 1-X8, 20–50 mesh ionic form Cl^-; (b) Dowex 2-X4, 20–50 mesh ionic form Cl^-; (c) Dowex 2-X8, 20–50 mesh ionic form Cl^-; (d) Dowex 11, 16–20 mesh ionic form Cl^-; (e) Dowex 21K, 20–50 mesh ionic form Cl^-; (f) Dowex 44, 20–50 mesh ionic form Cl^-/OH^-.

The structure of the resins of the types a, d, e, and f is indicated in I and that of the types b and c in II.[14]



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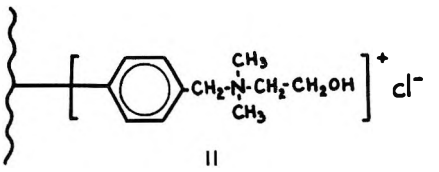

II

The results obtained are indicated in Tables I–V. In Table I we have summarized the results concerning the effect of various quaternary ammonium salts on the alkylation of phenylacetonitrile. Table II shows the effect of type and amount of resins, concentration of sodium hydroxide, temperature, and time on the reaction yield and selectivity (e.g., percent of dialkylated product). In Table III we have particularly examined the repeatability of the reaction using the same resins. Table IV indicates the result of the attempt made to protect the resin from contact with 50% sodium hydroxide by solvents of various type. Finally Table V shows the limit of the applicability of triphase catalysis. For this purpose we have alkylated different nitriles using this type of catalysis.

Discussion

Comparison of the different results obtained enables us to conclude that catalysis using resins (triphase catalysis) requires, in our case, more drastic conditions than biphase catalysis.

However, to make possible a better comparison we have determined by titration, and under our experimental conditions, the OH^- equivalent of 2 g of Dowex 1-X8 resin. We have found that 2 g of this resin is equivalent to a 0.0045 M aqueous solution of NaOH. Therefore, 4 g of Dowex 1-X8 used with 0.1 mol of substrate would be approximately equivalent to 10% of quaternary ammonium hydroxide per mole of substrate. This comparison shows again that for the resins to catalyze the reactions as efficiently as quaternary ammonium salts, the reaction conditions have to be more drastic.

Another remark is that whatever the catalyst (salt or resin) when the concentration of NaOH is low, the yield of hydrolysis of the nitrile and halide used is considerable.

To obtain information also on the behavior of alkyl iodide under our catalytic conditions, we have studied the alkylation of phenylacetonitrile with ethyl iodide. We have found that (see Experimental Section) the resins have no catalytic effect on this type of reaction: with or without a resin the overall yield of the alkylation was 30% after a reaction time of 2 h.

Table I. Alkylation of Phenylacetonitrile with Various Ammonium or Phosphonium Salts as Catalysts

Amount of catalysts[a]	Temp, °C	Reaction time, h	NaOH concn % by wt	% yield	
				Monoalkylation	Dialkylation
		Trimethylhexadecylammonium Bromide (CTAB)[b]			
1	70	5	50	60	1
10	35	10	10	32	1
		Triethylbenzylammonium Chloride (TEBA)[b]			
1	70	6	50	84	5
6	35	20	50	90	5
		Tetrabutylammonium Bromide (TBAB)[b]			
0.1	70	10	50	35	1
1	70	5	50	60	8–9
1	25	20	50	83	11
6	25	20	50	86	11
		Tributylhexadecylphosphonium Bromide (CTPB)[b]			
0.1	70	10	50	88	9
1	70	5	50	70	13
1	25	20	50	82	7
6	25	20	50	86	8

[a] In percent for 100% of substrate. [b] Registry no.: CTAB, 57-09-0; TEBA, 56-37-1; TBAB, 1643-19-2; CTPB, 14937-45-2.

Table II. Alkylation of Phenylacetonitrile

Amount of resin, g	Temp, °C	Reaction time, h	NaOH concn % by wt	Overall % yield	% dialkylation
			Dowex 1-X8[a]		
0.4	70	10	50	40	5
1	70	10	50	49	3
1	70	20	50	84	6
4	70	10	50	60	7
8	70	10	50	68	7
4	70	10	10	8.5	
4	70	5	50	20	
			Dowex 2-X4[a]		
1	70	10	50	72	4.5
4	70	10	50	69	7
			Dowex 2-X8[a]		
1	70	10	50	50	4
4	70	10	50	67	7
4	70	10	10	6	
			Dowex 11[a] 16–20 mesh		
1	70	10	50	58	1
4	70	10	50	55	5
			Dowex 21K[a]		
1	70	10	50	54	1
4	70	10	50	60	2
			Dowex 44[a]		
1	70	10	50	70	3
4	70	10	50	70	3
			Without Catalyst		
0	70	10	50	22	3

[a] Registry no.: Dowex 1-X8, 12627-85-9; Dowex 2-X4, 56996-51-1; Dowex 2-X8, 11138-20-8; Dowex 11, 9049-12-1; Dowex 21K, 9065-04-7; Dowex 44, 56996-52-2.

Table III. Repeatability of the Alkylation Reaction

Dowex 1-X8, 20–50 mesh		Dowex 2-X4, 20–50 mesh	
Run no.	Overall % yield	Run no.	Overall % yield
1	58	1	69
2	60	2	68
3	38	3	60
Dowex 2-X8, 20–50 mesh		Dowex 11, 16–20 mesh	
1	67	1	55
2	71	2	47
3	50	3	36
Dowex 21K, 20–50 mesh		Dowex 44, 20–50 mesh	
1	60	1	70
2	57	2	49
3	61	3	48

This result is different from those obtained with systems in which the ammonium groups are stoichiometric with respect to the anions.

The repeatability of the reaction is, however, not very good. This may be due to loss of catalytic activity by destruction of the resin backbone, or by dequaternization of the resin, which bears a benzyl group which behaves as good leaving group in such reaction.[15]

These overall results show that the use of resins in such reactions is possible but, with respect to the yields obtained with ammonium or phosphonium salts, the process is not the better one. New resins, which will lead to a better repeatability, will be necessary in such processes.

Experimental Section

(1) Biphase Catalysis. Phenylacetonitrile (0.1 mol), x mol % (see Table I) of catalyst per mole of substrate, 0.1 mol of n-butyl bromide, and 40 cm^3 of NaOH (50 or 10% by weight) are stirred magnetically at 70 °C (or other temperatures as stated). At the end of the reaction the crude products are washed with water and analyzed by GLC.

Table IV. Alkylation of Phenylacetonitrile Using Dowex 1-X8 Resin and Various Solvents

Amount of resin, g	Temp, °C	Reaction time, h	NaOH concn % by wt	Solvent	Overall % yield
4	80	10	50	Benzene	23
4	70	10	50	Cyclohexane	5
4	70	10	50	Dioxane (1) Cyclohexane (1)	10

Table V. Alkylation of other Nitriles

Registry no.	Nitriles[a]	% yield of monoalkylation
22364-68-7	o-methylphenylacetonitrile	60[b]
3215-64-3	2,6-Dichlorophenylacetonitrile	25[b]
124-12-9	n-Octylnitrile	0
766-05-9	Cyclohexylnitrile	0

[a] Using 4 g of Dowex 2-X4, 20–50 mesh, and a reaction time of 10 h for a reaction temperature of 70 °C. [b] The dialkylation yield found to be about 1%.

(2) Triphase Catalysis. Nitrile (0.1 mol), 0.1 mol of *n*-butyl bromide, 40 cm^3 of NaOH (50 or 10% by weight), and *x* g of resin (see Table II) were stirred vigorously at 70 °C for *x* h. At the end of the reaction the resin was removed by filtration, and the organic layer was separated and treated as usual.

(3) Use of an Alkyl Iodide. The same conditions as above were used, with 4 g of Dowex 1-X8, at a temperature of 70 °C for 10 h.

(4) Determination of the Equivalence of the Catalytic Action of the Salts and Resin. Dowex 1-X8 resin (2 g) was stirred for 30 min with 40 cm^3 of 50% (by weight) NaOH. After this time, the resin was removed by filtration and washed with distilled water (no reaction to phenolphthalein was observed). The resin was then titrated with dilute hydrochloric acid (helianthine used as indicator).

(5) Structure of the Products. The identification of the products has been carried out by GLC/MS (Varian MAT 111). Monoalkylated products: $C_{12}H_{15}N$ 173, 158, 144, 130, 129, 118, *117*, 116, 91, 90, 77, 57, 41; $C_{13}H_{17}N$ 187, 144, 143, 132, *131*, 130, 105, 104, 103, 91, 77, 65, 63, 57, 41; $C_{12}H_{13}NCl_2$ 245, 243, 241, 208, 206, 189, *185*, 182, 150, 114, 57, 41; $C_{10}H_{11}N$ 145 (45.8), 118 (8.3), 117 (100), 116 (87.5), 91 (41.6), 90 (29.1), 89 (20.8), 78 (4.1), 77 (4.1), 63 (8.3), 51 (8.3), 39 (6.2). Dialkylated product: $C_{16}H_{23}N$ 229, 187, *173*, 172, 158, 145, 130, 118, 117, 116, 91, 77, 58.

Registry No.—Butyl bromide, 109-65-9; ethyl iodide, 75-03-6; phenylacetonitrile, 140-29-4; α-butylphenylacetonitrile, 3508-98-3; α-butyl-o-methylphenylacetonitrile, 63866-33-1; α-butyl-2,6-dichlorophenylacetonitrile, 58830-65-2; α-ethylphenylacetonitrile, 769-68-6; α,α-dibutylphenylacetonitrile, 3508-99-4.

References and Notes

(1) S. L. Regen, *J. Am. Chem. Soc.*, **97**, 5956 (1975).
(2) S. L. Regen, *J. Am. Chem. Soc.*, **98**, 6270 (1976).
(3) E. V. Dehmlow, *Angew. Chem., Int. Ed. Engl.*, **13**, 170 (1974).
(4) A. W. Herriott and D. Picker, *J. Am. Chem. Soc.*, **97**, 2345 (1975).
(5) C. M. Starks, *J. Am. Chem. Soc.*, **95**, 3613 (1973).
(6) G. Cainelli and F. Manescalchi, *Synthesis*, 723 (1975).
(7) A. Bernardus, Petrolite Corp., U.S. Patent 3 904 625 (Sept 1975).
(8) J. Dockx, *Synthesis*, 441 (1973).
(9) D. L. Rakhmankulov, V. R. Melikyan, and S. S. Zlotska, *Khim. Tekhnol. Elementoorg. Soedin. Polim.*, 903 (1975).
(10) N. Yoshio, *Yuki Gosei Kagaku Kyokai Shi*, 903 (1975).
(11) G. Gelbard and S. Colonna, *Synthesis*, 113 (1977).
(12) M. Makosza, "Modern Synthetic Methods, Naked Anions", Phase-Transfer Conference Paper, International Workshop on Modern Synthetic Methods, Rolf Scheffold, Ed., University of Bern, 1976.
(13) M. Makosza, personal communication.
(14) According to the manufacturer of the resins used, the complete name for each resin will include: (1) type, i.e., Dowex 1, 2, 21K, Dowex 50. (2) "X number" or percent divinylbenzene, i.e., X8. The Dowex resins used are based on styrene divinylbenzene copolymer. Sulfonation of these copolymers with sulfuric acid yields strong cation resin, while "amination" with amines yields anion resins. (3) Mesh size, i.e., 20–50 mesh (based on U.S. standard screen). (4) Ionic form, i.e., Cl^-. Dowex 1, Dowex 2, Dowex 11 and Dowex 21K resins are strong-base anion-exchange resins. All incorporate a quaternary ammonium functionality. Dowex 1, Dowex 11, and Dowex 21K resins are type 1 resins. In type 1 resins the four substituents on the nitrogen atom are a polymeric benzyl and three methyl groups. Dowex 2 resin is a type 2 resin in which one of the methyl groups is replaced by an ethanol group. Type 1 and type 2 resins differ primarily in their affinities for the hydroxide ion relative to other anions, and in chemical stability. Type 2 resins are more efficiently converted to the hydroxide form than type 1 resins, but the type 1 resins are inherently more stable chemically especially in the hydroxide form.
(15) H. J. M. Dou, P. Hassanaly, R. Gallo, J. Metzger, to be submitted for publication.

Improved Syntheses of Bis(pentafluorophenyl)acetylene, (Pentafluorophenyl)phenylacetylene, and Hexakis(pentafluorophenyl)benzene

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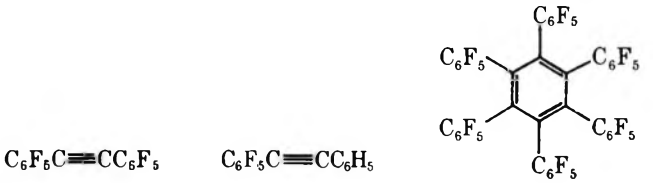
During the course of some recent investigations concerning the reactions of organometallic complexes with partially and completely halogenated diarylacetylenes,[1] we have been required to synthesize various quantities of bis(pentafluorophenyl)acetylene (1) and (pentafluorophenyl)phenylacetylene



1 2 3

(2). As a result, we have developed reliable experimental procedures based on the commercially available reagent bromopentafluorobenzene, from which reasonable quantities of these acetylenes can be obtained. Moreover, a new synthesis of hexakis(pentafluorophenyl)benzene (3) is also presented.

Several synthetic routes to 1 have been reported.[2-8] Many of these, however, are not convenient for the production of practical amounts of this acetylene. Birchall et al.[2] have described a useful but potentially hazardous preparation of 1 in 56% yield by the cobalt-catalyzed reaction of pentafluorophenylmagnesium bromide with diiodoacetylene. A major drawback of this method involves the use of diiodoacetylene, a compound well known for its thermal and mechanical instability.[9]

Perhaps the most useful preparation of bis(polyhaloaryl)acetylenes such as 1 has been suggested by Gilman and coworkers.[6] Their method utilizes the reaction of polyhaloarylcopper reagents or their complexes with polyhaloethylenes or polyhaloethanes. The use of this method for the synthesis of 1 has been alluded to several times in the literature, but unfortunately no detailed experimental procedures have ever been reported.[7,8] The preparation of 1 presented here is therefore based upon the original communication of Gilman et al.[6] and consists of the reaction of pentafluorophenylcopper, formed from pentafluorophenylmagnesium bromide and cuprous iodide, with tetrabromoethylene.

$$C_6F_5Br \xrightarrow[(2)\ CuI]{(1)\ Mg,\ THF} C_6F_5Cu \xrightarrow[\Delta]{C_2Br_4} 1$$

Of the several reported procedures for the synthesis of 2,[3,10-13] the most useful involves the reaction of iodopentafluorobenzene with phenylethynylcopper. A wide range of conditions, i.e., solvent, reaction temperature, and time, has been employed, and the yields vary from 20 to 74%.[3,11,12] Under similar conditions the reaction of bromopentafluorobenzene and phenylethynylcopper gave both lower yields of 2 as well as a more difficult purification. In the present synthesis of 2, we have found that by reversing the functionality of the aforementioned reagents, i.e., using pentafluorophenylcopper and phenyliodoacetylene, good yields of 2 can be conveniently obtained. This method thus eliminates the purchase or tedious preparation[11] of iodopentafluorobenzene.

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Table I. Cyclic Trimerization of Bis(pentafluorophenyl)-acetylene (1) with Bis(tetracarbonylcobalt)mercury

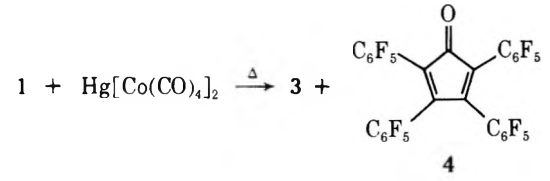
Method	Time, min	Temp, °C	% Yield[a] 3	% Yield[a] 4
A	25	230–240	57	Trace
B	30	245–250	49	4.5
C	270	101	7	0

[a] Based on unrecovered 1.

$$C_6F_5Cu + IC{\equiv}CC_6H_5 \xrightarrow{Et_2O} 2$$

Hexakis(pentafluorophenyl)benzene (3) has been suggested for use as a high mass marker in mass spectrometry.[1a] It is not a readily available compound, however, and has only been obtained as a product in the reactions of various rhodium- and iridium–carbonyl complexes with 1.[1a,b,e] The best yields of this trimerization product (40–70%) resulted from the use of $(\eta^5\text{-}C_5H_5)Rh(CO)_2$.[1a] More recent work in our laboratories has shown that the yields of 3 produced in this reaction fluctuate widely and are often not reproducible. Moreover, $(\eta^5\text{-}C_5H_5)Rh(CO)_2$ is an expensive reagent for use in this synthesis.

The cyclic trimerization of acetylenes in the presence of metal carbonyls is a well-known phenomenon in organometallic chemistry.[14] Employment of cobalt–carbonyl complexes such as $Co_2(CO)_8$,[14] $Hg[Co(CO)_4]_2$,[15] and $(\eta^5\text{-}C_5H_5)Co(CO)_2$[16] as reagents have produced good results for many disubstituted acetylenes. In an attempt to devise a more convenient and reproducible synthesis of 3, the reaction of 1 with bis(tetracarbonylcobalt)mercury was investigated.



4

Several methods were examined and the results are summarized in Table I. Method A consists of a melt-phase reaction in which the internal pressure of the reaction vessel is maintained at atmospheric pressure. This procedure gave the best overall results. Method B is a melt-phase reaction performed in a sealed tube, while method C consists of refluxing the reagents in dioxane.

Both methods A and B gave good yields of the trimer 3. Method B, however, also produced small but isolable amounts of tetrakis(pentafluorophenyl)cyclopentadienone (4). The formation of this carbonyl insertion product is probably enhanced by the large internal CO pressure generated in the sealed tube. Method C, while the method of choice for many other disubstituted acetylenes,[15] gave the poorest yield of 3.

Experimental Section

All reactions were carried out under a nitrogen atmosphere unless otherwise stated. Cuprous iodide[17] and bis(tetracarbonylcobalt)-mercury[18,19] were synthesized using published procedures. Tetrahydrofuran (THF) and diethyl ether were dried and distilled over sodium–benzophenone under nitrogen before use. Infrared spectra were recorded on a Beckman IR-10 instrument. Mass spectra were determined on a Perkin-Elmer-Hitachi RMU-6L instrument. Bromopentafluorobenzene and tetrabromoethylene were used as purchased from Bristol Organics, Ltd., Bristol, England, and the Columbia Organic Chemicals Co., Charleston, S.C., respectively. Melting points are uncorrected and were taken in open capillaries.

Preparation of Bis(pentafluorophenyl)acetylene (1). A 250-mL three-necked flask fitted with a magnetic stirrer, a nitrogen inlet valve, a condenser with a mercury overpressure valve, and a pressure-equalizing addition funnel was evacuated and flushed with nitrogen. Into this flask were placed dry magnesium turnings (2.43 g, 0.10 mol) and 35 mL of THF. A solution of bromopentafluorobenzene (24.7 g, 0.10 mol) in 50 mL of THF was added dropwise at such a rate as to promote a gentle reflux. After the addition was complete, the reaction mixture was refluxed for 20 min.

The reaction mixture was then cooled to 0 °C, freshly prepared cuprous iodide[1] (21.0 g, 0.11 mol) and 20 mL of THF (to facilitate stirring) were added, and the temperature was maintained for 3 h. A solution of tetrabromoethylene (11.6 g, 0.034 mol) in 50 mL of THF was then added and the mixture refluxed for 40 h.[20] The reaction mixture was cooled and hydrolyzed with 60 mL of water, and the THF was removed by means of a water aspirator. The residue was extracted with three 100-mL portions of ether. The extracts were combined and then dried over anhydrous magnesium sulfate. The solution was filtered and the solvent was removed.

Sublimation of the resulting brown residue at 50 °C (10^{-2} Torr) produced small amounts of unreacted tetrabromoethylene. Further sublimation at 90 °C (10^{-2} Torr) gave 8.6 g (66%) of 1: mp 108–109 °C. Recrystallization from hexane or methanol afforded 6.4 g (52%) of product: mp 121–122 °C (lit.[2] 123–123.5 °C).

Preparation of (Pentafluorophenyl)phenylacetylene (2). Pentafluorophenylcopper was prepared in diethyl ether as indicated above from pentafluorophenylmagnesium bromide, formed from magnesium (0.54 g, 0.022 mol), 70 mL of diethyl ether, bromopentafluorobenzene (5.48 g, 0.022 mol) and cuprous iodide (4.18 g, 0.022 mol).

Simultaneously,[21] to a solution of phenylacetylene (2.24 g, 0.022 mol) in 40 mL of diethyl ether which had been cooled in a dry ice–acetone bath was added 9.8 mL of a 2.25 M *n*-butyllithium–hexane solution at such a rate to maintain the temperature at −70 °C. To this stirred solution was added iodine (5.58 g, 0.022 mol) in 30 mL of ether dropwise until a faint red color persisted. Throughout the addition the temperature was held at −70 °C.

The phenyliodoacetylene solution was then transferred under nitrogen to a jacketed addition funnel maintained at −70 °C and added dropwise over a period of 20 min to the pentafluorophenylcopper reagent at 0 °C. The reaction mixture was then allowed to stir for 30 min each at 0 °C and at room temperature. The reaction mixture was subsequently hydrolyzed with 150 mL of 6% hydrochloric acid and washed with two 250-mL portions of water, 5% sodium bicarbonate solution, and water in that order. The resulting ether solution was then decolorized with charcoal, dried over magnesium sulfate, and filtered. To the solution was added silica gel (30–40 g) and the solvent was removed. The coated silica was placed on a silica gel column (4 × 50 cm) which had been packed dry. Elution of this column with ca. 1 L of hexane produced 5.2 g of the acetylene 2. Recrystallization from hexane yielded 4.9 g (82%) of 2, mp 92–93 °C (lit.[11] 93–94 °C; lit.[12] 105–106 °C).

Reaction of Bis(pentafluorophenyl)acetylene (1) and Bis-(tetracarbonylcobalt)mercury. Method A. Bis(pentafluorophenyl)acetylene (1.08 g, 3.02 mmol) and bis(tetracarbonylcobalt)-mercury (0.100 g, 0.184 mmol) were added to a Schlenk tube (4 × 15 cm) fitted with a mercury overpressure valve and which had been evacuated and flushed with nitrogen. The Schlenk tube was heated to 230–240 °C via a Wood's metal bath for 25 min. The tube was then cooled and the contents extracted with methylene chloride and filtered. The extraction was continued until the filtrate remained colorless. The residual gray-black solid was dried and sublimed at 205–210 °C (10^{-3} Torr) to give 0.446 g (41%, 57% based on unrecovered 1) of a white solid identified by infrared and mass spectrometry and by comparison to an authentic sample[1a] as hexakis(pentafluorophenyl)benzene (3).

The solvent was removed from the filtrate and the residue sublimed at 90 °C (10^{-2} Torr) to give 0.302 g (28% recovery) of unreacted 1. TLC analysis of the residue from the sublimation indicated the presence of trace amounts of tetrakis(pentafluorophenyl)cyclopentadienone (4) (vide infra).

Method B. Bis(pentafluorophenyl)acetylene (1.70 g, 4.75 mmol) and bis(tetracarbonylcobalt)mercury (0.100 g, 0.184 mmol) were introduced into a thick-walled (3 mm) Pyrex tube (2 × 12.5 cm) and the tube was sealed under vacuum. The sealed tube was then immersed in a Wood's metal bath maintained at 245–250 °C for 30 min, allowed to cool, and *cautiously* opened. The reaction mixture was extracted with methylene chloride and filtered. The extraction was continued until the filtrate remained colorless. The residual gray-black solid was dried and sublimed at 205–210 °C (10^{-3} Torr) to give 0.396 g (23%, 49% based on unrecovered 1) of 3.

The solvent was removed from the orange filtrate and the residue

sublimed at 90 °C (10^{-2} Torr) to give 0.890 g of unreacted **1** (52% recovery). A red solid remained which was dissolved in methylene chloride. Alumina (1 g) was added, the solvent was removed in vacuo and the material was added to a dry alumina column (2 × 20 cm). Elution with benzene gave a red band. The solvent was removed and the residue was crystallized from chloroform to give 0.075 g (5%) of tetrakis(pentafluorophenyl)cyclopentadienone (**4**), which was identified by comparison to a known sample: mp 243–244 °C (lit.[2] 231–231.5 °C); M^+ 744 (mass spectrometry) (calcd: 744).

Method C. Bis(pentafluorophenyl)acetylene (1.00 g, 2.79 mmol) and bis(tetracarbonylcobalt)mercury (0.100 g, 0.184 mmol) were refluxed in 25 mL of dioxane for 4.5 h under nitrogen with magnetic stirring. The reaction mixture was cooled and filtered in air, and the residue was washed with methylene chloride to give small amounts of metallic mercury. The solvent was removed from the filtrate and the residue sublimed at 90 °C (10^{-3} Torr) to give 0.834 g (83% recovery) of unreacted **1**. Further sublimation of the residue at 200–205 °C (10^{-3} Torr) gave 0.012 g of **3** (1.2%, 7.2% based on unrecovered **1**).

Acknowledgments. Acknowledgment is made to the National Science Foundation and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work. The authors are also grateful to Dr. H. Gilman and Dr. W. Hübel for helpful suggestions concerning the syntheses of **1** and **3**, respectively. The assistance of Mr. David Levine in certain aspects of the experimental work is also appreciated. M.D.R. is grateful to the Alexander Von Humboldt-Stiftung, Bonn/Bad Godesburg, West Germany, for a fellowship.

Registry No.—**1**, 13551-43-2; **2**, 13509-88-1; **3**, 35525-35-0; **4**, 15070-92-5; bromopentafluorobenzene, 344-04-7; tetrabromethylene, 79-28-7; pentafluorophenylcopper, 18206-43-4; phenylacetylene, 536-74-3; phenyliodoacetylene, 932-88-7; bis(tetracarbonylcobalt)-mercury, 13964-88-0.

References and Notes

(1) (a) M. D. Rausch, P. S. Andrews, and S. A. Gardner, *Organomet. Chem. Synth.*, **1**, 289 (1970); (b) S. A. Gardner, P. S. Andrews, and M. D. Rausch, *Inorg. Chem.*, **12**, 2396 (1973); (c) S. A. Gardner, E. F. Tokas, and M. D. Rausch, *J. Organomet. Chem.*, **92**, 69 (1975); (d) R. G. Gastinger, M. D. Rausch, D. A. Sullivan, and G. J. Palenik, *J. Am. Chem. Soc.*, **98**, 719 (1976); (e) R. G. Gastinger, M. D. Rausch, D. A. Sullivan, and G. J. Palenik, *J. Organomet. Chem.*, **117**, 355 (1977).
(2) J. M. Birchall, F. L. Bowden, R. N. Haszeldine, and A. B. P. Lever, *J. Chem. Soc. A*, 747 (1967).
(3) R. Filler and E. W. Heffern, *J. Org. Chem.*, **32**, 3249 (1967).
(4) E. J. Soloski, W. E. Ward, and C. Tamborski, *J. Fluorine Chem.*, **2**, 361 (1971).
(5) R. D. Chambers, M. Clark, J. A. H. McBride, W. K. R. Musgrave, and K. C. Srivastava, *J. Chem. Soc., Perkin Trans. 1*, 125 (1969).
(6) A. E. Jukes, S. S. Dua, and H. Gilman, *J. Organomet. Chem.*, **12**, P44 (1968).
(7) A. F. Webb and H. Gilman, *J. Organomet. Chem.*, **20**, 281 (1969).
(8) A. E. Jukes, *Adv. Organomet. Chem.*, **12**, 272 (1974).
(9) K. M. Smirnov, A. P. Tomilov, and A. I. Shchekotikhin, *Russ. Chem. Rev.*, **36**, 326 (1967).
(10) M. R. Wiles and A. G. Massey, *Chem. Ind. (London)*, 663 (1967); *Tetrahedron Lett.*, 5137 (1967).
(11) M. D. Rausch, A. Siegel, and L. P. Klemann, *J. Org. Chem.*, **34**, 468 (1969).
(12) J. Burdon, P. L. Coe, C. R. Marsh, and J. C. Tatlow, *J. Chem. Soc., Perkin Trans. 1*, 763 (1972).
(13) M. R. Wiles and A. G. Massey, *J. Organomet. Chem.*, **47**, 423 (1973).
(14) W. Hübel in "Organic Synthesis Via Metal Carbonyls", Vol. I, I. Wender and P. Pino, Ed., Interscience, New York, N.Y., 1968, p 343.
(15) W. Hübel and C. Hoogzand, *Chem. Ber.*, **93**, 103 (1960).
(16) M. D. Rausch and R. A. Genetti, *J. Org. Chem.*, **35**, 3888 (1970).
(17) G. B. Kaufman and R. P. Pinell, *Inorg. Synth.*, **6**, 3 (1960).
(18) W. Hieber, E. O. Fischer, and E. Böckly, *Z. Anorg. Allg. Chem.*, **269**, 308 (1952).
(19) R. B. King, "Organometallic Syntheses", Vol. I, Academic Press, New York, N.Y., 1965, p 101.
(20) A shorter reflux period may be used, although **1** is obtained in somewhat lower yield.
(21) The preparations of pentafluorophenylcopper and phenyliodoacetylene were timed to coincide as closely as possible in order to minimize the formation of undesirable coupling products.

Preparation of 9-(5-Deoxy-α-D-arabinofuranosyl)adenine from D-Ribose[1]

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Aldofuranose derivatives that have three contiguous hydroxyl groups, with the hydroxyls at C-2 and C-3 in a cis relationship, will undergo epimerization at C-2 when acetolyzed in a mixture containing acetic acid, acetic anhydride, and sulfuric acid. This reaction was originally discovered by Jerkeman[2] and later studied in greater detail by Sowa[3] and others.[4] In recent years, it has been developed into a useful preparative reaction with hexofuranose derivatives, and optimal conditions have been found to consist of 10:1 acetic acid–acetic anhydride and 3–5% concentrated sulfuric acid.[5] This reaction has been useful in the development of new routes to rare sugars and in the synthesis of novel hexofuranosyl nucleosides.[6] Usually, no significant amounts of the reactant sugars or of their nucleosides have been found upon isolation of products. In more recent, unpublished experiments, it was found that certain 6-deoxyhexofuranosyl derivatives afforded only about a 50% yield of the C-2 epimerized products upon acetolysis. There was an interesting structural property of these latter derivatives that was striking. All of the original group of hexofuranose derivatives had hydroxyl groups at C-2 and C-3 which were on the same side of the furanose ring as the C-4 tail end of the sugar. In the cases involving incomplete epimerization the hydroxyl groups were on the opposite side of the ring from the C-4 group. It was of some interest, therefore, to compare results with a pentose having the same structural relationship. Because of the continuing interest in nucleosides of potential biological value, the preparation of 9-(5-deoxy-α-D-arabinofuranosyl)adenine (**5**) was undertaken starting from D-ribose.

D-Ribose was converted to methyl 2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranoside (**1**) in two steps (Scheme I).[7] The terminal carbon atom was reduced with sodium borohydride in dimethyl sulfoxide[8] to afford methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**2**). Acetolysis of **2** gave a syrup (**3**) which was coupled with 6-benzamidochloromercuripurine in refluxing 1,2-dichloroethane in the presence of titanium tetrachloride.[9] The blocked nucleoside (**4**) was treated with sodium methoxide in methanol and **5** was obtained after purification by chromatography on an anion-exchange column.[10]

The elemental analysis of **5** indicated a nucleoside with the correct empirical formula. The UV spectrum supported a sugar linked to adenine at N-9. The melting point and optical rotation data are clearly different from either 9-(5-deoxy-β-D-ribofuranosyl)adenine[11] or 9-(5-deoxy-β-D-xylofuranosyl)adenine.[12] The slow rate of periodate consumption (0.87 molar equiv in 48 h) provided proof that the hydroxyl groups at C-2 and C-3 were arranged trans to each other, and this again eliminated the ribo configuration and, in addition, the lyxo configuration for the nucleoside. The data suggested that the product was **5**, which was what was expected from recent experience with this reaction pathway.[5,6]

The configuration of **5** at the anomeric carbon could not be deduced from the NMR spectrum because a trans arrangement for the H-1′, H-2′ protons can only be unequivocally concluded if $J_{1',2'} < 1$ Hz.[13] In this case, **5** had $J_{1',2'} = 4$ Hz. A comparison of the optical rotation of **5** with that of other pentofuranosyladenine nucleosides supported an α-D configuration. A proof of configuration was obtained by periodate

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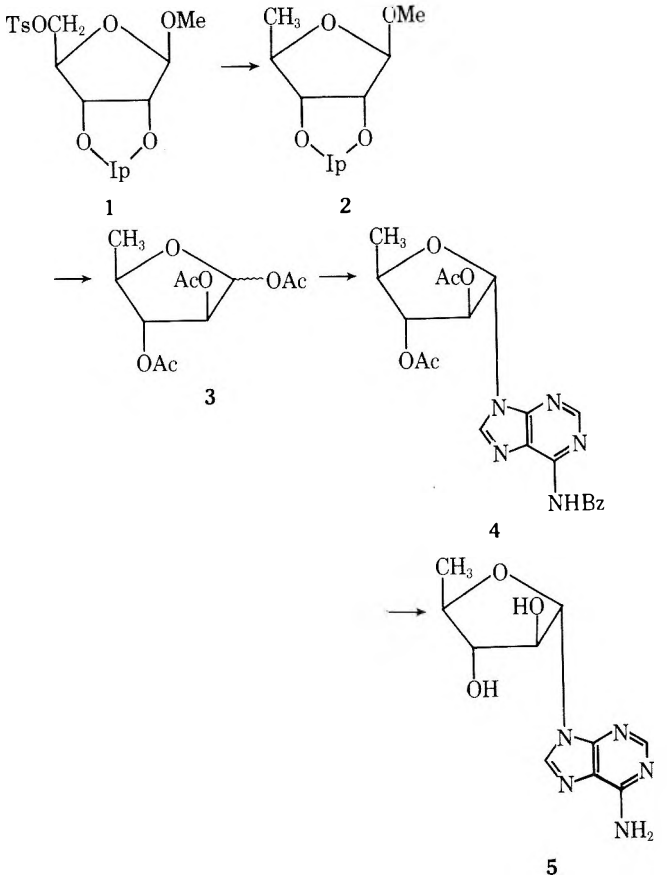
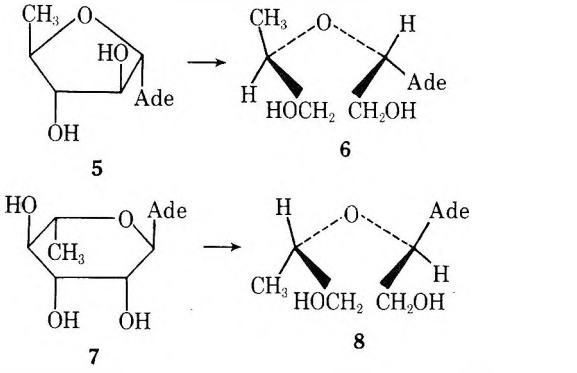
Scheme I



oxidation, followed by sodium borohydride reduction of the aldehyde groups to give alcohol **6**. This nucleoside alcohol is the enantiomer of the known dialcohol **8**, the optical rotation of which was previously obtained in a similar experiment.[5] Compound **8** has also been prepared as a pure, crystalline



substance from 9-α-L-rhamnopyranosyladenine (**7**).[14] The latter had to be used as the reference because the D form has never been prepared. The optical rotations of **6** and **8** were nearly equal in value, but opposite in sign.

Experimental Section[15]

Methyl 5-Deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (2). To a solution containing 5.45 g (15.2 mmol) of methyl 2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranoside[7] (**1**) in 40 mL of dimethyl sulfoxide was added 2.3 g of sodium borohydride and the mixture was stirred at 80–85 °C for 22 h. After cooling the flask to room temperature, the mixture was poured into 125 mL of 1% aqueous acetic acid solution and stirred for 15 min, and the product was extracted with chloroform (5 × 25 mL). The chloroform solution was washed with water (4 × 250 mL) and dried (anhydrous magnesium sulfate). Evaporation of the chloroform gave a clear, colorless liquid which gave 2.01 g (70% yield) of **2** upon distillation: bp 29–30 °C (0.05 mmHg); $[\alpha]^{26}_D$ −116° (*c* 2.57, ethanol) [lit.[16] $[\alpha]^{23}_D$ −109° (*c* 2, ethanol)].

9-(5-Deoxy-α-D-arabinofuranosyl)adenine (5). The sugar derivative **2** (1.95 g, 10.4 mmol) was dissolved in a mixture containing 6 mL of acetic anhydride and 60 mL of acetic acid and chilled in an ice bath while 3.3 mL of concentrated sulfuric acid was slowly added dropwise. The mixture was kept at room temperature for 69 h, poured into 125 mL of ice, and stirred until the ice had melted. The mixture was extracted with chloroform (4 × 30 mL), and the chloroform solution was washed with water (2 × 200 mL), saturated sodium bicarbonate (200 mL), and water (200 mL), and dried (anhydrous magnesium sulfate). Evaporation and coevaporation with benzene several times to remove traces of acetic acid gave a syrup, 1.92 g (71% yield), of crude product **3**.

The entire syrup was dissolved in 255 mL of 1,2-dichloroethane, 4.2 g of 6-benzamidochloromercuripurine and 4.2 g of Celite-545 were added, and 40 mL of the solvent was distilled to ensure the absence of moisture. A solution containing 1.1 mL of titanium tetrachloride in 40 mL of fresh, dry 1,2-dichloroethane was added and the mixture was stirred under reflux for 21 h, protected from moisture. The flask was allowed to cool to room temperature, treated with 150 mL of saturated sodium bicarbonate, and stirred for 1.5 h. The insoluble material was removed by filtration through a pad of Celite and the filter cake was washed with 100 mL of hot solvent. The organic layer was separated and the solvent was removed by evaporation. The remaining foam was dissolved in 75 mL of chloroform, washed with 30% aqueous potassium iodide (2 × 100 mL) and water (150 mL), and dried (anhydrous magnesium sulfate). Evaporation of the solvent afforded a pale-yellow foam, 2.37 g. The foam was dissolved in 60 mL of methanol and treated with 5 mL of 1 N sodium methoxide in methanol. The solution was heated under reflux for 1 h, cooled to room temperature, and adjusted to neutral pH with Amberlite CG-120 (H^+) resin. The resin was removed by filtration and washed thoroughly with methanol. The methanol was evaporated, and the residue was dissolved in a minimum amount of water and applied to a column (28 cm × 2.3 cm) of Bio-Rad AG 1-X2 (OH^-, 200–400 mesh) ion-exchange resin. Elution was performed with 7:3 water–methanol and 11-mL fractions were collected. The only major peak appeared in tubes 13–36. These were pooled, the solvents were evaporated, and the residue was dried by coevaporation with absolute ethanol several times, leaving a white foam (850 mg). Crystallization was effected by dissolution in methanol, addition of ethyl acetate, and concentration by boiling on a steam bath until the temperature changed from 64 to 74 °C. The solution was kept at room temperature and crystallization proceeded to afford 516 mg, mp 187–189 °C. Two additional crops of crystals were obtained by concentrating the mother liquors, which brought the yield to 758 mg (40.8% from **3**). An analytical sample was obtained by recrystallization from a large volume of ethyl acetate in an open flask. Clusters of crystals formed on the walls: 417 mg; mp 193–195 °C with softening starting at 185 °C; $[\alpha]^{27}_D$ +78.1° (*c* 0.741, 1:1 dimethylformamide–water); UV max (H_2O) 259 nm (ε 14,800); NMR (Me_2SO-d_6) δ 8.15, 8.02 (both s, 1 proton each, H-8, H-2), 7.12 (br s, 2, NH_2), 5.77 (d, $J_{1',2'}$ = 4 Hz, H-1'), 1.20 (d, 3, C-5' CH_3).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.21; N, 27.88. Found: C, 47.75; H, 5.18; N, 27.87.

Periodate Uptake. The consumption of periodate was followed by the spectrophotometric procedure of Rammler and Rabinowitz.[17] It required 48 h for **5** to consume 0.87 molar equiv of periodate.

Polarimetric Study. Nucleoside **5** (12.10 mg) was dissolved in 0.75 mL of hot water, cooled to room temperature, 0.5 mL of 0.25 M sodium periodate added, and the sample placed in the dark. Three days later, 0.1 mL of 0.503 M formic acid was added and the solution was then treated with 60 mg of sodium borohydride. After 1 h, 0.4 mL of 20% aqueous acetic acid was added to destroy excess hydride. Effervescence stopped after 2 h, the solution was adjusted to 2 mL, and the optical rotation recorded, $[\alpha]^{26}_D$ −71°. Treatment of **7** in the same manner gave $[\alpha]_D$ +74°.

Registry No.—**1**, 4137-56-8; **2**, 23202-81-5; **3**, 63903-44-6; **4**, 63865-81-6; **5**, 63865-82-7; 6-benzamidochloromercuripurine, 17187-65-4.

References and Notes

(1) This work was supported by Grant CA 13802 from the National Cancer Institute, National Institutes of Health.
(2) P. Jerkeman, *Acta Chem. Scand.*, **17**, 2769 (1963).
(3) W. Sowa, *Can. J. Chem.*, **49**, 3292 (1971); **50**, 1092 (1972).
(4) G. J. F. Chittenden, *Carbohydr. Res.*, **22**, 491 (1972); P. J. Boon, A. W. Schwartz, and G. J. F. Chittenden, *Carbohydr. Res.*, **30**, 179 (1973).
(5) L. M. Lerner, *J. Org. Chem.*, **37**, 4386 (1972).
(6) L. M. Lerner, *Carbohydr. Res.*, **36**, 392 (1974); *J. Org. Chem.*, **40**, 2400 (1975); *Carbohydr. Res.*, **44**, 13 (1975); *J. Org. Chem.*, **41**, 306 (1976).
(7) L. M. Lerner, *Carbohydr. Res.*, **53**, 177 (1977).
(8) H. Weidmann, N. Wolf, and W. Tempe, *Carbohydr. Res.*, **24**, 184 (1972).

(9) B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 12 (1955); J. Prokop and D. H. *Murray, J. Pharm. Sci.*, **54**, 359 (1965).
(10) C. A. Dekker, *J. Am. Chem. Soc.*, **87**, 4027 (1965).
(11) H. M. Kissman and B. R. Baker, *J. Am. Chem. Soc.*, **79**, 5534 (1957).
(12) R. H. Shah, H. J. Schaeffer, and D. H. Murray, *J. Pharm. Sci.*, **54**, 15 (1965).
(13) L. B. Townsend in "Synthetic Procedures in Nucleic Acid Chemistry", W. W. Zorbach and R. S. Tipson, Ed., Wiley-Interscience, New York, N.Y., 1973, pp 330–331.
(14) L. M. Lerner and R. R. Rossi, *Biochemistry*, **11**, 2772 (1972).
(15) Melting points were determind on a Koffler micro hot stage and are corrected values. Elemental analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich. NMR spectra were recorded on a Varian T-60A spectrometer using Me_4Si as the internal reference. Evaporations were performed on a rotary evaporator under reduced pressure with a bath temperature of 40–45 °C.
(16) C. H. Shunk, J. B. Lavigne, and K. Folkers, *J. Am. Chem. Soc.*, **77**, 2210 (1955).
(17) D. H. Rammler and J. C. Rabinowitz, *Anal. Biochem.*, **4**, 116 (1962).

Steroid *B*-Ring Lactones: a Reinvestigation

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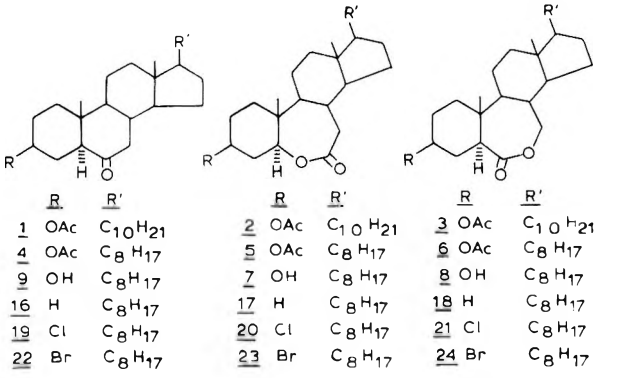
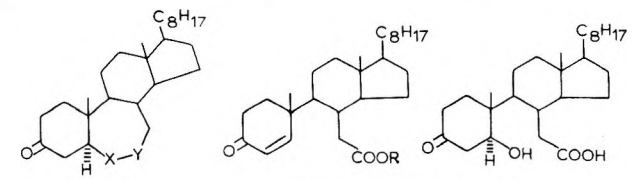
In the Baeyer–Villiger oxidation, the migratory aptitude of alkyl groups decreases in the order tertiary, secondary, primary, and methyl. This tendency is a function of the ability of the migrating group to support a positive charge in the transition state.[1] Accordingly, Fonken and Miles[2] showed that the peracid oxidation of 6-keto steroids is a stereospecific process leading exclusively to 6-oxa steroids by preferential migration of the more substituted C-5. Subsequently, we also reported similar observations.[3] Lately we noted that 6-keto-5α-β-sitostanyl acetate (**1**) on perbenzoic acid (1 molar equiv) oxidation gave the anticipated 6-oxa lactone **2** as well as its 7-oxa isomer **3** arising through migration of the less substituted C-7,[4,5] structures being established spectroscopically beyond doubt. This apparently unusual observation forced us to reexamine the reactions which had led to previous conclusions.[2,3]



	R	R′
1	OAc	$C_{10}H_{21}$
4	OAc	C_8H_{17}
9	OH	C_8H_{17}
16	H	C_8H_{17}
19	Cl	C_8H_{17}
22	Br	C_8H_{17}

	R	R′
2	OAc	$C_{10}H_{21}$
5	OAc	C_8H_{17}
7	OH	C_8H_{17}
17	H	C_8H_{17}
20	Cl	C_8H_{17}
23	Br	C_8H_{17}

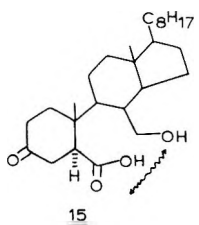
	R	R′
3	OAc	$C_{10}H_{21}$
6	OAc	C_8H_{17}
8	OH	C_8H_{17}
18	H	C_8H_{17}
21	Cl	C_8H_{17}
24	Br	C_8H_{17}



	X	Y
10	O	CO
11	CO	O

	R
12	H
13	CH_3

14



15

Similarly, 5α-cholestan-6-one (**16**) provided the isomeric lactones **17** and **18**, and its 3β-halogen analogues **19** and **22** furnished **20**, **21**, and **23**, **24**, respectively. On sodium–pentyl alcohol reduction **20** and **23** afforded **17**, while **21** and **24** were transformed into **18**.

An interesting feature of the NMR spectra of both 6- and 7-oxa lactones was the appearance of one of the C-7a protons as a broadened singlet and the other as a doublet with J = 3–5 Hz. Examination of the Dreiding models of the isomeric lactones revealed that the dihedral angle between the planes of C-8–βH (axial) and C-7a–βH (pseudoequatorial) is almost 90°, which may account for its (C-7a–βH) appearance as a broadened singlet, as splitting will be almost negligible. On the other hand, C-8–βH splits C-7a–αH (pseudoaxial) into a doublet.

The point which emerges from this restudy is that a secondary carbon (C-7) competes quite effectively with a tertiary one (C-5) for migration to an electron-deficient oxygen in the Baeyer–Villiger oxidation of 6-keto steroids. In fact, in the presence of C-3 substituents, migration of C-7 is more pronounced than in their absence. Further, the bulk of the C-3 substituent seems to have a pronounced effect on the preferred migratory aptitude of C-7 in relation to C-5, as is evidenced by the behavior of the chloro (**19**) and the bromo (**22**) ketones toward perbenzoic acid.

Experimental Section

All melting points are uncorrected. IR spectra were determined in Nujol with a Perkin-Elmer 237 spectrophotometer. NMR spectra were run in $CDCl_3$ on a Varian A60 instrument with Me_4Si as the internal standard. UV spectra were obtained in methanol with a Beckman DK 2 spectrophotometer. TLC plates were coated with silica gel. A 20% aqueous solution of perchloric acid was used as the spraying agent. Light petroleum refers to a fraction of bp 60–80 °C. Anhydrous sodium sulfate was used as the drying agent. (IR: s, strong; w, weak. NMR: dd, double doublet; d, doublet; br, broad; s, singlet; mc, multiplet centred at; a, axial; e, equatorial.)

6-Oxa-*B*-homo-7-oxo-5α-β-sitostanyl Acetate (*2*) and 7-Oxa-*B*-homo-6-oxo-5α-β-sitostanyl Acetate (3). To a solution of 6-keto-5α-β-sitostanyl acetate (**1**) (obtained by acetylation, nitration, and zinc–acetic acid reduction of β-sitosterol) (2 g) in chloroform (30 mL) was added a chloroform solution of perbenzoic acid (1 molar equiv) and a few crystals of *p*-toluenesulfonic acid monohydrate as catalyst, and the reaction mixture was allowed to stand at room temperature for 1 week. The solvent was removed under reduced pressure and the residue extracted with ether. The ethereal solution was washed successively with water, $NaHCO_3$ solution (5%), and water and dried. Removal of the desiccant and the solvent provided a residue (ca. 2 g) which was chromatographed over silica gel (40 g) (each frac-

tion of about 25 mL was collected). Elution with light petroleum–ether (10:1) gave the unreacted **1** (500 mg), mp and mmp 120 °C. Elution with light petroleum–ether (6:1) afforded **3**, crystallized from light petroleum as shining needles (380 mg): mp 130–131 °C; IR 1740 s (CH_3COO), 1715 s (ε-lactone), 1250 s (acetate), 1210, 1040 cm^{-1} (C–O); NMR δ 4.66 (br, $w_{1/2}$ = 14 Hz, C-3–αH), 4.08 (br s, C-7a–βH), 3.98 (d, C-7a–αH, J = 3.5 Hz), 2.91 (dd, C-5–αH, $J_{a,a}$ = 11 Hz; $J_{a,e}$ = 5 Hz), 2.01 (s, CH_3COO), 0.9, 0.8, 0.7 (methyl protons). Anal. Calcd for $C_{31}H_{52}O_4$: C, 76.23; H, 10.65. Found: C, 76.37; H, 10.56. Further elution with light petroleum–ether (5:1) furnished **2**, crystallized from light petroleum (365 mg): mp 163–164 °C; IR 1740 s (CH_3COO), 1720 s (ε-lactone), 1240 s (acetate), 1040 cm^{-1} (C–O); NMR δ 4.75 (br, $W_{1/2}$ = 14 Hz, C-3–αH), 4.29 (dd, C-5–αH, $J_{a,a}$ = 11, $J_{a,e}$ = 5.5 Hz), 2.5 (br s, C-7a–βH), 2.43 (d, C-7a–αH, J = 3.5 Hz), 2.03 (s, CH_3COO), 0.9, 0.8, 0.7 (methyl protons). Anal. Calcd for $C_{31}H_{52}O_4$: C, 76.23; H, 10.65. Found: C, 76.33; H, 10.60.

3β-Acetoxy-6-oxa-*B*-homo-5α-cholestan-7-one (5) and 3β-Acetoxy-7-oxa-*B*-homo-5α-cholestan-6-one (6). Reaction of 3β-acetoxy-5α-cholestan-6-one[7] (**4**) (2 g) with perbenzoic acid was performed in the manner described for **1** to provide a semisolid material which was chromatographed over silica gel. Elution with light petroleum–ether (10:1) gave the unreacted **4** (450 mg), mp[7] and mmp 127 °C. Elution with light petroleum–ether (7:1) afforded **6**, crystallized from light petroleum as needles (460 mg): mp 181 °C; IR 1740 s, 1715 s, 1250 s, 1205, 1035 cm^{-1}; NMR δ 4.66 (br, $W_{1/2}$ = 14 Hz, C-3–αH), 4.1 (br s, C-7a–βH), 4.0 (d, C-7a–αH, J = 3.5 Hz), 2.92 (dd, C-5–αH, $J_{a,a}$ = 11, $J_{a,e}$ = 5 Hz), 2.03 (s, CH_3COO), 0.9, 0.8, 0.7 (methyl protons). Anal. Calcd for $C_{29}H_{48}O_4$: C, 75.65; H, 10.43. Found: C, 75.75; H, 10.33. Further elution with light petroleum–ether (6:1) gave **5**, crystallized from light petroleum (455 mg): mp 174 °C (lit.[2] mp 162–163 °C);[8] IR 1740 s, 1718 s, 1245 s, 1035 cm^{-1}; NMR δ 4.75 (br, $W_{1/2}$ = 14 Hz, C-3–αH), 4.29 (dd, C-5–αH, $J_{a,a}$ = 10, $J_{a,e}$ = 5.5 Hz), 2.52 (br s, C-7a–βH), 2.42 (d, C-7a–αH, J = 3.5 Hz), 2.03 (s, CH_3COO), 0.9, 0.8, 0.7 (methyl protons). Anal. Calcd for $C_{29}H_{48}O_4$: C, 75.65; H, 10.43. Found: C, 75.51; H, 10.47.

3β-Hydroxy-6-oxa-*B*-homo-5α-cholestan-7-one (7). A solution of **5** (250 mg) in 50 mL of methanolic NaOH (2%) was heated under reflux for 1 h. The solution was acidified with HCl and poured into water. The usual workup provided **7**, crystallized from light petroleum–ether (200 mg): mp 202 °C (lit.[2] mp 139–141 °C);[9] IR 3300 br (OH), 1718 s, 1225, 1025 cm^{-1}. Anal. Calcd for $C_{27}H_{46}O_3$: C, 77.51; H, 11.00. Found: C, 77.42; H, 11.07.

3β-Hydroxy-7-oxa-*B*-homo-5α-cholestan-6-one (8). The acetate function in **6** (250 mg) was hydrolyzed in the manner described for **5**. Subsequent workup gave **8**, crystallized from light petroleum (210 mg): mp 124 °C; IR 3430 br, 1715 s, 1195, 1060 cm^{-1}. Anal. Calcd for $C_{27}H_{46}O_3$: C, 77.51; H, 11.00. Found: C, 77.45; H, 10.90.

Baeyer–Villiger Oxidation of 3β-Hydroxy-5α-cholestan-6-one (9). The ketone **9**[7] (2 g) was treated with perbenzoic acid in the usual manner to provide a residue which was chromatographed over silica gel. Elution with chloroform–benzene (8:1) gave the unreacted **9** (345 mg), mp[7] and mmp 143 °C. Elution with chloroform furnished **8** (380 mg), mp and mmp 124 °C. Continued elution with the same solvent provided **7** (370 mg), mp and mmp 202 °C.

6-Oxa-*B*-homo-5α-cholestane-3,7-dione (10). The lactone **7** (300 mg) was dissolved in acetone (40 mL) and cooled below 10 °C in ice bath. Jones' reagent[6] (0.5 mL) was added slowly with continuous stirring. Water (40 mL) was added to it and the precipitate thus obtained was taken in ether. Usual workup provided **10**, crystallized from light petroleum–ether (260 mg): mp 191 °C; IR 1722 s, 1720 s, 1275, 1040 cm^{-1}. Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.88; H, 10.57. Found: C, 77.93; H, 10.46.

Attempted Base-Catalyzed Hydrolysis of 11, 5, and 6. The lactone **11** was subjected to base-catalyzed hydrolysis and worked in the manner described by Fonken and Miles.[2] Immediate TLC of the residue showed two spots of about equal intensity (one lactone **11** and the other probably seco acid **15**). However, on standing the ethereal solution of the mixture at room temperature for some time (3–4 h), relactonization occurred, as was evident from a single spot (TLC) identical with lactone **11**. Efforts were made to separate them by column chromatography over silica gel, but **15** relactonized during the passage through silica gel, as elution afforded only the lactone **11**.

The aforesaid observations were noted for lactones **5** and **6** also, in which relactonized products **7** and **8** were obtained from **5** and **6**, respectively.

7-Oxa-*B*-homo-5α-cholestane-3,6-dione (11). The lactone **8** (300 mg) was treated with Jones' reagent[6] in the manner described for **10**. Subsequent workup afforded **11**, crystallized from light petroleum–ether as needles (250 mg): mp 195 °C; IR 1725 s, 1720 s, 1230, 1185, 1085 cm^{-1}. Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.88; H, 10.57. Found: C, 77.80; H, 10.59.

3-Oxo-5,6-secocholest-4-en-6-oic acid (12). A solution of **10** (200 mg) in 40 mL of methanolic NaOH (5%) was heated under reflux for 2 h. The excess of methanol was removed under reduced pressure, and the residue was poured into water, acidified with dilute HCl, and extracted with ether. Usual workup provided **12** as a noncrystallizable oil (170 mg): UV 230 nm (ε 10 000); IR 3550–3200 br (COOH), 1725 s (COOH), 1675 s (C=C—C=O), 1610 w (C=C), 1180 cm^{-1}. Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.88; H, 10.57. Found: C, 77.79; H, 10.50.

Methyl 3-Oxo-5,6-secocholest-4-en-6-oate (13). An ethereal solution of **12** (120 mg) was treated with an excess of an ethereal solution of diazomethane and allowed to stand for 10 min in the cold. Usual workup provided **13** as a noncrystallizable oil (110 mg): UV 230 nm (ε 9860); IR 1735 s ($COOCH_3$), 1680 s (C=C—C=O), 1615 w (C=C), 1190 cm^{-1} (methyl ester); NMR δ 6.75 (d, C-5–H, J = 10 Hz), 5.68 (d, C-4–H, J = 10 Hz), 3.6 (s, $COOCH_3$), 2.51 (mc, C-2–H_2 and C-7–H_2), 1.2, 0.9, 0.8, 0.66 (methyl protons). Anal. Calcd for $C_{28}H_{46}O_3$: C, 78.13; H, 10.69. Found: C. 78.16; H, 10.68.

6-Oxa-*B*-homo-5α-cholestan-7-one (17) and 7-Oxa-*B*-homo-5α-cholestan-6-one (18). Reaction of 5α-cholestan-6-one[10] (**16**) (2 g) with perbenzoic acid in the usual manner gave a solid residue which was chromatographed over silica gel. Elution with light petroleum–ether (14:1) gave the unreacted **16** (300 mg), mp[10] and mmp 98–99 °C. Elution with light petroleum–ether (11:1) provided **18**, crystallized from light petroleum as needles (250 mg): mp 126 °C; IR 1722 s, 1185, 1135, 1080 cm^{-1}; NMR δ 4.26 (br s, C-7a–βH), 4.16 (d, C-7a–αH, J = 3.5 Hz), 2.66 (dd, C-5–αH, $J_{a,a}$ = 10, $J_{a,e}$ = 5 Hz), 0.9, 0.8, 0.7 (methyl protons). Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.59; H, 11.44. Found: C, 80.45; H, 11.39.

Continued elution with the same solvent system furnished **17**, crystallized from light petroleum as needles (760 mg): mp 155 °C (lit.[2] mp 143–144 °C);[11] IR 1720 s, 1275, 1035 cm^{-1}; NMR δ 4.16 (dd, C-5–αH, $J_{a,a}$ = 10, $J_{a,e}$ = 5 Hz), 2.5 (br s, C-7a–βH), 2.41 (d, C-7a–αH, J = 3.5 Hz), 0.9, 0.8 (methyl protons). Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.59; H, 11.44. Found: C, 80.47; H, 11.51.

3β-Chloro-6-oxa-*B*-homo-5α-cholestan-7-one (20) and 3β-chloro-7-oxa-*B*-homo-5α-cholestan-6-one (21). 3β-Chloro-5α-cholestan-6-one[12] (**19**) (2 g) on treatment with perbenzoic acid in the usual fashion and subsequent workup gave a residue which was chromatographed over silica gel. Elution with light petroleum–ether (11:1) gave the unreacted **19** (540 mg), mp[12] and mmp 129 °C. Elution with light petroleum–ether (8:1) furnished **21**, crystallized from light petroleum as fine needles (350 mg): mp 145 °C; IR 1715 s, 1195, 1130, 1085, 735 cm^{-1}; NMR δ 4.09 (br s, C-7a–βH), 4.0d (C-7a–αH, J = 5 Hz), 3.70 (br, $W_{1/2}$ = 14 Hz, C-3–αH), 2.85 (dd, C-5–αH. $J_{a,a}$ = 11, $J_{a,e}$ = 5 Hz), 0.9, 0.8, 0.7 (methyl protons). Anal. Calcd for $C_{27}H_{45}O_2Cl$: C, 74.22; H, 10.30. Found: C, 74.35; H, 10.25. Further elution with light petroleum–ether (7:1) gave **20**, crystallized from light petroleum (345 mg): mp 185 °C (lit.[3] mp 167–168 °C);[13] IR 1718 s, 1280, 1045, 740 cm^{-1}; NMR δ 4.21 (dd, C-5–αH, $J_{a,a}$ = 11, $J_{a,e}$ = 5 Hz), 3.66 (br, $W_{1/2}$ = 14 Hz, C-3–αH), 2.5 (br s, C-7a–βH), 2.41 (d, C-7a–αH, J = 5 Hz), 0.9, 0.8, 0.7 (methyl protons). Anal. Calcd for $C_{27}H_{45}O_2Cl$: C, 74.22; H, 10.30. Found: C, 74.20; H, 10.34.

3β-Bromo-6-oxa-*B*-homo-5α-cholestan-7-one (23) and 3β-Bromo-7-oxa-*B*-homo-5α-cholestan-6-one (24). 3β-Bromo-5α-cholestan-6-one[14] (**22**) (2 g) was treated with perbenzoic acid in the usual manner to provide a residue which was chromatographed over silica gel. Elution with light petroleum–ether (12:1) gave the unreacted **22** (620 mg), mp[14] and mmp 124 °C. Elution with light petroleum–ether (8:1) afforded **24**, crystallized from light petroleum as fine needles (460 mg): mp 171 °C; IR 1712 s, 1190, 1130, 1080, 720 cm^{-1}; NMR δ 4.1 (br s, C-7a–βH), 4.01 (d, C-7a–αH, J = 5 Hz), 3.68 (br, $W_{1/2}$ = 14 Hz, C-3–αH), 2.84 (dd, C-5–αH, $J_{a,a}$ = 11, $J_{a,e}$ = 5 Hz), 0.9, 0.8, 0.7 (methyl protons). Anal. Calcd for $C_{27}H_{45}O_2Br$: C, 67.35; H, 9.35. Found: C, 67.42; H, 9.32. Further elution with light petroleum–ether (7:1) furnished **23**, crystallized from light petroleum (375 mg): mp 183 °C (lit.[3] mp 179 °C);[15] IR 1715 s, 1280, 1035, 720 cm^{-1}; NMR δ 4.2 (dd, C-5–αH, $J_{a,a}$ = 11, $J_{a,e}$ = 5 Hz), 3.70 (br, $W_{1/2}$ = 14 Hz, C-3–αH), 2.51 (br s, C-7a–βH), 2.41 (d, C-7a–αH, J = 5 Hz), 0.9, 0.8, 0.7 (methyl protons). Anal. Calcd for $C_{27}H_{45}O_2Br$: C, 67.35; H, 9.35. Found: C. 67.45; H, 9.36.

Sodium–Pentyl Alcohol Reduction of 20 and 23. The lactone **20** (200 mg) was dissolved in warm pentyl alcohol (10 mL) and to this solution was added sodium metal (1 g) in small portions with intermittent heating during 30 min. The solution was kept warm for an additional period of 2 h. When all the metal had dissolved, the reaction mixture was poured into cold water and worked up in the usual manner, followed by column chromatography over silica gel, to provide **17** (120 mg), mp and mmp 155 °C. In similar manner **23** afforded

17.

Sodium–Pentyl Alcohol Reduction of 21 and 24. The lactone **21** (200 mg) was subjected to reduction in the manner described for **20**. Usual workup followed by column chromatography over silica gel afforded **18** (100 mg), mp and mmp 126 °C. Similarly **24** was transformed into **18**.

Acknowledgment. We thank Professor Wasiur Rehman, Head, Chemistry, for the facilities and CSIR (New Delhi) for financial assistance (G.M. and I.A.K.).

Registry No.—**1**, 63903-45-7; **2**, 63866-15-9; **3**, 63866-16-0; **4**, 1256-83-3; **5**, 20104-89-6; **6**, 20104-90-9; **7**, 20104-95-4; **8**, 20104-91-0; **9**, 1175-06-0; **10**, 20104-96-5; **11**, 20104-92-1; **12**, 63866-17-1; **13**, 63904-21-2; **16**, 570-46-7; **17**, 31239-55-1; **18**, 63866-18-2; **19**, 1056-93-5; **20**, 31239-53-9; **21**, 63866-19-3; **22**, 63866-20-6; **23**, 31239-57-3; **24**, 63866-21-7; diazomethane, 334-88-3.

References and Notes

(1) P. A. S. Smith in "Molecular Rearrangements", Part 1, P. De Mayo, Ed., Wiley-Interscience, New York, N.Y., 1963, pp 577–591.
(2) G. J. Fonken and H. M. Miles, *J. Org. Chem.*, **28**, 2432 (1963).
(3) M. S. Ahmad, Shafiullah, M. Mushfiq, and M. Asif, *Indian J. Chem.*, **8**, 1062 (1970).
(4) A. Lardon, J. Schmidlin, A. Wettstein, and T. Reichstein, *Helv. Chim. Acta*, **40**, 662 (1957).
(5) P. Bladon and W. McMeekin, *J. Chem. Soc.*, 3504 (1961).
(6) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 142.
(7) R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948).
(8) An admixture of the isomeric lactones **5** and **6** in the ratio of 1:1 showed the melting point corresponding to the reported[2] melting point of **5**. It obviously indicates that the product obtained by Fonken and Miles[2] was a mixture of **5** and **6**.
(9) As the initial product of oxidation reported by Fonken and Miles[2] seems to have been a mixture of **5** and **6**, its acetate hydrolysis would only have given another mixture of isomeric hydroxy lactones **7** and **8**. This was shown to be the case as revealed by a mixture melting point determination of a mixture of **7** and **8** in the ratio of 1:1, which corresponded with the reported[2] melting point for **7**.
(10) C. W. Shoppee, R. H. Jenkins, and G. H. R. Summers, *J. Chem. Soc.*, 1657 (1958).
(11) A mixture of **17** and **18** in the ratio of 1:1 melted at 110–121 °C. However, when mixed in the ratio of the yield of **17** and **18**, the melting point was observed at 142–144 °C, corresponding to the melting point reported[2] for **17**.
(12) A. Windaus and O. Dalmer, *Ber.*, **52**, 162 (1919).
(13) From the melting point range (158–164 °C) of an admixture of isomeric lactones **20** and **21**, which is very close to the melting point of **20** reported[3] earlier, there appears no doubt that the reported lactone **20** was, in fact, a mixture of **20** and **21**.
(14) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 1786 (1952).
(15) A mixture of **23** and **24** in the ratio of their respective yields melted at 177–179 °C corresponding to the melting point reported[3] for **23**. It clearly indicates that the earlier reported lactone **23** was a mixture of **23** and **24**.

Rotational Deactivation in the Triplet Photochemistry of 5,5-Diphenylcyclohepta-1,3-diene[1a]

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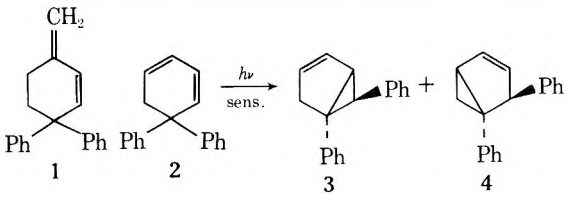
The importance of rotational deactivation on the excited-state processes of numerous systems has now been established.[2,3] An early example illustrating this phenomenon was the divergent triplet chemistry of the exocyclic diene **1**[4] vs. the endocyclic diene **2**.[5] Thus, while **1** was unreactive in the triplet state, **2** undergoes facile rearrangement to a ca. 90:10 mixture of **3** and **4** ($\Phi = 0.24$). To examine the effect of ring size on the



1 2 3 4

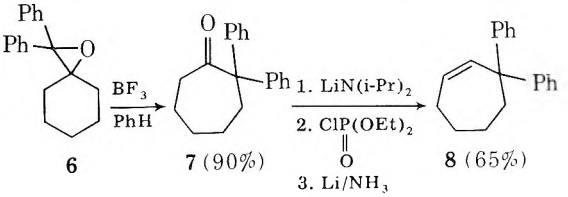
Table I. Quantum Yields for Irradiation of 5,5-Diphenylcyclohepta-1,3-diene (5)

Run	Conc of diene × 10^{-3} M	Sensitizer	λ (nm)	mE absorbed	Φ_{dis}[b]	Φ_{app}
1[a]	19.6	2-Acetonaphthone	345	0.068	0.30	0.25
2	19.6	Benzophenone	345	0.069	0.30	0.20
3[a]	20.6	None	255	0.039	0.42	0.38

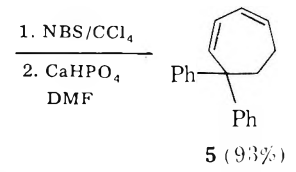
[a] These values are an average of two determinations. [b] Conversions of 5–8% were utilized for these measurements.

triplet chemistry of endocyclic dienes, we have prepared 5,5-diphenylcyclohepta-1,3-diene (**5**) and studied its singlet and triplet photochemistry. The change from the six-membered ring of **2** to the seven-membered ring of **5** has a dramatic effect on the triplet photochemistry of the endocyclic diene.[6]

The required diene **5** was synthesized from the epoxide **6** as outlined below. The singlet chemistry of **5** was studied first,

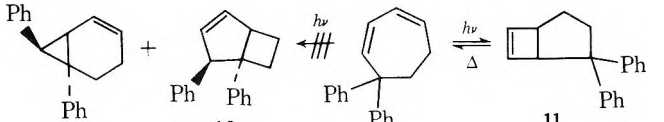


6 7 (90%) 8 (65%)



5 (93%)

since phenyl migration would allow a comparison of the efficiency of the Woodward–Hoffmann allowed product **9** with that of the forbidden product **10**.[5a] Direct preparative irradiation of **5** in cyclohexane with Vycor-filtered light afforded 59% of an isomeric hydrocarbon. The NMR spectrum of the material showed two vinyl protons at δ 5.92 (d, J = 3 Hz, 1 H) and 5.52 (m, 1 H), in addition to two broad one-hydrogen singlets at δ 3.95 and 3.30 and aromatic absorption. The coupling constant was suggestive of a cyclobutene fragment;[7] thus, structure **11** was favored. This structure assignment was



9 10 5 11

confirmed by pyrolysis of **11** at 500 °C to afford **5** (67%), a known process for cyclobutenes.[8] The preparative sensitized reaction of **5** using 2-acetonaphthone as sensitizer again afforded **11** as the major product (68% isolated) after chromatography on neutral alumina.

For comparison of the efficiencies of these reactions, the quantum yields for the 2-acetonaphthone- and benzophenone-sensitized reactions as well as that for the direct excitation were measured. For both the singlet and triplet excited state, the cyclobutene **11** is formed with reasonable efficiency.

While the photoproducts from both direct and sensitized irradiations are the same, their mechanism for formation is probably different. The low intersystem crossing efficiency in the excited diene together with the well-precedented excited singlet-state diene–cyclobutene conversion suggest the

5 → **11** conversion in the singlet state occurs via the electrocyclic ring-closure route. For the sensitized reaction, decay of the twisted diene triplet state to a highly strained cis–trans isomer followed by rapid ring closure to the cyclobutene appears most reasonable. This route has been rigorously established for the conversion of triplet 1,3-cyclooctadiene to bicyclo[4.2.0]oct-6-ene by isolation of the cis–trans isomer[9a,b] and has been suggested for the sensitized formation of the respective cyclobutene from 3,5-cycloheptadienone.[9c] The absence of di-π-methane products in the triplet chemistry of **5** indicates that the seven-membered ring allows sufficient flexibility for rotational deactivation to be the dominant pathway for the excited triplet state. A comparison of the direct irradiation products of **2** vs. **5** suggests that both the Woodward–Hoffmann allowed cyclohexadiene ring opening (i.e., **2**) and cycloheptadiene ring closure (i.e., **5**) are preferred over the di-π-methane rearrangement in the spin-paired reactant.

Experimental[10] Section

2,2-Diphenylcycloheptanone (7). To a benzene solution (25 mL) of 2.5 g (9.5 mmol) of cyclohexylidenediphenylmethane epoxide was added 1.3 mL of freshly distilled boron trifluoride etherate, the reaction mixture being protected from moisture. After stirring for 1 h at room temperature, the reaction mixture was decomposed with water (20 mL) and worked up as usual to afford a solid which was recrystallized from ethanol to yield in two crops 2.23 g (90%) of the desired 2,2-diphenylcycloheptanone (**7**): mp 92–94 °C (lit.[11] 92–94 °C).

3,3-Diphenylcycloheptene (8). To a lithium diisopropylamide solution [100 mL of THF, 2.05 g (0.020 mol) of diisopropylamine, and 11.55 mL of 1.82 M methyllithium] was added 5.24 g (0.02 mol) of **7** in 25 mL of THF. After 30 min, 30 mL of *N,N,N′,N′*-tetramethylethylenediamine was added followed by 3.79 g (0.02 mol) of diethylchloro phosphate. After stirring for 18 h at room temperature workup in the usual manner afforded a clear colorless oil which was chromatographed on silica gel (2.6 × 40 cm column slurry-packed in 10% ether–hexane). Elution proceeded as follows: 250 mL, 10% ether–hexane, nil; 1000 mL, 10% ether–hexane, 1.1 g of recovered 2,2-diphenylcycloheptanone; 250 mL, 10% ether–hexane, nil; 150 mL, ether, nil; 600 mL of ether, 4.99 g (62% overall, 79% based upon recovered starting material) of the desired product as a colorless oil: IR (neat) 3.45 (s), 6.10 (w), 6.30 (w), 6.78 (m), 6.92 (m), 7.20 (w), 7.32 (w), 7.80 (s, br), 8.50 (s), 8.90 (s), 9.62 (s, br), 10.20–10.60 (s, br), 10.90 (s), 11.13 (s), 11.43 (m), 12.75 (m), 12.40 (m, br), 12.58 (m), 13.35 (s, br), 14.42 (s, br) μm; NMR (CCl_4) δ 7.22 (s, 10 H), 6.15–5.90 (m, 1 H), 3.83–3.30 (pent, 4 H, J = 7 Hz), 2.7–2.4 (m, 2 H), 2.4–2.0 (m, 4 H), 1.65–1.25 (m, 4 H), and 1.06 (t, 6 H, J = 7 Hz).

The phosphate as obtained was dissolved in 45 mL of THF and 175 mL of ammonia and reduced by slow addition of 0.245 g (0.035 mol) of lithium wire. The reaction was quenched with saturated ammonium chloride, diluted with water, and worked up in the standard manner. Molecular distillation (125 °C/0.15 mm) yielded 2.47 g (83%) of 3,3-diphenylcycloheptene as a colorless oil: IR (neat) 3.25 (m), 3.36 (s), 6.23 (m), 6.73 (s), 6.95 (s), 9.63 (m), 13.35 (s), and 14.35 (2) μm; NMR (CCl_4) δ 7.17 (s, 10 H), 5.90 (m, 2 H), 2.57–2.3 (m, 2 H), 2.3–2.0 (m, 2 H), and 1.7–1.4 (m, 4 H).

Exact mass measurement calculated: 248.15649; observed: 248.15691.

5,5-Diphenylcyclohepta-1,3-diene (5). To a solution of 2.47 g (10 mmol) of **8** in 50 mL of carbon tetrachloride was added 1.87 g (10.05 mmol) of *N*-bromosuccinimide and 3–4 mg of benzoyl peroxide, and the solution was refluxed for 1 h. The original yellow solution that contained the *N*-bromosuccinimide as an insoluble solid on the bottom of the flask was clear and contained a white solid (succinimide). After filtration and solvent removal in vacuo, a clear oil was isolated and characterized spectrally: IR (neat) 3.28 (w), 3.38 (m), 6,24 (w), 6.76 (m), 6.96 (m), 8.26 (w), 8.48 (w), 8.76 (w), 9.88 (w), 10.06 (w), 11.23 (w), 12.86 (s), 13.36 (s), and 14.46 (s) μm; NMR (CCl_4) δ 7.17 and 7.06 (10 H), 5.95 (s with shoulder at δ 6.0, 2 H), 4.9–4.65 (m, br, 1 H), 3.2–2.3 (m, 2 H), and 2.3–1.4 (m, 4 H).

The mixture of diphenylcycloheptenyl bromides was dissolved in 50 mL of dimethylformamide containing 2.72 g (0.02 mol) of calcium hydrogen phosphate, and the solution was stirred at 80 °C for 12 h. After cooling, the reaction mixture was poured into 200 mL of water and worked up as usual. Molecular distillation (85 °C/1 mmHg) afforded 2.31 g of clear, colorless **5**, greater than 99% pure as analyzed by VPC (25 ft × ⅛ in., 5% SE-30 on 60/80 Chrom G, column temp 200 °C): IR (neat) 3.28 (w), 3.39 (w), 6.24 (w), 6.75 (w), 6.97 (w), 9.75 (w, sh), 9.82 (w), 11.92 (w), 13.44 (s), 14.39 (s), and 14.75 (m, sh) μm; NMR (CCl_4) δ 7.40–7.10 (d, 10 H), 6.0–5.7 (complex q, 4 H, J = 4 Hz), 2.87 (d, 2 H, J = 4 Hz), 2.49 (complex t, J = 7 Hz, 1 H), and 2.00 (complex d, 1 H).

Anal. Calcd for $C_{19}H_{18}$: C, 92.64; H, 7.36. Found: C, 92.15; H, 7.68.

Sensitized Irradiation of 5,5-Diphenylcyclohepta-1,3-diene (5). A mixture of 0.4635 g (1.88 mmol) of the diene and 1.520 g of 2-acetonaphthone in 225 mL of cyclohexane was irradiated for 1 h in a stirred reactor under nitrogen with Pyrex-filtered light from a 450-W Hanovia medium-pressure source. The reaction was monitored by VPC analysis (13 ft × ⅛ in., 5% SE-30 on 60/80 Chrom G, column temp 200 °C). After solvent removal in vacuo, the resulting oil was chromatographed over neutral alumina (2.5 × 33 cm). Elution proceeded as follows: petroleum ether (30–60 °C), 750 mL, nil; 1825 mL, 0.3160 g (68%) of 2,2-diphenylbicyclo[3.2.0]hept-6-ene (**11**) 750 mL, 0.0740 g of material consisting of the major photoproduct **11** and an unidentified photoproduct; 750 mL, 0.0802 g of material consisting of a mixture of photoproduct, starting diene, and a high-molecular-weight material. The cyclobutene **11**, obtained as white needles (EtOH), showed: mp 56–57 °C; IR (KBr) 3.23 (m), 3.36 (s), 6.25 (m), 6.73 (s), 6.97 (s), 7.73 (m), 9.78 (m), 11.77 (m), 12.08 (m), 12.93 (s), 13.25 (s), 13.46 (s), 13.96 (s), and 14.35 (s) μm; NMR (CCl_4) δ 7.11 (d, 10 H), 5.92 (d, 1 H, J = 3 Hz), 5.52 (m, poorly resolved d, 1 H, J = 3–4 Hz), 3.95 (m, 1 H), 3.30 (m, 1 H), 2.87–2.45 (m, 1 H), 2.15–1.77 (m, 1 H), and 1.65–1.10 (m, 2 H).

Anal. Calcd for $C_{19}H_{18}$: C, 92.64; H, 7.36. Found: C, 92.50; H, 7.32.

Direct Irradiation of 5,5-Diphenylcyclohepta-1,3-diene (5). A stirred solution of 0.5760 g (2.34 mmol) of **5** in 225 mL of purified cyclohexane was irradiated for 1 h with Vycol-filtered light from a Hanovia 450-W medium-pressure source in a nitrogen atmosphere. The reaction was monitored by VPC analysis (0.125 in. × 13 ft, 5% SE-30 on 60/80 Chrom G, column temp 200 °C). After solvent removal in vacuo, the reaction mixture was chromatographed over neutral alumina (2.0 × 31 cm column slurry packed in petroleum ether). Elution proceeded as follows: 250 mL, 30–60 °C, petroleum ether, nil; 375 mL, petroleum ether, 0.340 g (59%) of crystalline 2,2-diphenylbicyclo[3.2.0]hept-6-ene; 600 mL, 0.0291 g of material consisting of the major photoproduct and an unidentified photoproduct; 375 mL, 0.0486 g of material consisting mainly of starting material and a high-molecular-weight material not characterized. The IR and NMR spectra of the photoproduct were identical with that isolated from the sensitized irradiation of 5,5-diphenylcyclohepta-1,3-diene.

Pyrolysis of 2,2-Diphenylbicyclo[3.2.0]hept-6-ene (11). A solution of 99.4 mg (0.40 mmol) of **11** in 50 mL of benzene was pyrolyzed at 550 °C by the slow addition of the solution (ca. 2 h) to a 3 × 90 cm vertical glass column packed 45 cm with 6-mm glass beads under a stream of nitrogen. Analysis by VPC (6 ft × ⅛ in., 3% SE-30 on 60/80 Chrom G, column temp 200 °C) indicated unreacted starting material and one product which had an identical retention time with **5**. After solvent removal in vacuo, the resulting oil was molecularly distilled (90 °C/0.02 mm) to yield 95.8 mg (96%) of a yellow oil consisting of a 7:3 mixture of **5** and **11**, as analyzed by NMR. Characterization of the diene was rigorously established by comparison of the IR of material purified by preparative VPC (10 ft × 0.25 in., 5% SE-30 on Chrom W, column temp 200 °C) with that of authentic diene.

Quantum Yields. The measurements were essentially done as previously described using potassium ferrioxalate actinometry.[5a] Analysis of these quantum-yield runs was by VPC (13 ft × ⅛ in., 5% SE-30 Chrom G, column temp 185 °C). The results of the determinations are given in the table.

Registry No.—**5**, 57304-01-5; **6**, 63865-83-8; **7**, 50390-71-1; **8**, 63865-84-9; **11**, 63865-85-0; 7,7-diphenylcyclohept-1-en-1-ol diethyl phosphate, 63904-40-5; 3-bromo-7,7-diphenylcyclohept-1-ene, 63865-86-1; 4-bromo-7,7-diphenylcyclohept-1-ene, 63865-87-2; diethylchloro phosphate, 814-49-3.

References and Notes

(1) (a) Abstracted in part from the Ph.D. Thesis of G.L.S., 1975; (b) Alfred P. Sloan Fellow, 1972–1973: Camille and Henry Dreyfus Teacher–Scholar, 1972–1977.

(2) For leading references, see: J. S. Swenton, R. M. Blankenship, and R. Sanitra, *J. Am. Chem. Soc.*, **97**, 4941 (1975).

(3) For more recent examples, see: (a) S. S. Hixon and J. C. Tausta, *Tetrahedron Lett.*, 2007 (1974); (b) H. E. Zimmerman, K. S. Kamm, and D. P. Werthemann, *J. Am. Chem. Soc.*, **96**, 7823 (1974); (c) H. E. Zimmerman, T. X. Albrecht, and M. J. Hare, *ibid.*, **97**, 3726 (1975); (d) P. S. Engel and M. A. Schexnayder, *ibid.*, **97**, 145 (1975); (e) P. S. Engel, M. E. Schroder,

and M. A. Schexnayder, *ibid.*, **98**, 2683 (1976); (f) M. J. Bullivant and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 249 (1976); (g) D. I. Schuster, J. Eriksen, P. S. Engel, and M. A. Schexnayder, *J. Am. Chem. Soc.*, **98**, 5026 (1976); (h) K. G. Hancock, J. D. Condie, and A. J. Barkovich, *J. Org. Chem.*, **42**, 2794 (1977).
(4) H. E. Zimmerman and G. E. Samuelson, *J. Am. Chem. Soc.*, **89**, 5971 (1967); *ibid.*, **91**, 5307 (1969).
(5) (a) J. S. Swenton, J. A. Hyatt, T. J. Walker, and A. L. Crumrine, *J. Am. Chem. Soc.*, **92**, 1406 (1970); *ibid.*, **93**, 4808 (1971); (b) H. E. Zimmerman and G. A. Epling, *ibid.*, **92**, 1411 (1970); *ibid.*, **94**, 8749 (1972).
(6) For a detailed study of the photochemistry of 3-phenylcycloheptene, see: S. J. Cristol and C. Ilenda, *J. Am. Chem. Soc.*, **97**, 5862 (1975).
(7) O. L. Chapman, *J. Am. Chem. Soc.*, **85**, 2016 (1963).
(8) (a) O. L. Chapman, D. J. Pasto, G. W. Borden, and A. A. Griswold, *J. Am. Chem. Soc.*, **84**, 1220 (1962); (b) G. R. Branton, H. M. Frey, D. C. Montague, and I. D. R. Stevens, *Trans. Faraday Soc.*, **62**, 659 (1966).
(9) (a) R. S. H. Liu, *J. Am. Chem. Soc.*, **89**, 112 (1967); (b) W. J. Nebe and G. J. Fonken, *ibid.*, **91**, 1249 (1969); (c) see also D. I. Schuster and C. W. Kim, *ibid.*, **96**, 7437 (1974); D. I. Schuster and D. J. Blythin, *J. Org. Chem.*, **35**, 3190 (1970).
(10) IR spectra were recorded with a Perkin-Elmer Infracord Model 137 spectrometer. The mass spectra were measured with an AEI MS-9 mass spectrometer. NMR spectra were measured at 60 MHz using tetramethylsilane as internal standard. Elemental analyses were determined by Scandinavian Microanalytical Laboratory, Herlev, Denmark. All irradiations were performed in an atmosphere of purified nitrogen. Workup as usual refers to extraction with ether, washing with dilute acid or base if appropriate, washing with saturated brine solution, drying over calcium sulfate, and removal of solvent in vacuo.
(11) R. E. Lyle and G. C. Lyle, *J. Am. Chem. Soc.*, **74**, 4059 (1952).

Photochemistry of Some Pteridine *N*-Oxides[1]

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Purine *N*-oxides, like many heterocyclic aromatic *N*-oxides,[2] undergo deoxygenation and migration of the oxygen to the adjacent carbon under the influence of ultraviolet light.[3-6] 1-Hydroxyxanthine (**1**), which has an *N*-hydroxyimide structure, shows the expected photoreduction, but it also undergoes an unusual 1:3 isomerization of the 1-hydroxyl group to afford 3-hydroxyxanthine[7] (**3**). It was suggested that the isomerization of **1** to **3** proceeds via the enol nitrone (**2**) and two successive oxazirane migrations (Scheme I).

Recently, the pteridine analogues of **1** and **3**, i.e., 3-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropteridine (**4**) and its 1-hydroxy isomer **6**, were reported.[8,9] To investigate whether a pteridine would undergo the unusual *N*-hydroxy rearrangement, we examined the possible photochemical conversion of **4** to **6**. However, the main photoproduct from **4** over the pH range 2 to 12 (Figure 1) was the reduction product **5**, together with a trace of ring-opened compound. Under the same conditions of irradiation, the possible rearrangement product **6** showed little change, although with prolonged irradiation it could be slowly reduced to **5** (Φ 5.9×10^{-5} at pH 7.0). The hydroxyl isomerization of **1** was deduced to occur via the singlet state.[5] The lack of *N*-hydroxyl isomerization by the pteridine **4** indicates that the apparent structural similarity of the pyrimidine ring in **1** and **4** is not paralleled by the formation of a tautomer in the excited singlet comparable to **2**. The absence of this tautomer in the excited state precludes *N*-hydroxyl isomerization and the only photoprocess then observed is deoxygenation via the triplet, i.e., **4** to **5**. That process is quite sensitive to change in pH (Figure 1). Changes in pH from 3 to 8 did not affect the quantum yield for the conversion of **4** to **5**. Decreasing the pH from 3 to 1 caused a steep decline in the quantum yield for photoreduction of **4**, and at pH 1 there was no reduction of **4**. This effect of acid is similar to that on the photoreactions of quinoline *N*-oxide[10] and isoquinoline *N*-oxide.[11] Between pH 8 and 10 the quantum yield of reduction of **4** decreased, and then remained unchanged with further increases in pH. Significantly, the inflection in the curve in Figure 1 at pH 9.0 coincides with one of the pK_as of **4**. In contrast to the relatively small spectral changes accompanying the first ionization of **4** (pK 5.6), the second ionization (pK 9.0) is associated with the appearance of a band of high extinction at 261 nm. These data indicate that the sequence of ionization of **4** is N-1 H to **4a**, and then N-3 OH to **4b**. This ionization sequence parallels that of **1**[12,13] (N-3 H, N-1 OH). The close correspondence of the inflection point in Figure 1 with the second ionization pK_a to **4b** would accord with the assignment of positions of ionization and indicates that photoreduction of the *N*-hydroxy species, **4** or **4a**, has a higher quantum efficiency than does that of the enolate anion **4b**. In contrast to the relatively large effects of changes in pH and ionic form on the quantum efficiency for photoreduction observed with **4**, changes in the ionic form of **6** (pK_as 6.50 and 9.35)[9] did not greatly affect the quantum yield for the appearance of **5**.

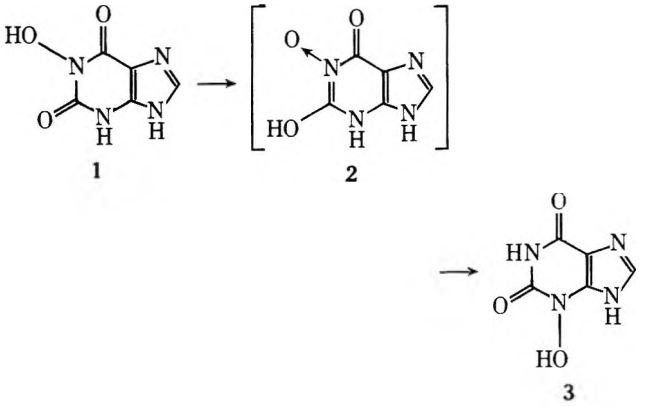
The photoreactivity of 1-hydroxy-2-oxo-1,2-dihydropteridine (**7**)[9] was also examined. In contrast to the facile photoreduction of 3-hydroxy-2-oxopurine,[14] neither the anion nor the neutral molecule of **7** yielded the anticipated photoreduction product, 1,2-dihydro-2-oxopteridine (**10**). Instead, both produced the C-4 oxidation product **5** in 9 and 38% yields, respectively, as the only UV-absorbing product after irradiation (Corex filter) for 4 h. Irradiation of the neutral molecule of **10** under the same conditions also produced **5** (18%). This indicates that the deoxygenation process at N-1 of **7** is not correlated with oxidation at C-4. Both **7** and **10** form stable hydrates, **8** and **9** (Scheme II), in solution, and air oxidation of **9** is known to yield **5**.[15] These observations suggest that the photochemical formation of **5** probably proceeds via the hydrate **9**. No oxidation of **8** and **9** to **5** occurred under the ex-

Table I. 3-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydropteridine

pH	Species	λ_{max}, nm, $\epsilon \times 10^{-3}$	pK_a
		231 (13.7)	
2	0		
		322 (7.4)	
			5.61 ± 0.1[a]
		217 (15.7)	
6.8	−1		
		243 (8.7)	
		327 (8.0)	
		338[b] (7.5)	
			9.0 ± 0.3
12	−2	217 (17.5)	
		261 (19.0)	
		356 (8.4)	

[a] pK_as calculated at isosbestic points of isosbestic spectra. [b] Shoulder.

Scheme I



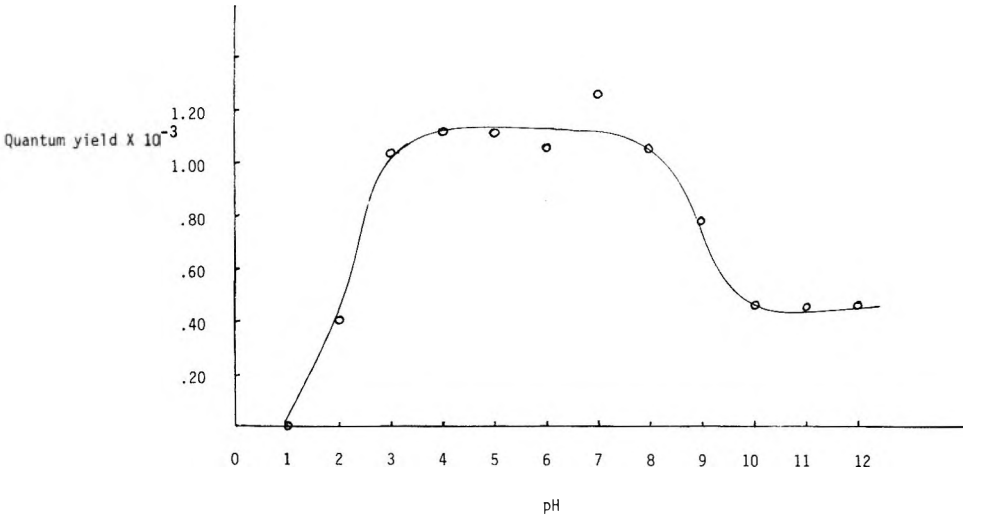
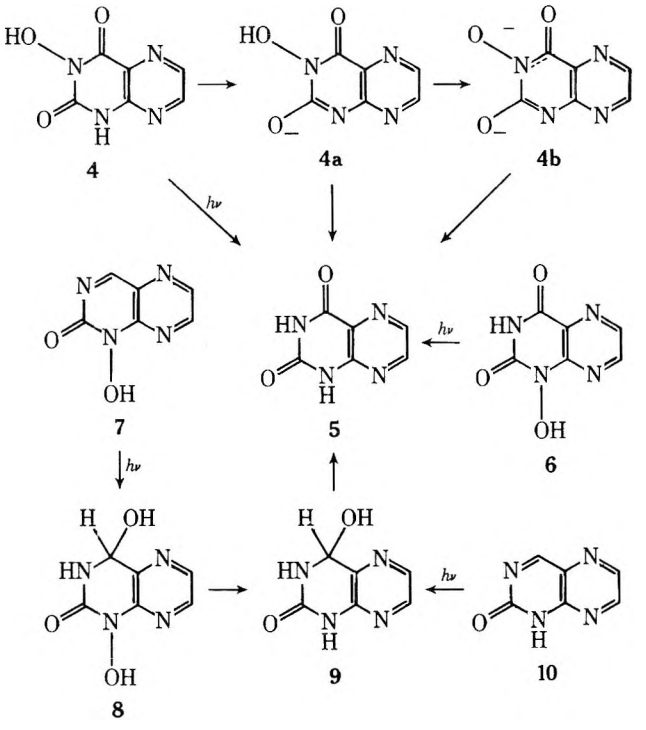


Figure 1. Effect of pH on quantum yields of formation of 2,4-dioxo-1,2,3,4-tetrahydropteridine from 3-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropteridine.

Scheme II



perimental conditions without irradiation. Hence, this represents a novel photochemical oxidation that has not been previously described for pteridines.

Experimental Section

Photolysis. Method A. A sample of compound (~1.0 mmol) was dissolved in 350 mL of H_2O or buffer solution. The solution was degassed and irradiated in an immersion-type apparatus equipped with a 450-W Hanovia high-pressure Hg lamp with a pyrex or corex filter. The disappearance of the starting material was monitored by change in the UV absorption. After the photolysis was discontinued, the solution was then reduced to a small volume in vacuo. The products were then separated and isolated by chromatography over a Bio-Rad AG-50 × 8 (H^+), 200–400 mesh column (9 × 450 mm). Yields of reaction products were calculated from their known ϵ_{max}.

Method B. The quantum-yield study was performed in a Rayonet photochemical reactor equipped with 2537 A and 3000 A and a merry-go-round apparatus. Potassium ferrioxalate was used as the chemical actinometer.[16]

Chromatography. For routine quantitation, a 2.0 × 1000 mm analytical high-pressure liquid chromatography column of Bio-Rad A-6 resin eluted with 0.4 M NH_4OOCH buffer of pH 4.7 and a Laboratory Data Control (LDC) UV monitor were used. The volume values (mL) of compounds **4**, **6**, **5**, **7**, and **10** were found to be 10.5, 10.1, 11.1, 8.0, and 9.0, respectively. The column's temperature was maintained at 50 °C with a flow rate of 16.6 mL/h.

Acknowledgment. We are indebted to Dr. L. Bauer for a sample of **4** and thank Drs. J. C. Parham and G. B. Brown for their continued interest and discussions, and Ms. M. A. Templeton for assistance with the pK_a determination.

Registry No.—**4**, 10579-28-9; **5**, 487-21-8; **7**, 37440-31-6.

References and Notes

(1) This investigation was supported in part by funds from the United States Energy Research and Development Administration, Contract No. E(11-1)-2931, and by Public Health Service Research Grants CA 15274, CA 17085, and CA 08748 from the National Cancer Institute.
(2) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).
(3) G. B. Brown, G. Levin, and S. Murphy, *Biochemistry*, **3**, 880 (1964).
(4) A. Giner-Sorolla, C. Gryte, M. L. Cox, and J. C. Parham, *J. Org. Chem.*, **36**, 1228 (1971).
(5) F. L. Lam and J. C. Parham, *J. Org. Chem.*, **38**, 2397 (1973).
(6) F. L. Lam and J. C. Parham, *J. Am. Chem. Soc.*, **97**, 2839 (1975).
(7) F. L. Lam, G. B. Brown, and J. C. Parham, *J. Org. Chem.*, **39**, 1391 (1974).
(8) L. Bauer, C. N. V. Nambury, and F. M. Hershenson, *J. Heterocyl. Chem.*, **3**, 224 (1966).
(9) T.-C. Lee, *J. Org. Chem.*, **38**, 703 (1973).
(10) G. Farao, *Mol. Photochem.*, **2**, 323 (1970).
(11) I. Ono and N. Hata, *Bull. Chem. Soc. Jpn.*, **46**, 3658 (1973).
(12) J. C. Parham, J. Fissekis, and G. B. Brown, *J. Org. Chem.*, **32**, 1151 (1967).
(13) J. C. Parham, T. G. Winn, and G. B. Brown, *J. Org. Chem.*, **36**, 2639 (1971).
(14) T.-C. Lee, F. L. Lam, and G. B. Brown, *J. Org. Chem.*, **40**, 1547 (1975).
(15) Y. Inoue and D. D. Perrin, *J. Chem. Soc.*, 2600 (1962).
(16) J. G. Calvert and J. N. Pitts, "Photochemistry", Wiley, New York, N.Y., 1966, p 783.

5,5,6,6,11,11,12,12-Octamethylcyclododeca-1,3,7,9-tetrayne

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3-Chloro-3-methyl-1-butyne (**1**) has been used in C, O, and N alkylations[1,2] as a convenient method for introducing the 1,1-dimethyl-2-propynyl group. It has also been employed as a precursor of dimethylvinylidene carbene (**2**).[3] Recently, when studying the alkylation of amines with **1**, a crystalline

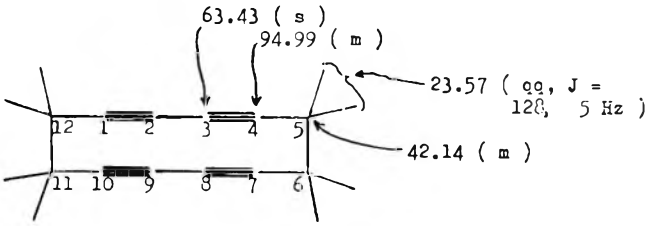


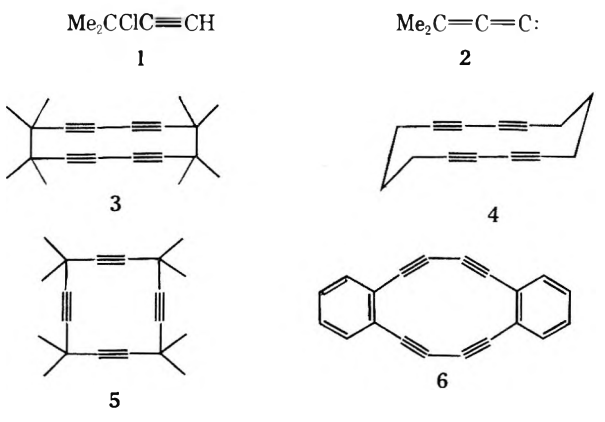
Figure 1. Carbon-13 chemical shifts of **3** in ppm downfield from tetramethylsilane, in $CDCl_3$ solution with the signal for $CDCl_3$ as internal standard.

side product **3** was obtained and its structure determination is reported herein.

Heating 3-chloro-3-methyl-1-butyne (**1**) with triethylamine and copper powder in benzene gave a crystalline compound after chromatography. High-resolution mass spectrometry and elemental analysis indicated a molecular composition of $C_{20}H_{24}$, while infrared spectroscopy showed **3** to be an acetylenic compound (2235 cm^{-1}). The ultraviolet spectrum of **3** in isooctane was very similar to that of cyclotetradeca-1,3,8,10-tetrayne (**4**),[4] and its proton nuclear magnetic resonance (^1H NMR) spectrum showed only one singlet attributed to methyl groups. These data suggested the structure 5,5,6,6,11,11,12,12-octamethylcyclododeca-1,3,7,9-tetrayne (**3**) for this new compound. A proton-decoupled ^{13}C NMR spectrum supported the above structure, and is consistent with spectra of similar 1,3-diacetylenes, especially that of **4**,[5] and excluded the possibility of the alternate structure 3,3,6,6,9,9,12,12-octamethylcyclododeca-1,4,7,10-tetrayne (**5**).[6] The observation of long-range coupling between the methyl protons and the external carbons of the diacetylenic units (i.e., C-1, -4, -7, and -10) and the absence of such coupling with the internal carbons (C-2, -3, -8, and -9) in the proton-coupled ^{13}C NMR spectrum (see Figure 1) supported the chemical-shift assignments and was consistent with those of similar 1,3-diacetylenes.[5,7]

Hydrogenation of **3** over platinum catalyst gave a compound with spectral properties consistent with 1,1,2,2,7,7,8,8-octamethylcyclododecane (see Experimental Section). In order to confirm the position of the methyl groups in structure **3** and its hydrogenation product, **3** was oxidized with neutral aqueous potassium permanganate. From the reaction mixture, a good yield of tetramethylsuccinic anhydride was obtained. The isolated tetramethylsuccinic anhydride was identified by its spectral data which were identical with those of authentic material prepared from diethyl tetramethylsuccinate.[8]

1,2:7,8-Dibenzocyclododeca-1,7-diene-3,5,9,11-tetrayne (**6**) has been synthesized,[9] and 1,3,7,9-cyclododecatetrayne was prepared in solution but was too unstable to be isolated.[10] Compound **3** represents the smallest, stable monocyclic compound (12-membered ring) containing two 1,3-diacetylenic units known to date.[11] The crude two-dimentional x-ray diffraction pattern of **6** revealed its structure to have two "bowed diacetylenic chains"[12] instead of the normal linear array of carbon atoms in diacetylenic units. In order to determine the actual molecular geometry of the macrocyclic tetrayne, single-crystal x-ray analysis of **3** is being undertaken and will be reported later. The formation of **3** from 3-chloro-3-methyl-1-butyne (**1**) can be rationalized in a number of ways but we favor a scheme in which two dimethylvinylidene carbenes (**2**) combine to give a cumulene with five double bonds. Dimerization of the latter might then produce the cyclic tetrayne **3**.



Experimental Section

Melting points determined on a Kofler hot-stage microscope or in a sealed tube using a Büchi SMP-20 melting point apparatus are corrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer and are reported in wavenumbers (cm^{-1}). The high-resolution mass spectrum (HRMS) was measured on a DuPont CEC-110B instrument; low-resolution mass spectra (MS) were determined on a Varian Mat 44 instrument. Nuclear magnetic resonance spectra were measured on a Varian T-60 (60 MHz) instrument for proton (^1H NMR), and on a Bruker HFX-90 (22.63 MHz) instrument for carbon-13 (^{13}C NMR), and are reported in parts per million (δ) downfield from tetramethylsilane; the abbreviations s, t, q, and m refer to singlet, triplet, quartet, and multiplet, respectively. Ultraviolet (UV) spectra were determined on a Cary-14 recording spectrophotometer and wavelengths are reported in nanometers (nm). Elemental analysis was performed by Robertson Laboratory, Florham Park, N.J.

5,5,6,6,11,11,12,12-Octamethylcyclododeca-1,3,7,9-tetrayne (3). To a solution of 3-chloro-3-methyl-1-butyne (**1**, 5 g, 48 mmol) in benzene (90 mL) in a 500 mL three-necked flask equipped with a condenser and a mechanical stirrer were added copper powder (5 g) and triethylamine (15 mL, 108 mmol). The stirred reaction mixture was heated at reflux for 16 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate evaporated to near dryness under reduced pressure. This residue was filtered through a short silica gel column using dichloromethane as solvent. The eluate was concentrated and chromatographed on four 20 × 20 × 0.2 cm silica gel plates using 10% dichloromethane in hexane as solvent to give **3**, crystallized from chloroform–methanol mixture as white needles (106 mg, 3.3% yield): mp sublimed at 167 °C, decomposed violently above 180 °C in a sealed tube; IR ($CHCl_3$) 2980, 2945, 2875, 2235, 1460, 1440, 1390, 1375, 1365, 1300, 1180, 1145, 1125, and 1095 cm^{-1}; HRMS *m/e* found 264.18878, calcd for $C_{20}H_{24}$ 264.18780; MS *m/e* (rel intensity %) 264 (M^+, 24.5), 180 (100), 132 (76.5), 131 (26.5), 117 (47.5), 115 (38.0), 91 (44.5), 77 (33.0), 76 (22.5), 65 (23.5), 63 (22.0), 51 (32.5), 41 (40.0), 39 (57.0); ^1H NMR ($CDCl_3$) δ 1.20 (s); ^{13}C NMR ($CDCl_3$) δ 23.57 (qq, J = 128 and 5 Hz), 42.13 (m), 69.43 (s), and 94.99 (m); UV λ_{max} (isooctane) 239 (ϵ 730), 249 (805), and 264 (515) nm; UV λ_{max} (95% C_2H_5OH) 250 (ϵ 1100) and 265 (750) nm.

Anal. Calcd for $C_{20}H_{24}$: C, 90.85; H, 9.15. Found C, 90.39; H, 9.38.

1,1,2,2,7,7,8,8,-Octamethylcyclododecane. PtO_2 (82 mg) was hydrogenated in glacial acetic acid (10 mL) until hydrogen uptake ceased. A solution of **3** (58 mg, 0.22 mmol) in glacial acetic acid–ethyl acetate (v/v, 4:1, 10 mL) was injected into the hydrogenation flask. After coming to equilibrium, **3** was hydrogenated and the amount of hydrogen uptake monitored. Reaction stopped spontaneously after taking up 8 equiv of hydrogen (41.5 mL). The catalyst was filtered off and the filtrate diluted with ether (50 mL). The ether solution was washed with saturated aqueous sodium carbonate solution (2

× 50 mL) and dried (anhydrous sodium sulfate). After evaporating the solvent under reduced pressure, the residue was crystallized from a dichloromethane–methanol mixture to give white needles (59 mg, 96% yield): mp 63.0–63.5 °C; IR ($CHCl_3$) 2950, 1470, 1395, 1380, 1370, 1265 cm^{-1}; MS *m/e* (rel. intensity %) 280 (M^+, 0.27), 97 (28.0), 85 (23.5), 84 (30.5), 83 (62.5), 82 (30.0), 71 (29.0), 70 (29.0), 69 (100), 57 (67.5), 56 (80.5), 55 (80.0), 43 (60.0), 42 (21.5), 41 (95.0); ^1H NMR ($CDCl_3$) δ 0.83 (s, 3) and 1.37 (s, 2).

Oxidation of 3. A suspension of **3** (52.6 mg, 0.2 mmol) in aqueous potassium permanganate (828 mg, 5.2 mmol, in 50 mL) was heated at reflux for 20 h. After cooling to room temperature, the remaining permanganate was destroyed with sodium bisulfite. The reaction mixture was then acidified with sulfuric acid and extracted continuously with ether for 4 days. The ether extract was evaporated under reduced pressure to give an oil (24 mg), 95% by VPC, and was purified further by vacuum sublimation to give tetramethylsuccinic anhydride as a white gummy solid: mp sublimed without melting in a sealed tube; IR ($CHCl_3$) 2980, 1860, 1810, 1785, 1475, 1460, 1450, 1400, 1385, 1375, 1275, 1145, 970, 955, 920 cm^{-1}; MS *m/e* (rel. intensity %) 157 ($M^+ + 1$, 0.95), 156 (M^+, 0.13), 84 (100), 83 (21.0), 69 (100), 41 (71.5), 39 (41.5), 28 (32.0); ^1H NMR ($CDCl_3$) δ 1.24 (s).

Diethyl Tetramethylsuccinate. Diethyl tetramethylsuccinate was prepared from ethyl 2-methylpropanoate according the the method of T. J. Brocksom and co-workers.[13] The product so obtained was contaminated by an unknown compound [bp 77–78 °C (1 mm)]. Diethyl tetramethylsuccinate was separated from the contaminant by chromatography (silica gel, 1% ethyl acetate in hexane) followed by vacuum distillation: bp 79–80 °C (1 mm); IR ($CHCl_3$) 2990, 1725, 1470, 1445, 1400, 1385, 1370, 1270, 1170, 1125, 1025 cm^{-1}; MS *m/e* (rel. intensity %) 230 (M^+, 0.17), 185 (31.5), 157 (74.5), 116 (84.5), 115 (47.5), 111 (69.5), 88 (84.0), 87 (100.0), 85 (32.0), 84 (59.0), 83 (100.0), 73 (65.5), 70 (64.0), 69 (70.0), 59 (55.5), 57 (50.5), 55 (58.5), 43 (60.0), 42 (40.5), 41 (99.5), 39 (44.0), 29 (100.0), 28 (40.0), 27 (72.5); ^1H NMR ($CDCl_3$) δ 1.25 (s, 6), 1.25 (t, 3, J = 7 Hz), and 4.08 (q, 2, J = 7 Hz).

Tetramethylsuccinic Anhydride. Diethyl tetramethylsuccinate was hydrolyzed with aqueous ethanolic sodium hydroxide followed by acidification to give crude tetramethylsuccinic anhydride according to the procedure of D. J. Trecker and R. S. Foote.[8] The crude anhydride was purified by vacuum sublimation to give a gummy white solid with spectral properties identical to those mentioned above.

Acknowledgments. This work was supported by the National Cancer Institute (Contract 1CP 33217). The high-resolution mass spectrum was measured in the National Institute of Health supported facility at Massachusetts Institute of Technology (Grant FR 00317) under the direction of Professor K. Biemann. We are indebted to Dr. D. D. Traficante of the Department of Chemistry of M.I.T. for the ^{13}C NMR spectra, and Ms. R. Lüthi of the same department for the low-resolution mass spectra.

Registry No.—**1**, 1111-97-3; **3**, 61414-48-0; 1,1,2,2,7,7,8,8-octamethylcyclododecane, 61414-47-9; tetramethyl succinic anhydride, 35046-68-5; diethyl tetramethyl succinate, 35367-54-3.

References and Notes

(1) R. V. Stevens and E. B. Reid, *Tetrahedron Lett.*, 4193 (1975).
(2) G. F. Hennion and J. F. Motier, *J. Org. Chem.*, **34**, 1319 (1969), and references cited therein.
(3) H. D. Hartzler, *J. Am. Chem. Soc.*, **83**, 4997 (1961); B. W. Bycroft, A. P. Johnson, and W. Landon, *J. Chem. Soc., D*, 463 (1969); R. W. Mills, R. D. H. Murray, and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 133 (1973); M. Santelli and M. Bertrand, *Bull. Soc. Chim. Fr.*, 2380 (1973); T. Sasaki, S. Eguchi, and T. Ogawa, *J. Org. Chem.*, **39**, 1927 (1974), and *Heterocycles*, **3**, 193 (1975); S. Julia, D. Michelet, and G. Linstrumelle, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, **278**, 1523 (1974).
(4) F. Sondheimer and Y. Gaoni, *J. Am. Chem. Soc.*, **81**, 6301 (1959).
(5) C. Charrier, D. E. Dorman, and J. D. Roberts, *J. Org. Chem.*, **38**, 2644 (1973).
(6) Compound **5** should give only three signals in the ^{13}C NMR spectrum but four were observed. See Experimental Section.
(7) R. Zeisberg and F. Bohlmann, *Chem. Ber.*, **107**, 3800 (1974).
(8) D. J. Trecker and R. S. Foote, *J. Org. Chem.*, **33**, 3527 (1968).
(9) O. M. Behr, G. Eglinton, A. R. Galbraith, and R. A. Raphael, *J. Chem. Soc.*, 3614 (1960); O. M. Behr, G. Eglinton, I. A. Lardy, and R. A. Raphael, *ibid.*, 1151 (1964).
(10) R. Wolovsky and F. Sondheimer, *J. Am. Chem. Soc.*, **87**, 5720 (1965), and references cited therein.
(11) Yields in this report were not optimized.
(12) W. K. Grant and J. C. Speakman, *Proc. Chem. Soc.*, 231 (1959).
(13) T. J. Brocksom, N. Petragnani, R. Rodrigues, and H. La Scala Teixeira, *Synthesis*, 396 (1975).

Addition of Diphenyldiazomethane to 7-Chloronorbornadiene. Implications for Orbital Control of 1,3-Dipolar Cycloadditions

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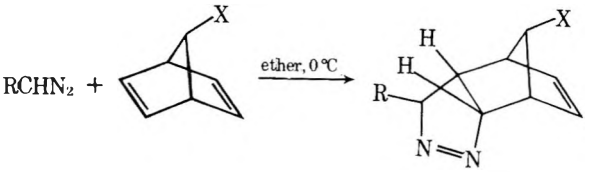
Theoretical treatment of the 1,3-dipolar cycloaddition reaction has shown remarkable sophistication, leading to a rather detailed knowledge of this fascinating process.[1] One aspect of the cycloaddition that still seems somewhat unclear is its exo–endo selectivity in norbornadienes. Although generally recognized as a typical exo-addition process on a wide variety of norbornenes, the reaction proceeds via both exo and endo pathways in a number of cases involving norbornadienes.[2] It is therefore startling that the addition of either diazomethane or (better) diazoethane to the 7-halonorbornadienes has been reported to occur *solely* via an endo,anti pathway (eq 1).[3] This specificity has been attributed to a



(1)

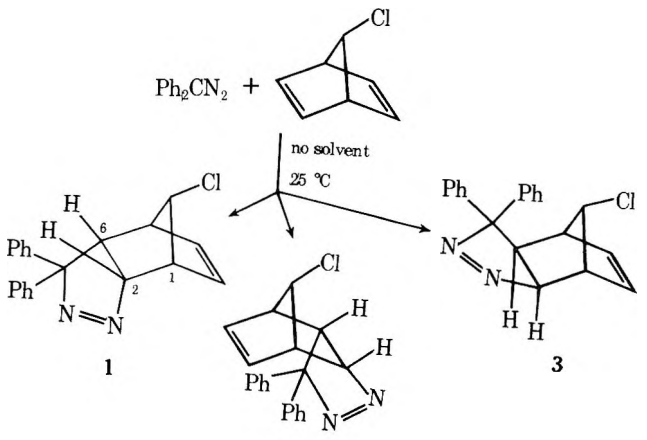
R = H, 35%
R = CH_3, 80%

contribution by the σ^* orbital of the C–X bond to the LUMO of the diene.[3] Because 1,3-dipolar cycloadditions of the present type are believed to be controlled by the interaction between the HOMO of the diazo component and the LUMO of the diene,[1] this σ^* contribution is considered to be significant, and to favor an endo,anti approach by the diazoalkane. However, such an interpretation seemingly places minor importance on the diazoalkane.

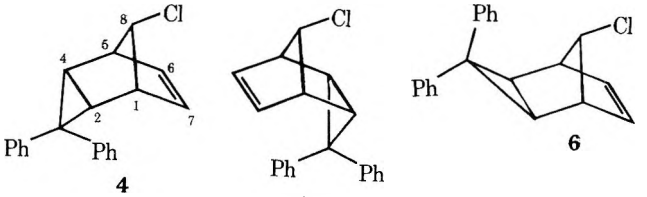
Because diphenyldiazomethane adds to 7-*tert*-butoxynorbornadiene to give all four possible monoadducts,[2a] we were curious about its addition to a 7-halonorbornadiene. In fact, its reaction with 7-chloronorbornadiene showed no such specificity as in eq 1. Three monoadducts were formed (Scheme I): the endo,anti (58%); the endo,syn (16%); and the exo,anti (26%) isomers, **1**, **2**, and **3**, respectively. The yield of isolated material was 47%.

The structures of the three adducts seem secure. The endo adducts **1** and **2** were differentiated from the exo adduct **3** by the value of the NMR coupling constant $J_{1,2} \sim 3.5$ Hz in the former pair and ~1 Hz in the latter compound. Further structural evidence was gained from their remarkably clean photolysis to the corresponding tricyclic chlorides. Adduct **1** was photolyzed in acetone at 366 nm[4] to the very labile chlo-

Scheme I



ride **4**, characterized by its symmetry-simplified NMR spectrum: δ (CCl_4) 6.9–7.5 (m, Ar-H), 5.07 (t, J = 2 Hz, H-6,7), 4.03 (shp m, H-8), 3.20 (six-line m, J = 2 Hz, H-1,5), 2.06 (t, J = 2 Hz, H-2,4). The syn nature of adduct **2** was demonstrated by its photolysis in benzene to chloride **5**, identical with that reported.[2a] Exo adduct **3** yielded chloride **6** upon photolysis in benzene, also readily characterized by its NMR spectrum: δ ($CDCl_3$) 7.0–7.4 (m, Ar-H), 6.37 (t, H-6,7), 3.58 (m, H-8), 3.10 (m, H-1,5), 1.75 (s, $W_{1/2}$ = 2 Hz, H-2,4).



The present results reaffirm the complexity inherent in such additions. It seems clear that the MO rationale[3] for eq 1 is not general and that it must somehow be modified to incorporate more features of the diazo component. A possible interpretation would involve a shift away from a type I cycloaddition (HOMO diazoalkane – LUMO diene control) in eq 1 toward a type II cycloaddition (all four frontier orbitals control) in Scheme I.[5] Such a shift would place less emphasis upon the LUMO of 7-chloronorbornadiene and thereby reduce the favorability of endo,anti approach. Alternatively, steric effects could be invoked, as in other comparisons of 1,3-dipolar cycloadditions of diphenyldiazomethane.[7] This seems unsatisfactory, however, in that the larger diazoethane was superior to the smaller diazomethane in its reaction in eq 1,[3] and in that the very crowded adduct **2** resulted as a significant product in Scheme I.

Experimental Section

Melting points were taken on a calibrated Fisher-Johns block. Infrared spectra were determined on a Perkin-Elmer Model 700 instrument. NMR spectra were recorded on a Varian A-60A spectrometer. Only significant absorptions for structural assignment are given for these spectra. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Addition of Diphenyldiazomethane to 7-Chloronorbornadiene. From the six additions carried out, a typical preparation is described. Diphenyldiazomethane (4.80 g, 24.7 mmol) was added to neat 7-chloronorbornadiene (used as received from Frinton Laboratories, 3.13 g, 24.7 mmol) and the homogeneous, liquid mixture was allowed to stand at room temperature for 12 weeks.[8] The dark, now solid mass was triturated with cold hexane, leaving adduct **1** [2.14 g, 27%, mp 161–162 °C dec from ether–hexane, IR ν (KBr) 1560 cm^{-1} (N=N), NMR δ ($CDCl_3$) 4.72 (dd, H-2, $J_{1,2}$ = 3.5 Hz). Anal. Calcd for $C_{20}H_{17}ClN_2$: C, 74.88; H, 5.34. Found: C, 74.68; H, 5.29]. Chromatography of the hexane-soluble material over alumina yielded upon elution (10% ether in hexane) benzophenone azine containing some adduct **2** [NMR δ ($CDCl_3$) 4.80 (dd, H-2, $J_{1,2}$ = 3.5 Hz)], followed by a mixture of **2** and **3** (Anal. Found: C, 74.83; H, 5.30), and finally pure adduct **3** [mp 164–166 °C dec from ether–hexane, NMR δ ($CDCl_3$) 5.22 (dd, H-2, $J_{1,2}$ = 1 Hz)]. Analysis of those fractions containing adducts **2** and **3** by NMR indicated a total weight of 0.61 g (8%) of the former and 0.97 g (12%) of the latter. Unidentified tarry material remained on the column.

Photolysis of the Adducts 1, 2, and 3. The appropriate adduct (200 mg) was dissolved in 5 mL of either acetone (adduct **1**) or benzene (adducts **2** and **3**) in a Pyrex test tube and irradiated at 366 nm in a small irradiation unit (Bradford Scientific, Inc., Marblehead, Mass.). After 2 h the photolyses were complete, as indicated by cessation of nitrogen evolution. The solvent was evaporated and the NMR spectrum of the crystalline residue was taken. The chlorides **4**, **5**, and **6** were fairly labile to chromatography on a variety of columns (alumina, Florisil, and silica gel), as well as thermally labile. Photolysis of **1** in benzene containing benzophenone gave only **4** also, exactly as did the use of acetone as solvent. Benzophenone appeared to be without effect in the photolyses of the other adducts.

Registry No.—**1**, 64011-10-5; **2**, 64044-01-5; **3**, 64044-02-6; **4**, 64044-03-7; **6**, 64044-04-8; diphenyldiazomethane; 883-40-9; 7-chlornorbornadiene, 1609-39-8.

References and Notes

(1) For recent treatments and leading references see: R. Sustmann, *Pure Appl. Chem.*, **40**, 569 (1974); R. Huisgen, *J. Org. Chem.*, **41**, 403 (1976); R. Sustmann, E. Wenning, and R. Huisgen, *Tetrahedron Lett.*, 877 (1977); J. Geittner, R. Huisgen, and R. Sustmann, *ibid.*, 881 (1977).
(2) (a) J. W. Wilt and D. R. Sullivan, *J. Org. Chem.*, **40**, 1036 (1975); (b) H. Taniguchi, T. Ikeda, Y. Yoshida, and E. Imoto, *Chem. Lett.*, 1139 (1976).
(3) M. Franck-Neumann and M. Sedrati, *Angew. Chem., Int. Ed. Engl.*, **13**, 606 (1974).
(4) Pyrolysis of adduct **1**, or its photolysis in benzene at 366 nm, gave chloride **4** along with other compounds not fully characterized.
(5) In a Sustmann approach,[1] the frontier orbital energy levels of 7-chloronorbornadiene would be held constant. The variables would be the position of the frontier orbitals of diazomethane and diphenyldiazomethane relative to the diene. Unfortunately, the frontier orbital energies of diazomethane are only estimates as yet,[6] and those for diphenyldiazomethane appear to be unreported.
(6) K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, **95**, 7287 (1973).
(7) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **11**, 633 (1963); K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Am. Chem. Soc.*, **95**, 7301 (1973).
(8) This is the most convenient method if time is not critical. Reaction in benzene solvent at 50 °C over 5 days gave similar results, but more tar was formed.

Thiol Addition to Crotepoxide and Dideacetylcrotepoxide[1a,b]

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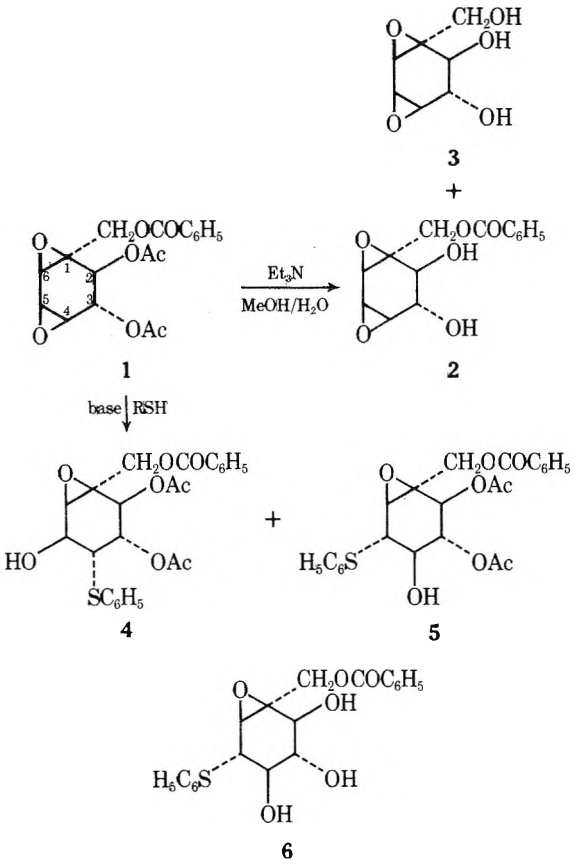
In the course of our continuing research on tumor inhibitory compounds from plant sources, we have observed a marked difference between the reactions of crotepoxide (**1**), a tumor-inhibitory cyclohexane diepoxide previously isolated from the dried fruits of *Croton macrostachys* Hochst ex A. Rich. (Euphorbiaceae),[2] and dideacetylcrotepoxide (**2**) toward thiophenol. Since a large number of the plant-derived tumor inhibitory drugs isolated in these laboratories show reactivity toward sulfhydryl-containing compounds[3–5] as a potential mode of biological action, we felt that crotepoxide (**1**) might also exhibit this reactivity.

Thiophenol reacted with **1** in methanolic solution containing 10% pyridine at 25 °C to yield the thioethers **4** and **5** in approximately equal amounts. Hydrolysis of **1** under mild conditions[6] (triethylamine–water–methanol, 1:1:8, 30 min, 25 °C) gave both dideacetylcrotepoxide (**2**) and debenzoyldideacetylcrotepoxide (**3**). The reaction of thiophenol with **2** was carried out under the same conditions employed for **1** and gave thioether **6** exclusively. Hydrolysis of either **4** or **5** using



the triethylamine–water–methanol (1:1:8) system also led exclusively to **6**.[7]

We suggest that a conformational difference between **1** and **2** would explain the differing reactivity of **1** and **2** toward thiophenoxide anion. In **1** the preferred conformation has the C-3 acetate in the equatorial position, thus allowing attack at both C-4 and C-5 and resulting in approximately equal amounts of both products. However, in **2** attack occurs exclusively at C-5. Consequently, the C-3 hydroxyl group appears to be axial and thus able to sterically hinder attack at C-4. An adverse steric interaction between diaxial C-3 and C-4 substituents is also suggested by the observation that hydrolysis of **4** leads exclusively to **6**.[8] The implication, therefore, is that hydrogen bonding between the C-2 hydroxyl group and the C-4,5 epoxide oxygen occurs in **2**, thus forcing the conformation in which the C-3 hydroxyl group is axial to be preferred and directing attack by thiophenoxide anion to C-5.

The reactivity toward thiophenol exhibited by **2** is analogous to that shown by other epoxide-containing antitumor agents[9] and may, in fact, mimic the biological mode of action.

Experimental Section

IR spectra were recorded on a Perkin-Elmer Model 257 grating infrared spectrophotometer. NMR spectra were done on a JEOL PS-100 p FT NMR spectrometer interfaced to a Texas Instruments JEOL 980A computer, with tetramethylsilane as an internal standard. UV spectra were determined on a Beckman DK-2A ratio recording spectrophotometer. Mass spectra were determined on a Hitachi Perkin-Elmer Model RMU-6E spectrometer. Optical rotations were taken on a Perkin-Elmer Model 141 automatic polarimeter. Melting points were determined on a Mettler FP2 hot stage instrument at a heating rate of 2 °C/min and are uncorrected. Microanalyses were carried out by either Spang Microanalytical Laboratory, Ann Arbor, Mich., or Micro-Tech Laboratories, Skokie, Ill. Thin-layer chromatography (TLC) was carried out on 20 × 20 cm × 0.25 mm E. Merck Silica Gel 60 F-254 plates (EM) or Mallinckrodt ChromAR 7GF plates (ChromAR); visualization was effected by either UV light, iodine spray, or cerium sulfate solution spray (0.125% cerium sulfate in 1:7 concentrated sulfuric acid–water) followed by heating.

Isolation of Crotepoxide (1). Crotepoxide (**1**) was obtained from roots, leaves, or dried fruits of *Croton macrostachys* in the manner previously reported.[5] Typically the plant material was placed in a Soxhlet extractor for 24 h with 95% ethanol. The concentrated material was partitioned between 90% aqueous methanol and petroleum ether (bp 60–68 °C). The methanol soluble material was further partitioned between 1-butanol and water. The 1-butanol layer was taken to dryness in vacuo and chromatographed on a large SilicAR CC-7 special (Mallinckrodt) column. The fractions eluting with 30% ether in carbon tetrachloride were retained for further chromatography. Extensive column chromatography of these fractions gave a highly enriched concentrate of **1** which crystallized from the concentrate upon addition of methanol. TLC of the mother liquors gave additional quantities of **1**. From 30 kg of plant material a yield of 2.462 g of pure, crystalline **1** (mp 147.6–148.6 °C; lit.[2] mp 150–151 °C) was obtained.

Reaction of Crotepoxide (1) with Thiophenol. To 100 mg of **1** (0.267 mmol) in 1 mL of 1:1 chloroform–methanol was added 0.1 mL of thiophenol (Aldrich, used without purification) and 0.1 mL of pyridine. The solution was stirred at 25 °C for 20 h and then subjected to PTLC on three EM plates developed with 8% methanol–chloroform. The band corresponding to unreacted **1** was crystallized from methanol to afford 47 mg of crotepoxide. A slightly lower R_f band was removed and subjected to PTLC on two ChromAR plates developed with 30% ethyl acetate–benzene. The band of highest R_f value was crystallized from carbon tetrachloride–hexane to afford 25 mg (36.2% based on recovered **1**) of **5**: mp 81.5–85 °C; $[\alpha]^{23}_D$ −78.0° (*c* 0.30, $CHCl_3$); UV (MeOH) λ_{max} (ϵ) 279 (1460), 251 (5040), 222 (18,800) nm; IR (KBr) 2.95, 5.79, 5.83, 7.03, 7.38, 8.08, 8.26, 9.07, 9.51, 9.89, 13.5, 14.3 μm; NMR ($CDCl_3$) δ 1.62 (1 H, s, OH), 2.06, 2.09, (6 H, 2s, $-OCOCH_3$), 3.43 (1 H, d, J = 9 Hz, 5-H), 3.60 (1 H, t, J = 9 Hz, 4-H), 3.64 (1 H, s, 6-H), 4.17, 4.48 (2 H, 2d, J = 12 Hz, 7-H), 5.15 (1 H, t, J = 9 Hz, 3-H), 5.54 (1 H, d, J = 8.5 Hz, 2-H), 7.26 (5 H, m, –SPh), 7.40, 7.45, 7.53, 7.62 (3 H, m, BX_2 portion of an A_2BX_2 system, *m*- and *p*-benzoate protons), 7.94, 7.95, 8.02 (2 H, m, A_2 portion of an A_2BX_2 system, o-benzoate protons); mass spectrum (*m/e*) 472 (M^+), 394, 352, 337, 295, 277, 235, 230, 217, 125, 110, 105, 77.

Anal. Calcd for $C_{24}H_{24}O_8S \cdot H_2O$: C, 58.77; H, 5.34; S, 6.54. Found: C, 58.82; H, 5.11; S, 6.63.

The thiophenol adduct to C-4 (**4**) was obtained from the band of lower R_f as an oil, 19 mg (27.5%): $[\alpha]^{27}_D$ −90° (*c* 0.01, MeOH); UV (MeOH) λ_{max} (ϵ) 254 (6815) nm; IR (KBr) 2.86, 3.28, 3.43, 5.70, 5.77, 6.22, 6.30, 6.76, 6.88, 6.95. 7.27, 7.58, 7.86, 8.10, 8.47, 8.98, 9.33, 9.74, 13.35, 13.95, 14.4 μm; mass spectrum M^+ at *m/e* 472.1198 (Calcd for $C_{24}H_{24}O_8S$: 472.1191), 352, 227, 295, 277, 235, 231, 230, 217, 110, 109, 105, 77, 69; NMR ($CDCl_3$) δ 1.26 (1 H, s, OH), 2.11, 2.14 (6 H, 2s, $-OCOCH_3$), 3.49 (1 H, d, J = 9.5 Hz, 4-H), 3.63 (1 H, s, 6-H), 3.80 (1 H, d, J = 9.5 Hz, 5-H), 4.15, 4.46 (2 H, 2d, J = 12 Hz, 7-H), 4.94 (1 H, t, J = 9.8 Hz, 3-H), 5.38 (1 H, d, J = 9 Hz, 2-H), 7.21–8.02 (10 H, m, aromatic protons).

Hydrolysis of Crotepoxide (1). To 675 mg (1.86 mmol) of **1** in 2 mL of chloroform was added 15 mL of (1:1:8) triethylamine–water–methanol. The solution was swirled and allowed to stand for 30 min. The volume was reduced in vacuo and the mixture was subjected to PTLC on four EM plates developed with 8% methanol–chloroform. Bands corresponding to **2** and **3** were removed and set aside; the band corresponding to unreacted **1** was recovered and resubjected to the above hydrolysis conditions, followed by TLC, etc. This process was continued until all but 9 mg of **1** had been hydrolyzed. The combined bands of **3** were eluted with chloroform–acetone, evaporated, and crystallized from methanol–ether giving debenzoyldideacetylcrotepoxide (**3**, 138 mg, 43.1%): mp 94.0–95.0 °C (lit.[2] mp 101–102 °C). The combined bands of **2** were eluted with acetone–chloroform, evaporated, and crystallized from methanol–methylene chloride giving dideacetylcrotepoxide (**2**, 104 mg, 20.3%): mp 136.0–137.0 °C; $[\alpha]^{24}_D$ +23.5 °C (*c* 0.034, MeOH); UV (MeOH) λ_{max} (ϵ) 281 (7950), 273 (985), 230 (13 850) nm; IR (KBr) 2.88, 3.11, 5.86, 6.93, 7.35, 7.49, 7.66, 7.80, 8.10, 8.16, 8.55, 8.88, 9.01, 9.22, 9.33, 9.40, 9.46, 10.2, 10.9, 11.7, 13.3, 14.3 μm; NMR (Me_2SO-d_6) δ 2.93 (1 H, br d, J = 4.5 Hz, 4-H), 3.42 (1 H, d, J = 4 Hz, 5-H), 3.64 (1 H, d, J = 2.5 Hz, 6-H), 3.86 (1 H, br d, J = 9 Hz, 3-H), 3.91 (1 H, d, J = 9 Hz, 2-H), 4.33, 4.61 (2 H, 2d, J = 12 Hz, 7-H), 5.4 (2 H, t, J = 6 Hz, OH), 7.47–8.03 (5 H, m, –OCOPh); mass spectrum *m/e* 279 $(M + 1)^+$, 218, 185, 167, 154, 149, 129, 109, 83, 82, 71, 70, 69.

Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.35; H, 5.09.

Reaction of Dideacetylcrotepoxide (2) with Thiophenol. To 65 mg (0.23 mmol) of **2** in 1 mL of 1:1 solution of methanol–chloroform was added 0.1 mL of thiophenol and 0.1 mL of pyridine. The mixture was flushed with nitrogen, stoppered, and stirred at 25 °C for 18 h.

The mixture was subjected to PTLC on two EM plates developed with 5% methanol–ethyl acetate. The band containing **6** was removed and again subjected to PTLC on four EM plates developed with 8% methanol–chloroform. Elution of the band corresponding to **2** afforded 12 mg of recovered **2**. The product band was removed and crystallized from acetone–benzene yielding 31 mg of **6** (41.9% based on recovered **2**). Recrystallization from acetone–carbon tetrachloride afforded a pure sample of **6**: mp 133.5–136.5 °C; $[\alpha]^{26}_{D}$ −133.7° (c 0.155, MeOH); UV (MeOH) λ_{max} (ϵ) 280 (1550), 270 (2600), 253 (5350), 223 (16,220) nm; IR (KBr) 2.97, 5.84, 6.95, 7.01, 7.68, 7.88, 8.99, 9.20, 9.38, 9.90, 10.3, 10.7, 11.5, 12.0, 13.4, 13.7, 14.3, 14.6 μm; NMR ($CDCl_3$) δ 1.60 (3 H, s, OH), 2.86 (1 H, br s, 4-H), 3.35 (1 H, d, J = 4 Hz, 5-H), 3.57 (1 H, s, 6-H), 3.65 (1 H, m, 3-H), 3.91 (1 H, d, J = 8.5 Hz, 2-H), 4.16, 4.87 (2 H, 2d, J = 12 Hz, 7-H), 7.26–8.07 (10 H, m, aromatic protons); mass spectrum M^+ at m/e 388.0985 (Calcd for $C_{20}H_{20}O_6S$: 388.0980), 357, 299, 284, 248, 230, 218, 217, 195, 178, 177, 165, 163, 152, 139, 135, 123, 122, 111, 110, 109, 106, 105, 77.

Hydrolysis of 4 or 5. The hydrolysis reaction of either **4** or **5** leads to the same product **6**. For simplicity, the description of the hydrolysis of **4** is given. To a 5-mL chloroform solution containing 27 mg of **4** was added 1 mL of a solution of triethylamine–water–methanol (1:1:8). The solution was allowed to stand for 5 min, the solvent was removed in vacuo, and the residue was subjected to PTLC on two EM plates developed with 8% methanol–chloroform. The band corresponding to **6** was removed and crystallized from acetone–hexanes to afford 15 mg of **6** (68.2%) which was identical by mixture TLC, mixture melting point, IR, and NMR with an authentic sample of **6**.

Anal. Calcd for $C_{20}H_{20}O_6S \cdot \frac{1}{2}H_2O$: C, 60.44; H, 5.32; S, 8.07. Found: C, 60.68; H, 5.10; S, 8.04.

Acknowledgments. We wish to thank Dr. Gary A. Howie of the University of Virginia for helpful discussions.

Registry No.—**1**, 20421-13-0; **2**, 64011-11-6; **3**, 20421-15-2; **4**, 64011-12-7; **5**, 64011-13-8; **6**, 64011-14-9; thiophenol, 108-98-5.

References and Notes

(1) (a) Tumor Inhibitors 127. For previous paper in the series, see S. M. Kupchan, K. L. Stevens, E. A. Rohlfing, B. R. Sickles, A. T. Sneden, R. W. Miller, and R. F. Bryan, *J. Org. Chem.*, submitted for publication. (b) This work was supported by grants from the National Cancer Institute (CA-11718) and the American Cancer Society (CH-42L) and a Postdoctoral Fellowship grant to W.L.S. from the National Cancer Institute, National Institutes of Health (CA-02888-02). (c) Deceased Oct 19, 1976.
(2) S. M. Kupchan, R. J. Hemingway, and R. M. Smith, *J. Org. Chem.*, **34**, 3898 (1969).
(3) S. M. Kupchan, *Fed. Proc.*, **33**, 2288 (1974), and references therein.
(4) R. L. Hanson, H. A. Lardy, and S. M. Kupchan, *Science*, **168**, 378 (1970).
(5) S. Remillard, L. I. Rebhun, G. A. Howie, and S. M. Kupchan, *Science*, **189**, 1002 (1975).
(6) S. M. Kupchan, S. P. Ericksen, and M. Friedman, *J. Am. Chem. Soc.*, **88**, 343 (1966); S. M. Kupchan, S. P. Ericksen, and Y.-T. S. Liang, *J. Am. Chem. Soc.*, **88**, 347 (1966).
(7) The structures of **4**, **5**, and **6** were assigned based on comparisons of the NMR signals of the C-4 and C-5 protons in each compound with the NMR data for the known monochlorohydrin and monoiodohydrin of crotepoxide given in ref 2.
(8) No product corresponding to addition at C-4 was obtained. As noted by a referee, it is possible that thiol addition occurs at both C-4 and C-5 and that rapid rearrangement then occurs to afford exclusively the C-5 addition product (**6**).
(9) S. M. Kupchan and R. M. Schubert, *Science*, **185**, 791 (1974).

Preparative Carbocation Chemistry. 13.[1] Preparation of Carbocations from Hydrocarbons via Hydrogen Abstraction with Nitrosonium Hexafluorophosphate and Sodium Nitrite–Trifluoromethanesulfonic Acid

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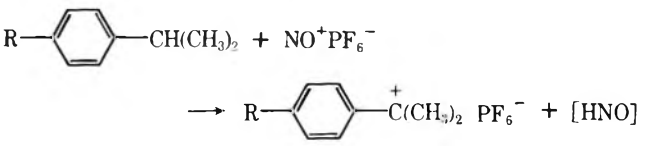
In 1966, we reported the observation that nitrosonium salts are capable of initiating the condensation reaction of cumene (cymene),[2] indicating that abstraction of a benzylic hydrogen occurs to generate the cumyl (cymyl) cation as an intermediate. The necessity of the presence of an activated, abstractable benzylic hydrogen was demonstrated in the observation that neither toluene nor *tert*-butylbenzene reacts with $NO^+PF_6^-$



under similar conditions.[2] Ring nitrosation of the alkylbenzenes was not observed. This is in accord with previous observations[3] that electrophilic aromatic nitrosation is successful only with highly activated systems such as phenol and *N,N*-dimethylaniline.

Various reactions involving NO^+ as a hydrogen-abstracting agent in the gas phase have been subsequently reported. Searles and Sieck[4] observed the reaction of normal, branched, and cyclic alkanes having three to six skeletal carbons with NO^+. Hunt and Ryan also noted that the nitrosonium ion can act as a hydrogen abstractor (or electrophile)[5] toward various organic substrates in the ion source of a mass spectrometer. Williamson and Beauchamp[6] studied the reaction of NO^+ with such simple organic molecules as acetaldehyde and isobutane by ion cyclotron resonance spectroscopy.

More recently, we have found that nitrosonium salts can also be used advantageously in synthetic reactions. Benzyl alcohols are oxidized to arylcarbonyl products and aliphatic or alicyclic secondary alcohols are converted into ketones in good yields via reaction of their trimethylsilyl or tributylstannyl derivatives with nitrosonium tetrafluoroborate.[7] Benzyl and benzhydryl esters are oxidatively cleaved to the parent carboxylic acids and benzaldehyde or benzophenone, respectively.[8] This latter reaction represents a mild procedure to deblock esters to the corresponding acids which is complementary to the existing reductive methods.[9] All these reactions include hydrogen abstraction as the initial step.

In continuation of our study of carbocation chemistry and broadening the scope of reactions initiated by nitrosonium and nitronium salts, we now wish to describe the preparation of stable carbocations by hydrogen abstraction from their hydrocarbon precursors with nitrosonium salts.

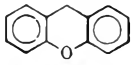
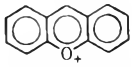
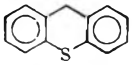
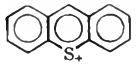
Results and Discussion

Representative hydrocarbons capable of forming stable carbocations upon hydrogen abstraction were reacted with nitrosonium hexafluorophosphate.

$$RH + NO^+PF_6^- \rightarrow R^+PF_6^- + [HNO]$$

The expected ions were cleanly formed. Nitrosonium hexafluorophosphate was used in the reactions because of its higher solubility in most of the suitable solvents than, for example, of the tetrafluoroborate salt. The reactions were carried out under a variety of conditions. Solvents used were sulfur dioxide, sulfuryl chlorofluoride, acetonitrile, and trifluoromethanesulfonic acid. Reaction of the precursor hydrocarbons with these solvents was not detectable by NMR spectroscopy within the durations normally required for their complete reaction with $NO^+PF_6^-$, although Nojima and Tokura[10] described the formation of cation radicals from electron-rich molecules in liquid sulfur dioxide. Kantner and Kreevoy[11] have, moreover, reported the disproportionation of the triphenylmethane in triflic acid. However, control experiments have indicated that such side reactions do not occur under our milder conditions, i.e., 0 °C, as neither the tri-

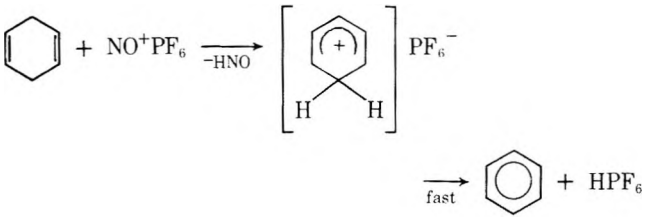
Table I. Hydrogen Abstraction from Hydrocarbons by Nitrosonium Ion

Hydrocarbon	Registry no.	Carbocation	Registry no.	% conversion[d] $NO^+PF_6^-$	% conversion[d] $NaNO_2$ + CF_3SO_3H
Ph_3CH	519-73-3	Ph_3C^+	13948-08-8	~100[a] ~100[b]	~100[a]
	544-25-2		26811-28-9	~100[a]	~100[a]
Ph_2CHCH_3	1612-00-0	$Ph_2C^+CH_3$	16805-85-9	88[c]	
Ph_2CH_2	101-85-5	Ph_2CH^+	709-82-0	71[c]	
$PhCH(CH_3)_2$	78-82-8	$PhC^+(CH_3)_2$	16804-70-9	83[c]	
	92-83-1		261-23-4	~100[a]	~100[a]
	261-31-4		261-32-5	~100[a]	~100[a]

[a] Based on ^1H NMR analysis of formed carbocation. [b] Yield of product isolated after recrystallization from CH_2Cl_2. [c] Based on GLC analysis of corresponding alcohol obtained after quenching the carbocation solution with H_2 (see Experimental Section). [d] Registry no.: $NO^+PF_6^-$, 16921-91-8; $NaNO_2$, 7632-00-0; CF_3SO_3H, 1493-13-6.

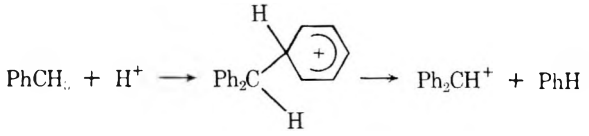
phenylmethyl nor diphenylmethyl cation was observed (by NMR) in these solutions. The products were identical to those previously reported.[12] Quenching with water or methanol yielded the expected alcohols or methyl ethers, respectively. These results are summarized in Table I.

When 1,4-cyclohexadiene is reacted with $NO^+PF_6^-$ in SO_2ClF at −78 °C,[13] the quantitative formation of benzene is observed. This observation, in view of the known instability of the parent benzenium ion, suggests the pathway shown below. This ionization–deprotonation route is reminiscent of

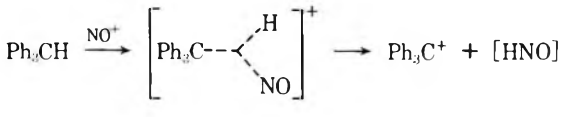


the cumene-α-methylstyrene transformation[2] and the dehydrogenation of 9,10-dihydroanthracene.[14]

The formation of the triphenylmethyl cation from the reaction of triphenylmethane with nitrosonium ion is of particular interest. The related ionization of triphenylmethane



with superacids leads to protolysis via C–C bond cleavage giving benzene and the diphenylmethyl cation.[11,15] In this case, the reaction most probably takes place by way of protonation of the aromatic ring, with the proton eventually shifting to the ipso carbon, followed by cleavage of the diphenylmethyl cation. On the other hand, electrophilic aromatic nitration occurs exclusively when triphenylmethane is reacted with nitronium salts.[16] The reversible nature of aromatic ring nitrosation, however, seems to allow the NO^+ ion



to migrate toward the exocyclic carbon and to insert into the tertiary C–H bond to form the two-electron three-center-bonded carbonium ion which subsequently cleaves to the triphenylmethyl cation.

The evolution of brown fumes of nitrogen dioxide has been repeatedly observed during reactions which were exposed to air. This implies that nitric oxide was formed and oxidized. Since the carbocation products are derived from their precursor hydrocarbons via hydrogen abstraction by NO^+, the required cleavage product is HNO. Harteck[17] has shown that HNO readily dimerizes to dihydroxydiazene, which decomposes into water and nitrous oxide. In order to demonstrate that hydrogen is indeed removed by NO^+ in the reactions to generate HNO, the gaseous product(s) of an anaerobic reaction was collected and analyzed by GC–MS. An identical GC retention time with that of an authentic sample, in addition to a strong *m/e* 44 peak in the mass spectrum, conclusively established N_2O as the major gaseous product.

$$2HNO \rightleftharpoons HON{=}NOH \rightarrow H_2O + N_2O$$

Having found a suitable new way to generate stable carbocations from hydrocarbons with nitrosonium salts, we further studied the simplification of this method by an in situ generation of NO^+. Nitrosonium triflate is readily produced according to the following equation:

$$3CF_3SO_3H + NaNO_2 \rightarrow NO^+CF_3SO_3^- + H_3O^+CF_3SO_3^-$$

The $NaNO_2$–CF_3SO_3H system was found to be particularly efficient in effecting hydrogen abstraction from hydrocarbons. Facile, quantitative reaction took place with the corresponding hydrogen donors, as exemplified by the rapid generation of the triphenylmethyl, cycloheptatrienyl, xanthyl, and thioxanthyl cations.

In conclusion, we have developed a novel procedure for preparing stable carbocations from hydrocarbons via hydrogen abstraction by nitrosonium salts. In our opinion, this method is superior to that employing the triphenylmethyl cation as the hydrogen-abstracting agent, because (1) the nitrosonium ion is more effective and of more general utility as demonstrated, for example, in its ability to generate the triphenylmethyl cation from triphenylmethane, and (2) no organic by-products are formed, a distinct advantage in terms of preparative and spectroscopic convenience. The preparation of carbocations from hydrocarbons via hydrogen abstraction with either NO^+ or $(C_6H_5)_3C^+$ salts is, however, by

necessity limited to systems which give sufficiently stabilized carbocationic products.

Experimental Section

All hydrocarbon precursors used were either commercially available or synthesized by known procedures. Nitrosonium hexafluorophosphate (Cationics, Inc.) and trifluoromethanesulfonic acid (3M Company) were used without further purification.

The ^1H NMR spectra were recorded on a Varian Associates A56/60A spectrometer and the ^{13}C NMR spectra were obtained on a Varian Associates XL-100 spectrometer operating in a pulsed FT mode. Chemical shifts were measured from an external (capillary) Me_4Si signal. Gas chromatographic analyses of the quenched products were obtained on a Hewlett-Packard 5700A gas chromatograph with a 2 ft × 1/8 in. SE-30 column eluted with helium at 250 °C.[18a] GC–MS were obtained on a DuPont 21-094 mass spectrometer coupled to a Varian Associates Aerograph 2700 gas chromatograph using a 10 ft × 1/8 in. Porapak Q column eluted with helium.

Hydrogen Abstraction from Hydrocarbons with Nitrosonium Hexafluorophosphate. To a solution of $NO^+PF_6^-$ (1.40 g, 8 mmol) in ca. 5 mL of liquid sulfur dioxide at −78 °C was slowly added an appropriate hydrocarbon (4 mmol). The reaction vessel was sealed and kept at room temperature for 3 h. Thereafter the solution was cooled to −20 °C, the vessel was opened, and aliquots were analyzed, upon transfer to NMR tubes by spectral analysis and, after hydrolysis, by GLC by comparison with known amounts of standard pure alcohols.

Triphenylmethyl (mp ~146 °C dec)[18b] and cycloheptatrienyl hexafluorophosphate (mp 210–215 °C dec) were isolated in quantitative yield upon recrystallization of the residue, obtained from the evaporation of the volatile components of the reaction mixture, from CH_2Cl_2.

Hydrogen Abstraction from Hydrocarbons by Nascent Nitrosonium Ion. To ice-cooled trifluoromethanesulfonic acid (6.75 g, 45 mmol) was added sodium nitrite (1.05 g, 15 mmol), followed by the hydrocarbon precursor (5 mmol) while the mixture was stirred with a Fisher Vortex stirrer. After 10 min, an aliquot was taken to record the NMR spectra. Complete consumption of the starting material was observed and the spectra observed were those of the carbocationic species.

Acknowledgment. Support of our work by the National Institutes of Health and the National Science Foundation is gratefully acknowledged.

Registry No.—Cycloheptatrienyl hexafluorophosphate, 29663-54-5; nitrosonium triflate, 51637-52-6.

References and Notes

(1) Part 12. G. A. Olah and T.-L. Ho, *Synthesis*, 798 (1976).
(2) G. A. Olah and N. Friedman, *J. Am. Chem. Soc.*, **88**, 5330 (1966).
(3) Z. J. Allan, J. Podstata, D. Snobl, and J. Jarkovsky, *Tetrahedron Lett.*, 3565 (1965).
(4) S. K. Searles and L. W. Sieck, *J. Chem. Phys.*, **53**, 794 (1970).
(5) D. F. Hunt and J. F. Ryan, *J. Chem. Soc., Chem. Commun.*, 620 (1972).
(6) A. D. Williamson and J. L. Beauchamp, *J. Am. Chem. Soc.*, 97, 5714 (1975).
(7) G. A. Olah and T.-L. Ho, *Synthesis*, 609 (1976).
(8) T.-L. Ho and G. A. Olah, *Synthesis* (in press).
(9) J. W. F. McOmie, Ed., "Protective Groups in Organic Chemistry", Plenum Press, London and New York, 1973.
(10) T. Ando, M. Nojima, and N. Tokura, *J. Chem. Soc., Chem. Commun.*, 989 (1975); M. Nojima, G. Nagao, N. Kakeya, M. Takagi, and N. Tokura, *ibid.*, 486 (1976).
(11) S. S. Kantner and M. M. Kreevoy, *J. Org. Chem.*, **42**, 865 (1977).
(12) (a) G. A. Olah and P. Westerman, *J. Am. Chem. Soc.*, **95**, 7530 (1973); (b) T. E. Young and C. J. Ohnmacht, *J. Org. Chem.*, **32**, 1558 (1967); (c) P. M. Bower, A. Ledwith, and D. C. Sherrington, *J. Chem. Soc. B*, 1511 (1971); (d) H. Spiesecke and W. G. Schneider, *Tetrahedron Lett.*, 468 (1961).
(13) Experiments were carried out by Dr. G. Asensio.
(14) W. Bonthrone and D. H. Reid, *J. Chem. Soc.*, 2773 (1959).
(15) (a) G. A. Olah, R. H. Schlosberg, R. D. Porter, Y. K. Mo, D. P. Kelly, and G. D. Mateescu, *J. Am. Chem. Soc.*, **94**, 2038 (1972); (b) M. Kreevoy, personal communication, on similar cleavage with trifluoromethanesulfonic acid.
(16) G. A. Olah and H. C. Lin, unpublished results.
(17) P. Harteck, *Ber.*, **66**, 423 (1933).
(18) (a) The yields and purities of the products in these reactions were conveniently determined upon comparison of the GC areas of the products obtained with those produced by standardized amounts of the compounds under identical instrument conditions; (b) G. A. Olah, J. J. Svoboda, and J. A. Olah, *Synthesis*, 544 (1972).
(19) J. J. K. Boulton and L. P. Ellinger, British Patent 1 134 736 (1968); *Chem. Abstr.*, **70**, 29545n (1969).

Carbon Monoxide–Hydrogen–Water: Reduction of Benzophenone, Diphenylcarbinol, and Diphenylmethane

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Introduction

A mixture of carbon monoxide and water is regarded to be superior to hydrogen as a reducing agent for the liquefaction of lignite.[1-5] How carbon monoxide functions in the lignite reduction is still largely a matter of speculation. Since a mixture of carbon monoxide and hydrogen can be made from lignite and its inherent water by the water gas reaction, the commercial utilization of carbon monoxide or a mixture of carbon monoxide and hydrogen as a reducing agent is promising. Sodium carbonate, ferrous sulfide, and the mineral matter in lignite are reported to be catalysts for liquefaction. Appell et al.[4] have proposed that sodium carbonate reacts with the water to form a basic medium, and the base interacts with carbon monoxide to give the formate ion. The formate ion is a reducing agent which augments the reducing power of the hydrogen present, particularly for carbonyl compounds. Appell et al.[4] has suggested that hydrogen more so than carbon monoxide favors the cracking of carbon chains.[4]

A study of the carbon monoxide reduction mechanism is of direct value for developing improved catalysts for the liquefaction process, as well as for reduction of other organic compounds. This study relates data on the reduction of model compounds which best represent critical chemical linkages in lignite. The three title compounds contain one-carbon linkages between aromatic rings. A comparison has been made with hydrogen, hydrogen–carbon monoxide–water, and carbon monoxide–water as reducing gases, sodium carbonate, sodium formate, sodium hydroxide, and iron oxide as possible catalysts, and tetralin as a hydrogen donor solvent.

Results and Discussion

The reduction products of benzophenone are diphenylcarbinol, diphenylmethane, benzene, and toluene. Diphenylcarbinol, under the same conditions, gives diphenylmethane, benzophenone, benzene, and toluene. Diphenylmethane is only converted in low yield, i.e., 1–3%, to benzene and toluene by even the most rigorous of conditions.

The order of conversion effectiveness of the reducing gases in the presence of sodium carbonate for the benzophenone reduction is hydrogen < carbon monoxide–water < carbon monoxide–water–hydrogen (Table I). For diphenylcarbinol, the order is hydrogen < carbon monoxide–water ≃ carbon monoxide–water–hydrogen (Table II). The hydrogen donor solvent tetralin has no influence on the conversion yields for the carbon monoxide–water–hydrogen reduction (runs 6 and 9, Table I), the carbon monoxide–water reduction (runs 2 and 8, Table I), and the hydrogen reduction (runs 5 and 10, Table I). However, tetralin did influence the product distribution by causing more diphenylmethane to be formed at the expense of diphenycarbinol (runs 2 vs. 8 and 5 vs. 10, Table I), though this is not consistent (run 6 vs. 9, Table I).

The reduction of diphenylcarbinol gives disproportionation in addition to reduction. Diphenylcarbinol, in the absence of reducing gases under the reaction conditions, gives a 1:1 molar ratio of benzophenone to diphenylmethane, cf. run 1, Table II. Sodium carbonate is not necessary for the disproportionation, cf. runs 1 and 2, Table II.

Table I. Reduction of Benzophenone[a]

Run	Temp, °C	Reducing agent[b]	Solvent[c]	Catalyst[d]	% $C_{10}H_{16}$	% $C_{10}H_{12}$	% Ph_2CHOH[e]	% Ph_2CH_2[e]	% PhH[e]	% $PhCH_3$[e]	% conversion[f]
1	400	CO, H_2O	None	Na_2CO_3			32.1	6.4	0.5		38.9
2	425	CO, H_2O	None	Na_2CO_3			22.4	19.2	0.7	0.03	42.3
3	450	CO, H_2O	None	Na_2CO_3			6.3	42.3	4.6	0.8	54.0
4	475	CO, H_2O	None	Na_2CO_3			3.9	45.0	19.3	1.8	60
5	425	H_2, H_2O	None	Na_2CO_3			25.4	6.2	1.2	0.03	32.8
6	425	CO, H_2, H_2O	None	Na_2CO_3			9.5	47.0	2.5	0.6	59.6
7	425	CO, H_2,[g] H_2O	None	Na_2CO_3			2.9	52.4	1.1	0.3	51.6
8	425	CO, H_2O	$C_{10}H_{16}$	Na_2CO_3	93.6	6.4	3.7	33.6	0.8	0.3	38.4
9	425	CO, H_2, H_2O	$C_{10}H_{16}$	Na_2CO_3	92.9	7.1	13.5	42.2	4.4	0.6	58.7
10	425	H_2, H_2O	$C_{10}H_{16}$	Na_2CO_3	95.2	4.8	21.1	11.8	1.7	Tr	35.0
11	425	CO, H_2O	None	None			0.0	6.8	0.2	0.3	7.2
12	425	CO, H_2O	None	NaOH			6.5	32.8	0.8	0.2	40.1
13	425	CO, H_2O	None	$NaCHO_2$			12.9	31.6	1.3	0.3	45.9
14	425	CO, H_2O	None	Fe_3O_4			Tr	31.9	0.9	0.3	33.0

[a] 0.15 mol, all results are duplicated. [b] Each gas at partial pressure of 750 psi and argon is added to bring the initial pressure to 1500 psi if necessary. [c] 0.015 mol of tetralin when used and 0.6 mol of water. [d] 0.015 mol. [e] Product mole percent yields normalized to converted benzophenone. [f] Based on recovered benzophenone. [g] 375 psi of CO and 375 psi of H_2.

Table II. Reduction of Diphenylcarbinol[a]

Run	Reducing agent[b]	Catalyst[c]	% Ph_2CO[d]	% Ph_2CH_2[d]	% PhH[d]	% $PhCH_3$[d]	% conversion[e]
1	H_2O	None	48.4	50.5	0.8	0.3	100.0
2	H_2O	Na_2CO_3	47.1	33.5	1.0	0.2	81.8
3	CO, H_2O	None	26.4	72.7	0.6	0.3	100.0
4	CO, H_2, H_2O	None	14.6	82.9	1.5	1.0	100.0
5	CO, H_2O	Na_2CO_3	12.8	83.1	1.9	1.3	99.1
6	H_2, H_2O	Na_2CO_3	11.6	76.0	1.3	0.4	89.3
7	CO, H_2, H_2O	Na_2CO_3	8.2	88.2	1.5	0.9	98.8
8	CO, H_2, H_2O	Fe_3O_4	0.0	94.4	2.7	2.8	100.0

[a] 0.15 mol, all results are duplicated and obtained at 425 °C. [b] The reducing gases used singly were at 750 psi initial pressure and when both were present each was at 375 psi. Argon is added to make the total initial pressure 1500 psi. [c] 0.015 mol. [d] Product mole percent yields normalized to converted diphenylcarbinol. [e] Based on recovered diphenylcarbinol.

The direct reduction of diphenylcarbinol to diphenylmethane is occurring in addition to the indirect route via benzophenone, since the presence of reducing gases does enhance the conversion, cf. run 2 vs. 5, 6, and 7, Table II. Further evidence that diphenylcarbinol is the precursor of diphenylmethane is that as the reaction temperature is lowered, the percentage of diphenylmethane decreases, and the amount of diphenylcarbinol increases, cf. runs 1–4, Table I.

Sodium formate and sodium hydroxide are equal to sodium carbonate in effectiveness for the carbon monoxide–water conversion of benzophenone, cf. runs 12 and 13 with run 2, Table I. This is evidence for the mechanistic sequence postulated by Appell et al. A new feature which does not fit this mechanistic scheme is that iron oxide, which is not basic, also catalyzes the conversion of benzophenone; cf. run 14, Table I. This perhaps catalyzes the reference production of hydrogen via the shift reaction.

Though benzene and toluene are formed from the reduction of diphenylmethane, the benzophenone reduction must also directly yield benzene in order to account for the abnormally high benzene–toluene ratio among the products, i.e., 1–23. Diphenylmethane reduces to give equimolar amounts of benzene and toluene. Therefore a second benzene formation reaction and/or a toluene destruction reaction must be operating. Both ethylbenzene and diphenylmethane are very slowly converted under the reaction conditions, i.e., in 1–3% yields for both; hence, toluene could not be expected to be a significant source of benzene.

The two likely precursors of the excess benzene are benzophenone and diphenylcarbinol. If diphenylcarbinol were the precursor to the extra benzene produced in the benzophenone reduction, the diphenylcarbinol reduction should produce a benzene–toluene ratio equal to or greater than that from benzophenone. However, it gives an intermediate value with an average ratio of 2.3 (Table II) vs. that of benzophenone at 9.1 (Table I). Therefore, the source of the extra benzene must be benzophenone, and most probably the benzene originates via the reaction sequence 1 → 2 → 3.

$$Ph_2CO \xrightarrow{\Delta} PhCO\cdot + Ph\cdot \quad (1)$$

$$PhCO\cdot \rightarrow Ph\cdot + CO \quad (2)$$

$$Ph\cdot + sh\ )solvent) \rightarrow PhH + S\cdot \quad (3)$$

By way of analogy, aliphatic aldehydes are known to decarbonylate with di-*tert*-butyl peroxide or other peroxides.[7,8] Aromatic aldehydes can also be decarbonylated using catalysts such as palladium or chlorotris(triphenylphosphine)rhodium.[9-11] Therefore, the decarbonylation of the benzoyl radicals at the temperatures of these reductions is not unreasonable.

Experimental Section

Batch Autoclave Reductions. All the reductions were done until duplicated results were obtained in two 250-mL Hastelloy alloy "C" batch autoclaves (Autoclave Engineers, Inc.) with a heater designed to accommodate both autoclaves and the mixing of contents achieved by rocking of the autoclaves. This procedure allowed two runs to be done simultaneously. The conditions of each run were varied, but each autoclave contained, when specified, a catalyst, solvent, water, and reducing gases. The time of each run was 2 h, which does not include heat-up and cool-down times.

After the autoclaves were cooled and decompressed, the organic and water layers were separated. The organic layers were filtered

through sintered glass funnels and analyzed by gas chromatography.

The gas chromatograph used in this study was a Varian Aerograph 90-P. The column used was ¼ in. × 8 ft 5% Carbowax 20M with Chromosorb G was column support and the column temperatures were 60–80 °C and 180–200 °C. The internal standard selected was 1-bromonaphthalene. In each run the results were normalized to the conversion percentage. Then the average of the duplicated results were entered into the tables. The precision in the yields is ±6%.

Preparation of Iron Oxide.[12] Ferrous sulfate (115 g) was dissolved in 1 L of water by heating and adding a small amount of concentrated sulfuric acid (~10 mL). Aqueous ammonium sulfide (22.3%, J. T. Baker, Phillipsburg, N.J.) was added until the precipitation was complete and then an additional 5 mL was added. Ammonium hydroxide was added until the acidity was gone, and the mixture was filtered and washed with water until a negative sulfate ion test was achieved ($BaCl_2$). The solid was air-dried and calcined at 500 °C for 3 h to a dark red solid powder which does not produce hydrogen sulfide on exposure to dilute sulfuric acid. Because the product is magnetic, it is probably Fe_3O_4.

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Registry No.—Benzophenone, 119-61-9; diphenylcarbinol, 91-01-0; diphenylmethane, 101-81-5; carbon monoxide, 630-08-0; hydrogen, 1333-74-0; water, 7732-18-5.

References and Notes

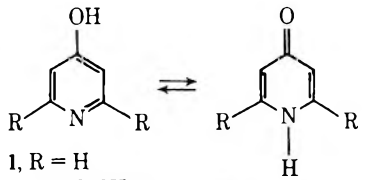
(1) H. R. Appell and I. Wender, *Am. Chem. Soc., Div. Fuel Chem., Prepr.*, **12**, No. 3, 220–222 (1968).
(2) H. R. Appell, I. Wender, and R. D. Miller, *Am. Chem. Soc., Div. Fuel Chem. Prepr.*, **13**, No. 4, 39–44 (1969).
(3) H. R. Appell, I. Wender, and R. D. Miller, *Chem. Ind. (London)*, 1703 (1969).
(4) H. R. Appell, private communication.
(5) R. J. Baltisberger, N. F. Woolsey, K. J. Kabunde, and V. I. Stenberg, Abstracts, 2nd Joint Conference, Chemical Institute of Canada-American Chemical Society, Montreal, Canada, May–June, 1977, COLL 18.
(6) M. I. Temkin, *Teor. Osn. Khim. Tekhnol.*, **9**, 387 (1975).
(7) L. H. Slaugh, *J. Am. Chem. Soc.*, **81**, 2262 (1959).
(8) J. D. Berman, J. H. Stanley, W. V. Sherman, and S. G. Cohen, *J. Am. Chem. Soc.*, **85**, 4010 (1963).
(9) J. Tsuji and K. Ohno, *Tetrahedron Lett.*, 3969 (1965).
(10) J. Tsuji, K. Ohno, and T. Kajimoto, *Tetrahedron Lett.*, 4565 (1965).
(11) J. Blum, *Tetrahedron Lett.*, 1605 (1966).
(12) H. N. Stokes, *J. Am. Chem. Soc.*, **29**, 304 1907.

Communications

Self-Association and the Protomeric Equilibria of 4-Hydroxypyridine–4-Pyridone and Related Compounds

Summary: Extensive self-association of 4-pyridone is reported and suggested to shift the apparent position of the protomeric equilibrium between 4-pyridone and 4-hydroxypyridine in favor of the former in chloroform and cyclohexane. Self-association of 4-pyridones is shown to be suppressed by 2,6-substitution of the ring.

Sir: We have estimated the protomeric equilibrium constant for 4-hydroxypyridine (**1**)–4-pyridone (**2**) to be ca. 10^{-5} (K_T = [NH]/[OH] = **2**/**1**) in the gas phase.[1,2] While it might be expected that **1** would also be the only detectable protomer in nonpolar weakly hydrogen bonding solvents,[3] a K_T of $10^{0.11}$ has been reported recently for this system in chloroform and a K_T of 10^{-1} may be estimated for cyclohexane.[4] Because of a continuing interest in this area we have reinvestigated that work. We wish to report that the apparent equilibrium between **1** and **2** in chloroform and cyclohexane, in fact, is dominated by the extensive oligomerization of **2** and that this self-association can be suppressed in derivatives of 4-pyridones by appropriate substitution of the 4-pyridone ring.



1, R = H
3, R = $C(CH_3)_3$
2, R = H
4, R = $C(CH_3)_3$

Multiwavelength analysis of the ultraviolet spectrum of **1**–**2** in cyclohexane and chloroform at 10^{-7} and 10^{-5} M, respectively, shows an absorption attributable to the chromophore of **2** to be the only detectable species. If that result is expressed in terms of K_T for **1**–**2** a value >10 in favor of **2** is obtained. Such an equilibrium would be even further from the expected predominance of **1** than suggested by the recent work from East Anglia.[3,4]

Vapor-pressure osmometry of solutions of 4-pyridone in chloroform establishes that **2** is very strongly associated by hydrogen bonding. We find, for example, the modal association number of 4-pyridone at 0.049 M in chloroform to be 9. In fact, some years ago Coburn and Dudek suggested that 4-pyridone was a hydrogen-bonded trimer at ca. 10^{-3} M in chloroform.[5,6] If the association of 4-pyridone is analyzed as a statistical distribution of oligomers, an association free energy of −6.1 kcal/mol, an association constant of 30 000 ± 700, and the distribution of oligomers shown in Figure 1 may be derived from studies of molecular weight as a function of dilution. For this model <30% of the material would be monomeric under the conditions of the ultraviolet determination. Direct determination of the association in cyclohexane was precluded by limited solubility.

The 6.1 kcal/mol self-association energy of **2** in chloroform is clearly more than sufficient to dominate the position of protomeric equilibrium for **1**–**2** under the conditions reported. In fact this energy of hydrogen bonding is 1.5 kcal/mol stronger than for the dimerization of 2-pyridone in chloroform. The apparent position of protomeric equilibrium between 2-pyridone and 2-hydroxypyridine also has been shown to be determined by self-association in chloroform and cyclohexane under most conditions of measurement.[5–9] It is noteworthy that the association of 2-pyridone in cyclohexane is several kilocalories per mole stronger than in chloroform, a result which is taken to suggest that the apparent equilibrium for **1**–**2** is also dominated by association in cyclohexane.

These results again show the importance of correctly assessing the effect of molecular environment and association effects on molecular energies of protomeric systems.[1,2,7] Interpretation of equilibria determined on associated material

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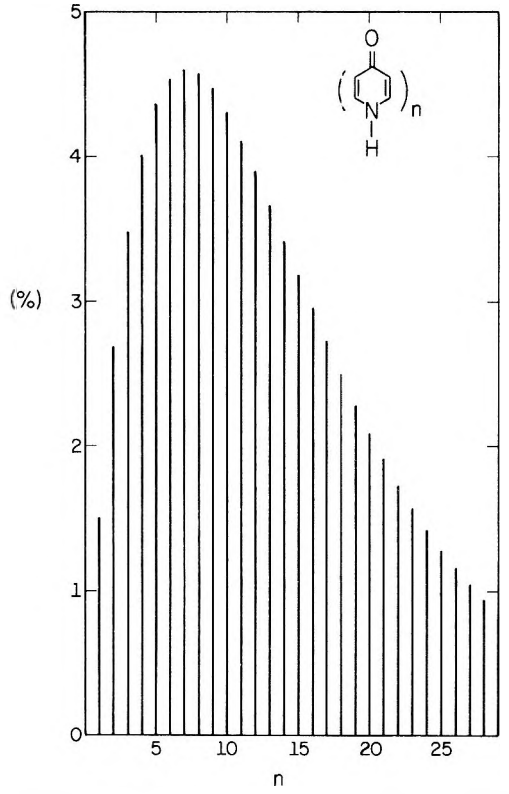

Figure 1. Composition of oligomers to $n = 29$ for 0.025 M 4-pyridone in chloroform.

in terms of the relative energies of the monomers would be erroneous and the significance of the suggested correlation of the overall equilibrium constants of 2-pyridone and 4-pyridone with solvent Z values is open to question.[4,10] It is essential that the nature of the species being compared be known if fundamental understanding of medium effects on protomeric equilibria is to be achieved.

While the complication of association may be removed, in principle, by operating at very low concentrations, for some solvents the necessary dilutions may provide solutions in which the chromophore of interest is beyond the present limits of detection. Another approach is suggested by the studies of 2,6-di-*tert*-butyl-4-hydroxypyridine (**3**)–2,6-di-*tert*-butyl-4-pyridone (**4**) and 3-decyl-2,8-dimethyl-4-hydroxyquinoline (**5**)–3-decyl-2,8-dimethyl-4-quinolone (**6**), compounds which

5 **6**

were chosen by Frank and Katritzky for their favorable solubility.[4] The structures of **3–4** and **5–6** might be expected to offer substantial hindrance to association by hydrogen bonding.[11] In fact, both **3–4** and **5–6** are shown by vapor-pressure osmometry to be essentially monomeric in chloroform at the concentrations used to measure their ultraviolet spectra. The possible association of these compounds in less polar solvents, their position of equilibrium in the vapor, and the effect of substitution on the position of equilibria need to be determined. Compounds which are designed and shown to be monomeric under the conditions of measurement should be useful in providing information about the effect of molecular environment on tautomeric equilibria.

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References and Notes

(1) P. Beak, F. S. Fry, J. Lee, and F. Steele, *J. Am. Chem. Soc.*, **98**, 171 (1976).
(2) P. Beak, *Acc. Chem. Res.*, **10**, 186 (1977).
(3) If the effect of non-hydrogen-bonding solvents on the position of equilibrium is, as a first approximation, attributed to differential stabilization of the dipoles of **1** and **2** by a dielectric effect, the equilibrium for **1–2** in solvents of low dielectric should still highly favor **1**. For example, on the basis of the Onsager equation with 4-methoxypyridine and 1-methyl-4-pyridone as models the equilibrium constant for **1–2** may be predicted to change from 10^{-5} in the vapor to $10^{-3.5}$ in cyclohexane and to $10^{-1.5}$ in chloroform. Such an application of the Onsager equation has been noted to provide a useful approximation of solvent effects on the protomeric equilibria of some 2-pyridones.[1,2] However, the limitations of this approach must be noted and our recent work suggests solvent hydrogen-bonding effects become significant in many cases: P. Beak and J. Covington, unpublished results.
(4) J. Frank and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 2*, 1428 (1976). The K_T in chloroform was determined by Frank and Katritzky by a single wavelength determination of the equilibrium constant. The K_T in cyclohexane is obtained by extrapolation of the linear correlation of log K_T and solvent Z values drawn by Frank and Katritzky.
(5) R. A. Coburn and G. O. Dudek, *J. Phys. Chem.*, **72**, 3681 (1968). These workers suggested the association of 4-pyridone was greater than that of 2-pyridone.
(6) The self-association of amides by hydrogen bonding is well known: R. B. Homer and C. D. Johnson, "The Chemistry of Amides", T. Zabicky, Ed., Interscience, New York, N.Y., 1970, pp 223–227; M. D. Joesten and L. J. Schaad, "Hydrogen Bonding", Marcel Dekker, New York, N.Y., 1973, pp 280–282.
(7) P. Beak, J. B. Covington, and S. G. Smith, *J. Am. Chem. Soc.*, **98**, 8284 (1976).
(8) The association of 4-pyridone is quite strong and persists in ethanol. Comparison of the association with that of 2-pyridone using the statistical distribution model of Figure 1 shows the free energies of hydrogen bonding in ethanol are: 4-pyridone, −2.6 kcal/mol; 2-pyridone, −1.95 kcal/mol.
(9) It is possible that the equilibrium constant for association of monomers is different from that for addition to the polymer chain. If previous work on amide association is a useful guide the dimer association constant would be less than the subsequent oligomer association constant and the amount of monomer present would be then less than the above estimate: L. L. Graham and C. Y. Chang, *J. Phys. Chem.*, **25**, 776, 784 (1977); M. Davies and D. K. Thomas, *ibid.*, **60**, 763, 767 (1956).
(10) We find that 4-pyridone is monomeric in acetonitrile, the other solvent in which the equilibrium constant for **1–2** was determined for the proposed correlation.[4]
(11) In private discussions with Professor A. R. Katritzky regarding possible problems of association of 2- and 4-pyridones which began in April, 1976, he also noted the possibility that **3–4** and **5–6** would be less associated than the parent materials. The correlations of the equilibrium constants of these substituted systems with Z values may be accorded more significance than those of the parent system.

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New Synthetic Methods for the Regioselective Annelation of Aromatic Rings: 1-Hydroxy-2,3-disubstituted Naphthalenes and 1,4-Dihydroxy-2,3-disubstituted Naphthalenes

Summary: Respective condensation of the anion of ethyl 2-carboxybenzyl phenyl sulfoxide and 1*H*-2-benzofuran-1-one 3-(phenyl sulfone) with α,β-unsaturated esters and ketones results in regioselective formation of 1-hydroxy-2,3-disubstituted naphthalenes in moderate yield and 1,4-dihydroxy-2,3-disubstituted naphthalenes in good yield.

Sir: Extension of our recently reported strategy for the construction of linear polynuclear aromatic systems[1,2] has resulted in the development of two new methods for the regioselective annelation of aromatic rings. Each route can be incorporated into the original strategy with the notable advantage that abbreviated syntheses of naphthalenes with a

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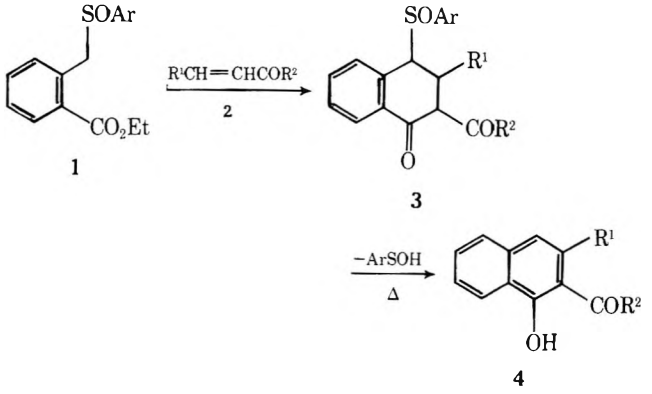
Table I. Regiospecifically Prepared 1-Hydroxy-2,3-disubstituted Naphthalenes (4) Prepared from Sulfoxide 1 and Various Michael Acceptors 2

R_1	R_2	% yield	Mp, °C
H	OEt	28	48–49 (lit.[8] 49)
H	CH_3	37	100–101 (lit.[9] 101)
CH_3	OEt	44	58–59 (lit.[10] 56–59)
CH_3	CH_3	70	93–93.5
CH_2SCH_3	OEt	64	59–60
$-(CH_2)_3-$		0	

Scheme I



broader diversity of functionalities[3] is facilitated. In both cases regiochemical control over the product is vested in the precursors.

Scheme I shows the route devised for the preparation of 1-hydroxy-2,3-disubstituted naphthalenes (**4**). Ethyl 2-carboxybenzyl phenyl sulfoxide (**1**)[4,6] was converted to an anion using lithium diisopropylamide (LDA) in tetrahydrofuran at −78 °C, then allowed to react with various Michael acceptors **2**. The initially formed conjugate addition product underwent intramolecular condensation to yield tetralone **3**.[7] Aromatization of tetralone **3** to 1-hydroxy-2,3-disubstituted naphthalene **4** by thermal elimination of phenylsulfenic acid was accomplished by heating the reaction mixture under reflux for 2 h. In this scheme, the sulfoxide group serves two purposes: initially, it provides essential stabilization for the carbanion generated on the benzyl carbon,[11] and later, it becomes a leaving group allowing aromatization of the newly formed ring. Table I lists 1-hydroxynaphthalenes **4** prepared by this procedure.

Modification of the previous approach accomplished the regioselective preparation of 1,4-dihydroxy-2,3-disubstituted naphthalenes (**7**) (Scheme II). The 1*H*-2-benzofuran-1-one 3-(phenyl sulfone) (**5**, R = H, mp 209–211 °C) was prepared in 87% overall yield by condensing phthaldehydic acid[12] with benzenethiol in benzene[13] followed by oxidation of the sulfide product with 2 equiv of *m*-chloroperbenzoic acid[14,15] in methylene chloride. Addition of **5** to a solution of LDA in tetrahydrofuran at −78 °C generated the corresponding yellow anion, which was allowed to react with Michael acceptors **2**.[16,17] The reaction proceeded through intermediate **6** to afford directly 1,4-dihydroxynaphthalenes **7** in good yield. Since the 1,4-dihydroxynaphthalene products **7** readily underwent air oxidation to naphthoquinones, they were converted to the dimethyl ethers **8** prior to final purification (Table II). This procedure provides a fundamentally new synthetic route to naphthoquinones.

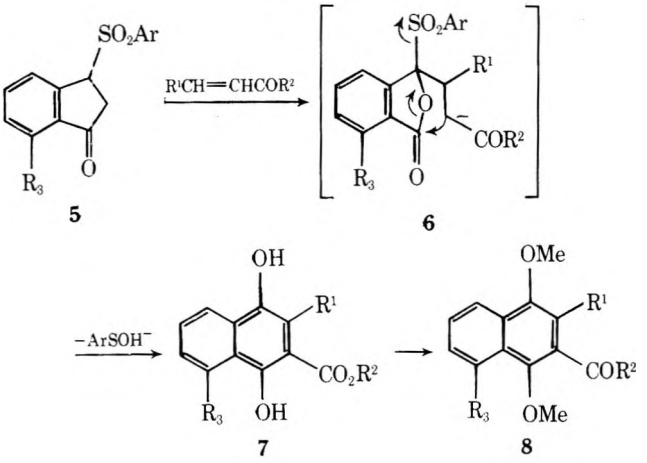
In each route to hydroxynaphthalenes (Schemes I and II) yields were highest when the Michael acceptors had a substituent on the β carbon. The increased yields of products from the phthalide sulfone reaction as compared with those ob-

Table II. Regiospecifically Prepared 1,4-Dimethoxynaphthalenes (8) from Phthalide Sulfone 5 and Michael Acceptors 2

R_1	R_2	R_3	% yield	Mp, °C
H	OEt	H	32	*a*
H	CH_3	H	29	59–60
CH_3	OEt	H	70	*a*
CH_3	CH_3	OCH_3	68	*a*
CH_3	CH_3	H	86	70–72
CH_2SCH_3	OEt	H	28	*a*
$-(CH_2)_3-$		H	69	119–120

[a] Oil.

Scheme II



tained from the sulfoxide reaction are probably due to the enhanced carbanion stabilization afforded by the sulfone.[18] Moreover, this may account for the fact that the phthalide sulfone **5** reacted smoothly with the poor Michael acceptor 2-cyclohexen-1-one,[19] while the corresponding yield of adduct from the sulfoxide was negligible. Since no effort was made to optimize reaction conditions, further studies undoubtedly will result in improved yields. An indication of the scope of the synthetic procedure for preparing 1-4-dihydroxynaphthalenes (Scheme II) is provided by the fact that condensation of methoxyl-substituted phthalide sulfone **5** ($R_3 = OCH_3$) with ethyl crotonate afforded the regiospecifically substituted naphthoate **8** ($R_1 = CH_3$, $R_2 = OEt$, $R_3 = OCH_3$) in virtually identical yield with that of the unsubstituted compound.

Acknowledgments. The authors wish to thank the National Cancer Institute of DHEW, Grant no. CA 18141, for support of this work.

Supplementary Material Available: Full ^1H NMR data for all the new products listed in Tables I and II as well as the procedures used to prepare and isolate these compounds (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) F. M. Hauser and R. P. Rhee, *J. Am. Chem. Soc.*, **99**, 4533 (1977).
(2) F. M. Hauser and R. P. Rhee, *J. Org. Chem.*, accepted for publication.
(3) The previously reported route[1] accomplished only the incorporation of a carboethoxy functionality.
(4) Ethyl 2-carboxybenzyl phenyl sulfoxide (**1**), an oil, was prepared by initial allylic bromination of ethyl *o*-toluate with *N*-bromosuccinimide followed by bromide displacement with sodium thiophenoxide in ethanol, and finally, oxidation with sodium periodate.[5]
(5) C. R. Johnson and J. E. Keiser, *Org. Synth.*, **46**, 78 (1966).
(6) Satisfactory mass, ^1H NMR, and IR spectra were obtained for all new compounds.
(7) Tetralone **3** was not isolated because it was unstable, slowly decomposing at room temperature to naphthalenes **4**. The available evidence does not completely rule out the possibility that the product observed (TLC analysis) is the initial uncyclized adduct from Michael addition.
(8) R. Schmitt and E. Burkland, *Ber.*, **20**, 2700 (1887).

(9) M. Imoto, *J. Chem. Soc. Jpn.*, **58**, 932 (1937).
(10) M. Pailer and O. Vostrowsky, *Monatsh. Chem.*, **102**, 951 (1971).
(11) Generation of the anion of ethyl *o*-toluate with LDA at −78 °C followed by attempted trapping with an ethyl crotonate resulted in the formation of the ethyl *o*-toluate dimer, 3-(2-methylphenyl)-1*H*-2-benzopyran-2-one.
(12) 6-Methoxyphthaldehydic acid was prepared from ethyl 2-methyl-6-methoxybenzoate by dibrominating the 2-methyl group followed by hydrolysis in acetic acid–hydrochloric acid medium. This conversion of an aromatic methyl group to an aldehyde follows a procedure described by E. L. Eliel, D. E. Rivard, and A. W. Burgstahler, *J. Org. Chem.*, **18**, 1679 (1953).
(13) D. D. Wheeler, D. C. Young, and D. S. Erley, *J. Org. Chem.*, **22**, 547 (1957).
(14) D. J. Brown and P. W. Ford, *J. Chem. Soc. C*, 2720 (1969).
(15) G. A. Russell and R. A. Ochrymowycz, *J. Org. Chem.*, **35**, 2106 (1970).
(16) The 3-phenylsulfoxide analogue was successfully used in the annelation reaction; however, the reaction was not as clean as with the sulfone compound (**5**).
(17) Initially, we intended to prepare the 3-cyano analogue of sulfone **5** and employ it in the condensation. The preparation of this compound was not accomplished in satisfactory yield.
(18) H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, New York, N.Y., 1972, p 494.
(19) B. D. Bergmann, D. Ginsberg, and R. Pappo, *Org. React.*, **10**, 179 (1959).

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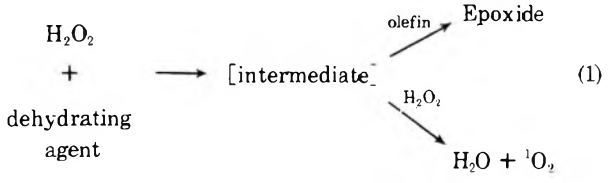
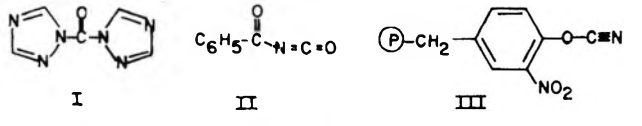
Singlet Oxygen and Epoxidation from the Dehydration of Hydrogen Peroxide

Summary: New epoxidizing reagents and chemical sources of singlet oxygen result from the action of dehydrating agents on hydrogen peroxide.

Sir: We have recently reported that the action of dehydrating agents I or II on H_2O_2 produces intermediates capable of olefin epoxidation.[1] Here we relate that a variety of dehydrating agents behave similarly (eq 1) and that the intermediates involved also lead to the production of singlet molecular oxygen.





When compounds I or II are added to THF solutions of H_2O_2, CO_2 and oxygen are rapidly evolved. That the oxygen is generated in its singlet ($^1O_2$) state can be demonstrated by its trapping with 9,10-diphenylanthracene (DPA).[2a] Table I shows the yields of $^1O_2$ as indicated by the formation of the endoperoxide of DPA and the β value (rate ratio of $^1O_2$ decay to trapping) determined for DPA in THF.[2b] The polymer-bound cyanate III[3] is also an efficient $^1O_2$ source. The reduced yield of $^1O_2$, probably due to quenching and diffusion effects of the polystyrene matrix, is offset by thee ase of handling and recyclability of this insoluble reagent.[2c] Compounds IV,[4] V,[5] and VI[6] also produce $^1O_2$ slowly under these conditions, but with much reduced efficiency.[2c]

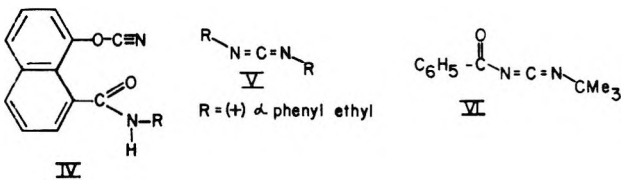
Table I

agent + H_2O_2 (4 M) $\xrightarrow[25\ °C]{THF}$ $^1O_2$

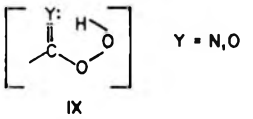
	I	II	III
Yield of $^1O_2$, %	94	98	61
Half-life, min	<10	<10	30

Table II

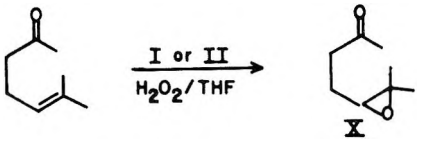
Compound	IV	VII[12]	VIII[13]	V
Asymmetric induction, %	7.5	7.1	5.2	2.0



The intermediates produced in these systems can be intercepted by olefins and epoxidation occurs at the expense of $^1O_2$ generation. Both products are formed in the presence of monoalkylethylenes, but di- and higher alkyl-substituted olefins divert the intermediates to the epoxidation pathway exclusively. Competition studies with a wide variety of olefins revealed that the behavior of these intermediates in epoxidation reactions resembles that of peracids. Epoxidation rates as a function of olefin substituents,[7] selectivities toward cis vs. trans olefins[8] or cyclohexene vs. norbornene,[9] and Baeyer–Villiger oxidations of 2-allylcyclohexanone[10] are, with minor variations, those found for typical peracids. Therefore, while the structures of the actual epoxidizing agents are unknown, intermediates such as IX are not unlikely. Indeed such structures, incorporating the peculiar intramolecular hydrogen bond of peracids, have provided the model for our selection of dehydrating agents.



For preparative epoxidations, reagents I and II were consistently the most effective, e.g., either of these reagents permitted the isolation of the labile epoxide X in >90% yield.



Further, a recent report[11] of the successful isolation of an arene oxide from an H_2O_2–carbodiimide epoxidation should encourage the increased use of such systems, since these reagents lead to products of low acidity. Somewhat less encouraging is the stereospecificity of the optically active reagents tested (Table II) for epoxidations of *trans*-β-methylstyrene. Compared to monoperoxycamphoric acid (4.1%)[15] these reagents offer only modest advantages at best.[14] The design of more effective systems is one of our present goals.

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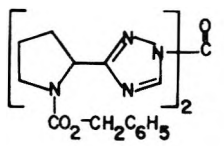
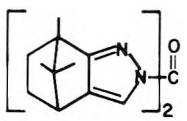

VII


VIII

Acknowledgments. We thank Professor C. S. Foote for his encouragement, advice, and aid in the determination of $^1O_2$. Financial support was provided by the National Science Foundation.

References and Notes

(1) J. Rebek, S. Wolf, and A. Mossman, *J. Chem. Soc. Chem. Commun.*, 711 (1974); presented at the 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Aug. 1976, Abstract ORGN 109.
(2) (a) E. McKeown and W. A. Waters, *J. Chem. Soc. B*, 1040 (1966). (b) The β value for DPA in THF was determined to be 0.016 M (R. H. Young, K. Wehrly, and R. Martin, *J. Am. Chem. Soc.*, **93**, 5774 (1971)). Reactions were run with excess DPA at 0.02 M, where 56% of the $^1O_2$ is trapped, and monitored by the decrease in absorption at 373 mm. (c) Singlet oxygen has been observed during the base-induced decomposition of peracids (ref 2a) and H_2O_2 (L. L. Smith and M. J. Kulig, *J. Am. Chem. Soc.*, **98**, 1027 (1976)). Evidence for $^1O_2$ from benzonitrile/H_2O_2, a system similar to the present cases, rests on chemiluminescence (E. McKeown and W. A. Water, *Nature (London)*, **203**, 1063 (1964)); however only II gave visually observable (blue) light in the presence of H_2O_2 and DPA. (d) For a discussion of the relative merits of chemical sources of $^1O_2$ see: J. W. Peters, P. J. Bekowies, A. M. Winer, and J. N. Pitts, Jr., *J. Am. Chem. Soc.*, **97**, 3299 (1975).
(3) The polymer-bound nitrophenol (R. Kalir, M. Fridkin, and A. Patchornik, *Eur. J. Biochem.*, **42**, 151 (1974)) was converted to its cyanate with BrCn/*N*-methylmorpholine: IR 2278 cm^{-1}; 1.7 mequiv/g (combustion analysis).
(4) Derived from 1,8-naphtholactone (F. M. Menger and H. T. Brock, *Tetrahedron*, **24**, 3453 (1968)) by aminolysis with (+)-α-phenylethylamine, then cyanation (BrCN/*N*-methylmorpholine): mp 136–137 °C; $[\alpha]^{25}_D$ 38.2° (*c* 1.7, $CHCl_3$). Consistent microanalyses were obtained for all new compounds.
(5) J. Rebek, D. Brown, and S. Zimmerman, *J. Am. Chem. Soc.*, **97**, 4407 (1975).
(6) O. Mitsunobu, M. Tomari, H. Morimoto, T. Sato, and M. Sudo, *Bull. Chem. Soc. Jpn.* **45**, 3607 (1972).
(7) D. Swern, "Organic Peroxides", Vol. II, Wiley-Interscience, New York, N.Y., 1970, p 452.
(8) K. B. Sharpless, J. M. Townsend, and D. R. Williams, *J. Am. Chem. Soc.*, **94**, 295 (1972).
(9) K. O. Bingham, G. D. Meakins, and G. H. Whitham, *Chem. Commun.*, 445 (1966).
(10) G. B. Payne, *Tetrahedron*, **18**, 763 (1962).
(11) S. Krishman, D. G. Kuhn, and G. A. Hamilton, *Tetrahedron Lett.*, 1369 (1977).
(12) The thiosemicarbazide and benzyloxycarbonyl-L-proline (M. Szekerke, *Acta Chem. Acad. Sci. Hung.*, **79**, 221 (1973)) were cyclized with NaOMe, then desulfurized with Raney nickel. The resulting triazole, mp 102–104 °C, $[\alpha]^{25}_D$ −50.1° (*c* 1.15, EtOH), was treated with 0.25 equiv of phosgene and used directly.
(13) Camphor was formylated (A. Bishop, L. Claisen, and W. Sinclair, *Justus Liebigs Ann. Chem.*, **281**, 328 (1894) and treated with hydrazine, and the resulting pyrazole was converted to VIII, mp 144–146 °C, IR 1730 cm^{-1}, with 0.25 equiv of phosgene.
(14) For successful asymmetric epoxidation of allylic alcohols see: S. Yamada, T. Mashiko, and S. Terashima, *J. Am. Chem. Soc.*, **99**, 1988 (1977); R. C. Michaelson, R. E. Palermo, and K. B. Sharpless, *ibid.*, **99**, 1990 (1977).
(15) See, however, W. H. Pirkle and P. Rinaldi, *J. Org. Chem.*, **42**, 2080 (1977), for improved asymmetric yields with peracids derived from camphoric anhydride.

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A Convenient Photosynthesis of Aziridinopyrrolo[1,2-*a*]benz[*f*]indoloquinone and Heterocyclic Quinones as Model Compounds of Mitomycins by a One-Pot Reaction

Summary: The photochemical reactions of 3-chloro-2-bis-(ethoxycarbonyl)methyl-1,4-naphthoquinone with various secondary amines provide a convenient, one-pot, preparative route to the title compounds (**4**) in good yields.

Sir: Recently we reported an example of a novel type of photoinduced intramolecular cyclization in various solvents using amino-1,4-naphthoquinones possessing an active methylene group at the 2 position to form indoloquinones.[1] In this communication we wish to describe a novel route to aziridinopyrrolo[1,2-*a*]benz[*f*]indoloquinone, a model compound of mitomycins, and related compounds by a one-pot reaction utilizing this procedure.

A solution of aminoquinones (**2a–e**)[2] prepared from the reaction of 3-chloro-2-bis(ethoxycarbonyl)methyl-1,4-naphthoquinone (**1**)[3] with various amines (pyrrolidine, piperidine, morpholine, hexamethylenimine, and diethylamine) in ethanol was irradiated with a high-pressure mercury arc lamp through Pyrex glass in a stream of nitrogen for 1–2 h (Scheme I). After allowing the irradiated solution of **2a–e** to stand for more than 24 h at room temperature followed by evaporation of the solvent, ring-closed quinones (**4a–e**) were obtained in high yields. In the case of **2e**, **5e**[4] was isolated as a minor product along with **4e**.The results are summarized in Table I. The structural assignments for **4a–f** were based on their analytical and spectral properties, which were in good agreement with their formulations. Their ^1H NMR spectra revealed the presence of a bridgehead methine proton at 4.50–5.00 ppm instead of an active methine.

We have also extended this photocyclization reaction to a simple synthesis of an aziridine-containing pyrroloindoloquinone ring system. A similar photoreaction[5] using 6-(4-bromophenyl)-3,6-diazabicyclo[3.1.0]hexane[6] as an amine gave aziridinopyrrolo[1,2-*a*]benz[*f*]indoloquinone (**4f**) in 63% yield, mp 189–191 °C (from ethanol). The stereochemistry of this compound was determined by ^1H NMR analysis. The

Scheme I

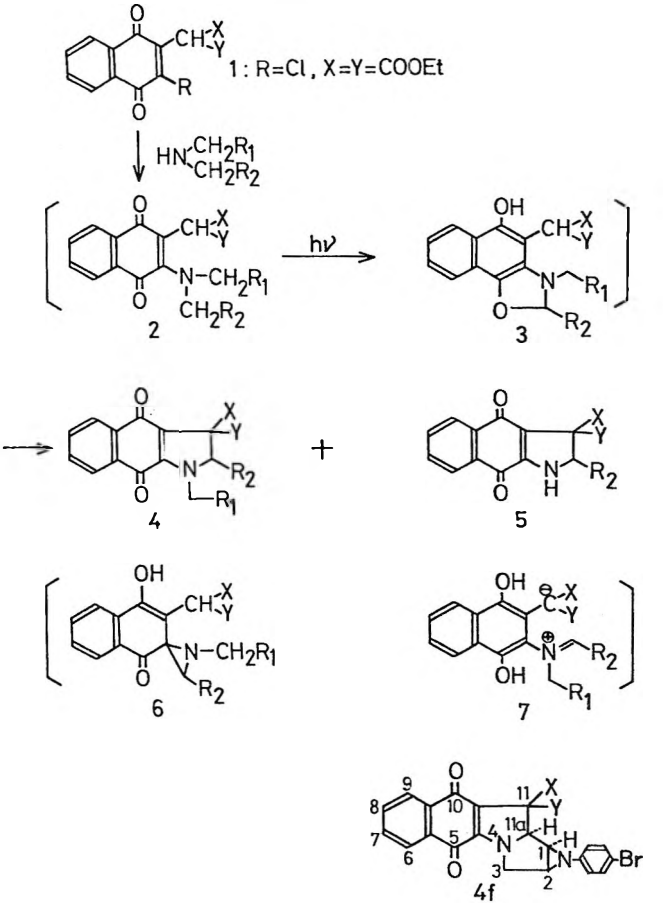
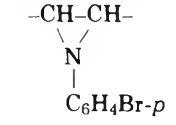


Table I. Photoproducts from Active Methylene-Containing Amino-1,4-naphthoquinones by a One-Pot Reaction

Substrate	R_1 R_2	Product	Mp, °C	Yield, %	NMR bridgehead CH, ppm	Mass (*m/e*), M^+
2a	$-(CH_2)_2-$	**4a**	158	70	4.80 (d, d)	383
b	$-(CH_2)_3-$	**b**	158	73	5.00 (d, d)	397
c	$-CH_2OCH_2-$	**c**	133	75	4.60 (d, d)	399
d	$-(CH_2)_4-$	**d**	137–139	78	4.50 (d, d)	411
e	CH_3 CH_3	**e**	oil	55	4.78 (q)	385
f		**f**	189–191	63	5.01 (d)	550

results from a 100-MHz NMR spectrum of **4f** in $CDCl_3$, together with those from a double irradiation experiment, permitted assignment of all of the proton signals and the determination of proton–proton coupling constants. The C-3 methylene protons at 4.52 and 3.56 ppm couple with the C-2 methine proton at 2.90 ppm unequally. In addition, the dihedral angle of H–C(2)–C(3)–H is 90°, since the vicinal coupling constants $J_{2,3} = 0$, consistent with the molecular geometry[7] for the solid phase indicated by x-ray analysis for the *N*-brosyl derivative of mitomycin A and $J_{2,3} = 2.5$ Hz.[8] On the other hand, the C(11a) methine proton at 5.01 ppm has a coupling of 2.5 Hz with the C(1) methine proton at 3.24 ppm. Therefore, the stereochemistry of the C(1) and C(11a) methine protons were assigned as a cis configuration, the same as that of mitomycin. The observed value of $J_{1,2} = 4.5$ Hz is also consistent with the cis coupled aziridine ring proton.[9] It is noteworthy that this photocyclization appears to be stereoselective, giving only one diastereomer.

Several reactions involving abstractions of hydrogen from the side chains of quinone have been reviewed previously.[10] The interest in the photochemistry of these and related systems has continued. To date, only a few examples of such photoreactions[11] were reported on quinones bearing certain secondary amino substituents. The photochemical formation of the ring-closed quinones presumably involves intramolecular hydrogen abstraction by the excited quinones as the first step. Subsequently the biradical[12] could lead to benzoxazoline (**3**)[13] via spiroaziridine species **6**[14] by hydrogen transfer, ring closure, and aromatization. In polar solvents, under conditions which might be expected to favor a zwitterion intermediate (**7**) (**3** ⇌ **7**), **7** undergoes the intramolecular nucleophilic attack to give ring-closed quinones followed by oxidation. In an attempt to trap the intermediate (**3**) in the photoreaction, **2f** was photolyzed in ethanol at low temperature (0–5 °C), giving unstable aziridinonaphthoxazoline (**3e**)[4] as a sole product. After allowing the solution of **3e** to stand in ethanol for a long time at room temperature, **4f** was obtained in a good yield. As shown in Table I, yields in the ring-closed quinone series increase with increasing size of the amino-containing ring. These facts may be rationalized by the ease of proton transfer from the methylene of the amino group, which would be held close to the quinone carbonyl in the excited state.

We believe that this photoinduced reaction of amino-substituted quinone may be of great utility in the simple synthesis of heterocyclic quinones in comparison to the Nenitzescu reaction.[15] The consecutive reactions (amino substitution, photolysis, and ring conversion) described above could also be carried out continuously as a one-pot reaction. For the purpose of the total synthesis of mitomycins,[16] the implication of the one-pot reaction in the photolysis of aminotoluquinones is being studied and will be reported elsewhere.

Acknowledgment. Our sincere thanks are offered to Professor S. Ohki for his continuous interest and encouragement on this work.

References and Notes

(1) M. Akiba, Y. Kosugi, M. Okuyama, and T. Takada, *Heterocycles*, **6**, 1113 (1977).
(2) The reaction solution of 3-chloro-2-bis(ethoxycarbonyl)methyl-1,4-naphthoquinone (**1**) with 2–4 equimolar amounts of amines in ethanol, without the isolation of amino-1,4-naphthoquinones (**2a–e**), was irradiated.
(3) G. A. Reynolds, J. A. van Allan, and R. E. Adel, *J. Org. Chem.*, **30**, 3819 (1965).
(4) Its structure was supported by spectral (UV, IR, and NMR) data.
(5) Photolysis was performed similarly for 1–2 h as appropriate.
(6) P. Scheiner, *Tetrahedron*, **24**, 2757 (1968).
(7) A. Tulinsky, *J. Am. Chem. Soc.*, **84**, 3188 (1962).
(8) J. W. Lown and A. Begleiter, *Can. J. Chem.*, **52**, 2331 (1974).
(9) R. W. Frank and Auerbach, *J. Org. Chem.*, **36**, 31 (1971).
(10) J. M. Bruce, *Q. Rev., Chem. Soc.*, **21**, 405 (1967).
(11) (a) E. P. Fokin and A. M. Detsina, *Chem. Abstr.*, **72**, 12500n (1970); (b) D. W. Cameron and R. G. F. Giles, *J. Chem. Soc. C*, 1461 (1968); (c) R. G. F. Giles, P. R. K. Mitchell, and G. H. P. Roos, *J. Chem. Soc., Perkin Trans. 1*, 493 (1973).
(12) S. Farid, *Chem. Commun.*, 303 (1970).
(13) The monitoring of the photoreaction of **1c** in $CDCl_3$ by NMR and UV spectroscopy revealed that the intermediate was formulated as the oxazoline and degradation of the oxazoline ring was observed with lapse of time.
(14) C. M. Orlando, H. Mark, A. K. Bose, and M. S. Manhas, *J. Org. Chem.*, **33**, 2512 (1968).
(15) C. D. Nenitzescu, *Chem. Abstr.*, **24**, 110 (1930).
(16) For approaches to the mitomycin structure, see F. Nakatsubo, A. J. Cocuzza, D. E. Keeley, and Y. Kishi, *J. Am. Chem. Soc.*, **99**, 4835 (1977), and references cited therein.

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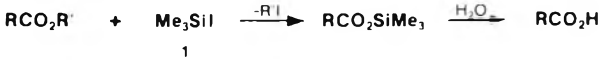
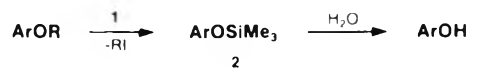
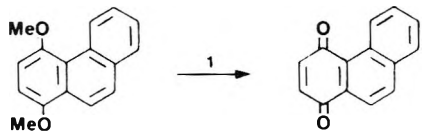
Iodotrimethylsilane (1) has been introduced by Jung[1] and Olah[2] as an efficient and convenient reagent for the cleavage of esters and ethers under neutral conditions. **Iodotrimethylsilane** has advantages over other dealkylating agents in that mild, homogeneous reaction conditions can be employed.[2] Hence, a mixture of **1** and a carboxylic ester, either neat[2] or in an aprotic solvent, gave the corresponding acid on heating and subsequent aqueous hydrolysis.



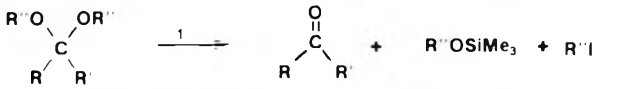
Jung and Lyster[1] have examined cleavage conditions for a wide variety of *ethers*. For example, heating an excess of **iodotrimethylsilane** with alkyl aryl ethers gave good yields of aromatic trimethylsilyl ethers **(2)**. These may be converted to their respective alcohols by simple hydrolysis.



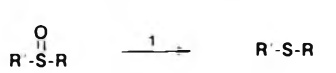
A recent extension of this cleavage reaction is the following:[4]



The conversion of ketals to ketones under nonaqueous conditions is rapidly achieved using **iodotrimethylsilane**.[5]



Alkyl sulfoxides are efficiently deoxygenated at room temperature using an equimolar amount of **iodotrimethylsilane**.[6]



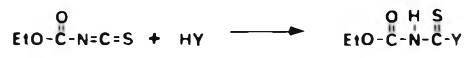
Alcohols are readily converted to the corresponding alkyl halides by **iodotrimethylsilane**.[7] The displacement occurs using either the alcohol directly or the corresponding silyl derivative.

References:

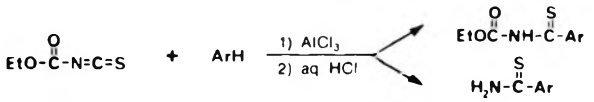
1) M.E. Jung and M.A. Lyster, *J. Am. Chem. Soc.*, **99**, 968 (1977).
2) T.-L. Ho and G.A. Olah, *Angew. Chem., Int. Ed. Engl.*, **15**, 774 (1976).
3) M.E. Jung and M.A. Lyster, *J. Org. Chem.*, **42**, 3761 (1977).
4) B.I. Rosen and W.P. Weber, *J. Am. Chem. Soc.*, **42**, 3463 (1977).
5) M.E. Jung, W.A. Andrus, and P.L. Ornstein, *Tetrahedron Lett.*, 4175 (1977).
6) G.A. Olah, B.G.B. Gupta, and C. Narang, *Synthesis*, 583 (1977).
7) M.E. Jung and P.L. Ornstein, *Tetrahedron Lett.*, 2659 (1977).

19,552-9 Iodotrimethylsilane **5g $9.60; 25g $32.00**

The chemistry of **ethoxycarbonyl isothiocyanate (ECI)** was reviewed by Esmail and Kurzer[1] in 1975. This reagent has wide application in the synthesis of heterocyclic compounds. The isothiocyanate group participates in linear and cycloaddition reactions with compounds containing an active hydrogen atom.



Furthermore, **ECI** is useful in the Friedel-Crafts thioacylation of aromatic compounds, yielding thioamides in one step.[2]



The resulting multifunctional intermediates can cyclize or condense with other molecules to yield a variety of heterocyclic structures, *e.g.*, thiazoles,[3] rhodanines,[4] triazinethiones,[5] triazines,[6-8] thiouracils,[9] and condensed *s*-triazines.[10-13]

References:

1) R. Esmail and F. Kurzer, *Synthesis*, 301 (1975).
2) E.P. Papadopoulos, *J. Org. Chem.*, **41**, 962 (1976).
3) C.W. Capp, A.H. Cook, J.D. Downer, and I. Heilbron, *J. Chem. Soc.*, 1340 (1948).
4) D.H.R. Barton, E. Buschmann, J. Haüsler, C.W. Holzapfel, T. Sheradsky, and D.A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1107 (1977), and references cited therein.
5) J. Goerdeler and J. Neuffer, *Chem. Ber.*, **104**, 1606 (1971).
6) J. Goerdeler and D. Wobig, *Justus Liebigs Ann. Chem.*, **731**, 120 (1970).
7) J. Goerdeler, *Q. Rep. Sulfur Chem.*, **5**, 169 (1970).
8) J. Goerdeler and D. Wobig, *Angew. Chem., Int. Ed. Engl.*, **6**, 262 (1967).
9) R.W. Lamon, *J. Heterocycl. Chem.*, **5**, 837 (1968).
10) B. Stanovnik and M. Tisler, *Synthesis*, 308 (1972).
11) M. Nagano, J. Tobitsuka, T. Matsui, and K. Oyamada, *Chem. Pharm. Bull.*, **20**, 2618 (1972).
12) R.A. Coburn and B. Bhooshan, *J. Org. Chem.*, **38**, 3868 (1973).
13) L. Capuano and H.J. Schrepfer, *Chem. Ber.*, **104**, 3039 (1971).

19,612-6 Ethoxycarbonyl isothiocyanate **5g $10.50**
25g $35.00